呼吸疾病国家重点实验室年报

2015 年

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前言

2015 年，是呼吸疾病国家重点实验室飞速发展和收获的一年，也是迎接 2016 年科技部评估，战略筹备性的一年。在国家科技部、省市各级科技部门、依托单位的领导和支持下，实验室的队伍日益壮大，围绕四个研究方向开展科学研究，取得令人瞩目的成绩。

实验室在承担国家级、省部级等各级部门的科研项目方面整体稳定发展，并取得突破性的科研成果，其中实验室以第一完成单位完成的“慢性阻塞性肺疾病发病与综合防治”研究项目荣获 “2015 年国家科学技术进步二等奖”，研究首次准确揭示了我国慢阻肺的流行病学状况，首次阐明生物燃料是我国慢阻肺的重要发病因素、及导致慢阻肺的机制，首次发现含巯基抗氧化药物治疗慢阻肺的作用，证实了茶碱等药物治疗慢阻肺的效果，为中国慢阻肺患者提供了有效、安全、经济、实用的治疗方法，首次研制符合国情的慢阻肺社区综合防治模式，对提高我国慢阻肺综合防治水平起到了积极的作用。给予该研究发表的论文《“厨房烹饪（生物）燃料和通风状况改善对肺功能 FEV1 和慢阻肺发病率的影响：为期 9 年的前瞻性队列研究”》也是我过首次荣获“ISEE 最佳环境流行病学论文奖”。

实验室官方出版期刊《Journal of Thoracic Disease》，获创刊以来的首个影响因子 1.783。JTD 的成绩，使得实验室在科研综合实力上又进步了一个台阶。

实验室逐步完善科研发展平台。在依托单位广州医科大学的支持下，根据实验室未来发展的要求，扩大实验室面积、购置仪器设备、引进科研人才。2016 年即将落成使用的 16 号楼，为科研人员提供更好的研究环境、增加配套精准的科研设备，提供优质的科研条件，为高水平科研产出打下夯实基础。

2015 的实验室充满朝气。合作开放，邀请专家、输送人才进行交流学习；互联网时代，实验室的发展也与时共进，官方网站全新改版，建立微信公众平台，发布科研进展最新消息；首次举办大学生夏令营，吸引优秀的学子壮大实验室人才队伍建设；产学研基地开幕，是实验室产学研建设的一个里程碑。

迎接科技部 2016 考核评估，是来年实验室工作的重中之重。实验室将以崭新的面貌、坚强的科研实力、坚韧的探究精神，坚持不懈，站在中国呼吸疾病领域的最前线，为我国经济社会稳定发展和人民身体健康作出应有的贡献。

呼吸疾病国家重点实验室

呼吸疾病国家重点实验室年报
2015 年

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呼吸疾病国家重点实验室

呼吸疾病国家重点实验室

一、实验室概况

（一）实验室布局

呼吸疾病国家重点实验室在去年取得了丰硕的科研成果，今年承接上一年度的建设精神，继续夯实基础，探索创新管理，积极引进人才，加快拓展平台。

重点实验室在政府、学院和医院支持下，本年度各项科研工作进展顺利，并取得了佳绩。实验室充分利用建设经费投入到仪器购置、实验耗材、平台环境改造、人才引进及培养等方面，经费总体使用情况基本符合最优配置的原则。实验室在科研方面保持优势，在国自然、省自然、青年基金等都获得了多项科研项目，高质量论文发表的数目稳步增长。

实验室继续以突发性重大呼吸系统传染病、支气管哮喘与慢性咳嗽、慢性阻塞性肺疾病、肺癌四大研究方向，进行科研开拓，招纳人才，截至今年底，实验室共拥有 42 位 PI。实验室基础实验部位于海印分院，占地面积约 4000 平方米，建有动物实验室、病毒实验室、PCR 实验室、肺癌实验室、睡眠呼吸实验室、变态反应实验室等；临床实验部位于总院，占地面积约 800 平方米，建有咳嗽实验室、免疫实验室、支气管镜实验室、肺功能实验室、临床药理等；联合实验室中国科学院广州生物与健康研究院位于科学城，占地面积约 39300 平方米，建有华南干细胞与再生医学研究所、化学生物学研究所、感染与免疫中心、公共健康研究所等；实验室产学研平台位于科学城，占地面积约 534.57 平方米。为进一步扩大规模、提高科研产出能力，实验室现筹备改建广州医科大学 16 号楼作为实验室使用，现已进入动工阶段，预期于 2016 年投入使用。

呼吸疾病国家重点实验室

呼吸疾病国家重点实验室课题组 PI

姓 名	性别	出生年月	职 称	实验室职务	研究方向或专业	工作性质	备 注
钟南山	男	1936.10	教授	实验室主任	呼吸病学	研究	院士（1996）
陈凌	男	1962.01	研究员	实验室常务副主任	病毒学	研究	杰出青年（2006）

姓 名	性别	出生年月	职 称	实验室职务	研究方向或专业	工作性质	备 注
王新华	男	1969.05	教授	实验室副主任	中医药学	研究	广州医科大学校长
陈荣昌	男	1959.12	教授	实验室副主任	COPD	研究	广州呼吸疾病研究所所长
陈小平	男	1956.08	研究员	实验室副主任	病原生物学	研究	
冉丕鑫	男	1962.09	教授		COPD	研究	新世纪百千万人才工程国家级人选（2007），广州医科大学书记
何建行	男	1963.02	教授		肺部肿瘤	研究	广州医科大学附属第一医院院长
黎毅敏	男	1964.04	教授		重症监护与感染	研究	广州医科大学附属第一医院副书记
郑劲平	男	1960.10	教授		COPD	研究	广州呼吸疾病研究所副所长
李时悦	男	1964.06	教授		肺部肿瘤	研究	广州呼吸疾病研究所副所长
刘劲松	男	1970.11	研究员		结构生物学	研究	中科院百人计划（2007）
彭涛	男	1965.07	研究员		病毒学	研究	
徐军	女	1953.02	教授		临床呼吸病理生理学	研究	

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姓 名	性别	出生年月	职 称	实验室职务	研究方向或专业	工作性质	备 注
李懿	男		研究员		免疫学	研究	
周荣	男	1965.03	研究员		病毒学	研究	
卓超	男	1967.11	研究员		细菌学	研究	广东省高校“千百十人才培养工程”省级培养人才
赖克方	男	1963.12	教授	临床实验部主任	慢性咳嗽与哮喘	研究	
刘志刚	男	1959.10	教授		慢性咳嗽与哮喘	研究	
李靖	女	1964.10	教授		慢性咳嗽与哮喘	研究	
王健	男	1962.12	教授		COPD 与肺血管病	研究	珠江学者（2007-2008）
罗远明	男	1962.09	教授		COPD	研究	
郑则广	男	1964.10	教授		COPD	研究	
卢文菊	女	1969.09	教授		COPD 与肺血管病	研究	珠江学者(2014),广东省高等学校"千百十工程"省级培养对象
张必良	男	1961.01	研究员		化学生物学	研究	
陶爱林	男	1968.05	教授		慢性咳嗽与哮喘	研究	

呼吸疾病国家重点实验室

姓 名	性别	出生年月	职 称	实验室职务	研究方向或专业	工作性质	备 注
张天宇	男	1976.02	研究员		致病菌与免疫学	研究	中科院百人计划
谭守勇	男	1955.06	教授		结核病	研究	
朱强	男	1972.06	研究员		有机化学	研究	
胡文辉	男	1973.09	研究员		药物化学	研究	
苏钟	男	1958.01	研究员		动物医学	研究	
张健存	男	1964.06	研究员		有机化学	研究	
蒋义国	男	1966.03	教授		化学致癌	研究	
吕嘉春	男	1967.02	教授		化学致癌	研究	
沈华浩	男	1959.06	教授		慢性咳嗽与哮喘	研究	
刘金保	男	1965.02	教授		慢性咳嗽与哮喘	研究	
张孝文	男		教授		慢性咳嗽与哮喘	研究	
周国瑛	女		教授		免疫学	研究	
丁克	男		研究员		化学生物学	研究	杰出青年(2013),中国科学院“百人计划”

呼吸疾病国家重点实验室

姓 名	性别	出生年月	职 称	实验室职务	研究方向或专业	工作性质	备 注
杨子峰	男	1977.11	副教授		临床病毒学	研究	广东省高等学校"千百十工程"省级培养对象
孙宝清	女	1970.10	研究员		临床免疫学	研究	
金方	女	1965.01	研究员		新药研发	研究	
白春学	男	1951.04	教授		肺损伤和肺癌	研究	
赵金存	男	1978.08	教授		呼吸道病毒发病机制	研究	

呼吸疾病国家重点实验室

实验室现有固定人员共 56 人，其中担任课题组长的科研人员 42 人，管理人员 2 人，技术人员 11 人，其中博士及以上 42 人，硕士 11 人；流动人员 71 人，其中博士及以上 22 人，硕士 23 人，副高以上职称 11 人，中级职称 49 人。

（二）固定资产

实验室严格依照专项经费使用的规章制度，规范、合理、科学利用科研经费购置仪器设备，以确保形成设备先进、科研硬件完善的研究支撑平台。截止 2015 年底，实验室总建筑面积为 5534.57 平方米（基础实验室部 4000 平方米，临床实验部 800 平方米，产学研平台 534.57 平方米），仪器设备总台数 548 台，总价值 7513.93 万元。

实验室固定资产情况

年度	建筑面积（平方米）	设备总台数（台）	设备总值（万元）
2015	5534.57	548	7513.93
2014	5534.57	328	5723.14
2013	4800	312	5267.75
2012	4800	295	4279.97

实验室 30 万元以上设备情况

类别	设备总台数（台）	设备总价值（万元）	平均每台仪器研究工作总机时（小时）	平均每台仪器服务工作总机时（小时）	机时率（%）
数值	60	4627.21	320.15	168.02	265.0

注：每台设备标准机时为 K=1800 小时/每年；研究工作总机时（D）是指每台仪器每年本实验室研究人员使用总时间；服务工作总机时（E）是指每台仪器每年非本实验室工作人员使用的总时间；机时率（%）=（D+E）/K。

呼吸疾病国家重点实验室

二、实验室总体运行情况

（一）承担科研项目

2015 年，实验室承担课题 27 项，国家自然科学基金项目 27 项，资助金额为 1762 万元；其他国家级项目 6 项，资助金额为 1335 万元；省部级、市级项目 58 项，资助金额为 76905 万元。实验室承担科研项目数量整体稳步发展，其中李靖教授的“尘螨免疫治疗对呼吸道上皮细胞 HBD-2 和树突状细胞的调节作用”和朱强教授的“过渡金属催化烯烃的氧化官能化新反应研究”获得了国家自然科学基金重大项目资助，王新华教授的“滇药臭灵丹靶向流感病毒和宿主免疫调节的新型活性成分药效机制及构效关系研究”获得云南-联合基金资助，卢文菊教授的“MUC1 对慢性阻塞性肺疾病气道炎症和重构的调节作用与机制研究”获得国际(地区)合作与交流项目资助，资助力度有较大进步，有利于开展科学研究。

国家自然科学基金项目

序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）
1	过渡金属催化烯烃的氧化官能化新反应研究	朱强	重大项目	2016	142
2	尘螨免疫治疗对呼吸道上皮细胞 HBD-2 和树突状细胞的调节作用	李靖	重大项目	2016	150
3	滇药臭灵丹靶向流感病毒和宿主免疫调节的新型活性成分药效机制及构效关系研究	王新华	云南-联合基金	2016	240
4	转录因子 Mnx1 调控爪蛙背胰前体细胞发育的分子机制研究	周国瑛	青年科学基金项目	2016	20
5	中药细辛治疗难治性慢性咳嗽的药效物质与多靶点作用机制研究	刘晓东	青年科学基金项目	2016	18
6	原发性 T790M 耐药突变在非小细胞肺癌 EGFR 基因两种敏感突变亚型之间的差异及其对靶向治疗效果的影响	梁文华	青年科学基金项目	2016	19
7	人博卡病毒 1 型与分化的人气道上皮细胞膜蛋白的相互	刘文宽	青年科学基金项目	2016	20

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序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）
8	全人源屋尘螨特异性单链抗体的构建及应用	冯木林	青年科学基金项目	2016	18
9	浅蓝霉素 A 生物合成通路中氨基转移酶 CrmG 的结构生物学研究	刘劲松	青年科学基金项目	2016	24
10	泛过敏原 Profillin 与人 IL-10 的嵌合蛋白 LTT 诱导免疫耐受的机制研究	陶爱林	青年科学基金项目	2016	21.6
11	迟发型超敏反应通过 IFN-γ 介导咳嗽高敏综合征的作用及机制研究	邓政	青年科学基金项目	2016	18
12	NKT 细胞在屋尘提取物暴露预防过敏性哮喘中的作用和机制研究	杨朝崴	青年科学基金项目	2016	18
13	lncRNA Rian 在肺癌发生中的作用及与 miR-370 互作机制研究	覃丽梅（陈小平）	青年科学基金项目	2016	20
14	AQP1 在低氧性肺动脉高压发病过程中的作用机制研究	赖宁	青年科学基金项目	2016	18
15	2 型登革热病毒蛋白酶 NS2B-NS3p 活性构象的晶体结构研究	李华（彭涛组）	青年科学基金项目	2016	18
16	选择性盘状结构域受体（DDRs）小分子抑制剂的设计、合成及生物活性研究	丁克	面上项目	2016	65
17	通过双调控体系条件性敲除红内期必需基因构建疟原虫减毒双期活疫苗的研究	秦莉	面上项目	2016	60
18	慢性咳嗽高敏豚鼠模型的建立及其在咳嗽治疗药物药效评价中的应用	赖克方	面上项目	2016	90
19	久咳要药五味子治疗慢性咳嗽高敏综合征的药效物质基础及药理机制研究	钟山	面上项目	2016	54
20	交通相关空气污染物（TRAP）致 COPD 大鼠模型的构建及其发病机制研究	周玉民	面上项目	2016	110
21	基于 miR-21 调控 PTEN/PI3K 信号途径探讨针刺改善 PCOS 卵巢局部 IR 的机制	马红霞	面上项目	2016	57

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序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）
22	呼吸紊乱事件相关鼾声的信号特征与识别研究	张孝文	面上项目	2016	57
23	尘螨过敏原组分抗体作为变应性哮喘和/或鼻炎脱敏疗效临床生物学评估指标的应用研究	孙宝清	面上项目	2016	55
24	SNX10/SNX11 调节内体溶酶体形态机理的结构生物学研究	刘劲松	面上项目	2016	74.4
25	circRNA 在苯并(a)芘诱导肺癌变发生中的作用及其机制	蒋义国	面上项目	2016	70
26	CaSR-TRPC 信号通路在低氧性肺动脉血管重塑中的作用及机制	彭公永	面上项目	2016	55
27	MUC1 对慢性阻塞性肺疾病气道炎症和重构的调节作用与机制研究	卢文菊	国际(地区)合作与交流项目	2016	250

其他国家级项目

序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）	下达年度
1	慢性阻塞性气道疾病肺功能检查规范化临床应用体系建设与推广	郑劲平	国家科技支撑计划	2015	689	2015
2	肿瘤组织靶向性 siRNA 分子的中式制备工艺	张必良	中国科学院全面战略合作项目	2015	100	2015
3	不同来源大气细颗粒物导致气道重塑的蛋白与非编码核酸调控网络的机理研究	周玉民（冉丕鑫组）	973 计划	2015	231	2015
4	（CAS-CSIRO 项目)抗分枝杆菌药物研发	张天宇	中国科学院国际合作局对外合作重点项目	2016	100	2016
5	腺病毒疫苗和效力评价腺病毒疫苗和效力评价	周荣	军队特需药品保密专项“十二五”	2015	120	2015
6	我国大气污染对居民健康的影响及防控策略研究	郑劲平	卫生部公益性行业科研专项	2015	95	2015

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省部级、市级项目

序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）	下达年度
1	基于治疗咳嗽高敏综合征中药细辛的药效物质、作用机制及新药开发研究	刘晓东	广东省自然科学基金		10	2015
2	神经源性炎症在上气道咳嗽综合征发病中的作用	陈如冲	广东省自然科学基金		5	2015
3	变应原蛋白芯片检测组分 sIgE 对变应性疾病诊断价值的研究	孙宝清	广州市科信局		20	2015
4	microRNA19b 对机械牵张引起的小气道上皮细胞凋亡的调控作用	刘晓青	广东省自然科学基金		10	2015
5	中期因子介导机械牵张诱导肺上皮细胞 EMT 的机制研究	黎毅敏	广东省自然科学基金		10	2015
6	丙型肝炎病毒（HCV）捕获宿主极低密度脂蛋白（VLDL）通路的分子机制研究	蔡华（彭涛组）	广东省自然科学基金（博士启动）		10	2015
7	2 型登革热病毒蛋白酶 NS2B-NS3p 活性构象的结构生物学研究	李华（彭涛组）	广东省自然科学基金（博士启动）		10	2015
8	广州市结核病临床医学研究与转化中心	谭守勇	广州市科信局		200	2015
9	基于卡介苗和表位的新型治疗性结核疫苗的研发	张天宇	广州市科技计划项目		180	2015
10	人腺病毒和流感病毒动物模型的建立及应用研究	李潇	广州市科技计划-科学研究专项		150	2015
11	人 3 型腺病毒中和抗原表位及其应用基础研究	周荣	广东省自然基金-面上项目		5	2015
12	“国家杰青、优青”后备培养人才项目	师宪平（刘金保组）	广州医科大学人才项目	2014	15	2015
13	尘螨组分 sIgE 和 sIgG4 在特异性免疫治疗中的免疫调控监测	郑佩燕（孙宝清组）	广州市卫生局	2015	1.5	2015

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序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）	下达年度
14	呼吸道变应性疾患者检测食物 sIgE 和 sIgG 抗体的辅助诊断价值及饮食调整治疗疗效评价	黄惠敏（孙宝清组）	广州市卫生局	2015	0	2015
15	吡啶硫酮铜络合物抑制去泛素化酶克服肿瘤硼替佐米耐药的机制研究	师宪平（刘金保组）	广州市属高校科研项目	2015	15	2015
16	变应原蛋白芯片检测组分 sIgE 对变应性疾病诊断价值的研究	孙宝清	广州市科信局	2015	20	2015
17	呼吸系统感染性疾病室内环境病原控制	孙宝清	广州市科信局	2015	30	2015
18	对抗肺癌免疫抑制的新策略和机制研究	周国瑛	广州市科技计划重大专项	2015	200	2015
19	结核病临床医学研究与转化中心	张天宇	广州市科技计划项目	2015	20	2015
20	产学研协同创新重大专项（二期）：基于卡介苗和表位的新型治疗性结核疫苗的研发	张天宇	广州市科技计划项目	2014	117	2015
21	广州市第二批临床医学研究与转化中心--传染病-结核病临床医学研究与转化中心	谭守勇	广州市科技创新委员会	2015	200	2015
22	应对新发/突发/重症呼吸系统病毒感染创新技术研究	陈凌	广州市教育局协同创新	2014	47.5	2015
23	利用 CRISPR/Cas9 介导的基因敲除人源细胞系对 NLRs 蛋白相关炎症小体的分子调控机制研究	张铁军（周国瑛组）	广州市教育局	2015	5	2015
24	内体溶酶体形态调控通路中 SNX11 的膜结合机制研究	徐进新（刘劲松组）	广东省自然科学基金	2015	10	2015
25	以气道上皮细胞 NOS3、cPLA2 活性为靶点的抗咳嗽高敏综合征中药活性成分筛选与药效评价	聂怡初（赖克方组）	广东省自然科学基金	2015	10	2015
26	吡啶硫酮铜络合物抑制去泛素化酶克服多发性骨髓瘤硼替佐米耐药的机制研究	师宪平（刘金保组）	广东省自然科学基金	2015	10	2015
27	我国常见过敏原诊断试剂研制及产业化	孙宝清，陶爱林	广东省科技厅产学研项目	2015	50	2015
28	2014 年高等教育“创新强校”工程专项-广东高校工程研究中心	王新华	广东省教育厅	2015	50	2015

国家重点实验室

序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）	下达年度
29	分子水平诊断技术解决广东地区呼吸道变应性疾病常见过敏原组分的交叉反应	孙宝清	广东省公益研究与能力建设专项资金	2015	10	2015
30	肺癌靶向治疗的疱疹溶瘤病毒开发研究	周国瑛	广东省高校重点科研项目	2015	50	2015
31	靶向非小细胞肺癌 EGFR vIII 的疱疹病毒免疫治疗研发	张雪雁（周国瑛组）	2014 年度广东省公益研究与能力建设专项	2015	10	2015
32	循环长链非编码 RNA 在化学物诱导肺癌发生中的作用和标志物意义	蒋义国	广东省自然科学基金重点项目	2015	30	2015
33	快速筛选抗 H7 亚型流感病毒高亲和力单克隆抗体及中和机制的研究	李正锋	广州市（科学研究一般项目）	2015	20	2015
34	多抗原联用的多价治疗性结核疫苗研究	冯立强	广州市（珠江新星专项）	2015	30	2015
35	分泌型磷脂酶 A2 Group IIE (sPLA2G2E) 在动脉粥样硬化发生中的分子机制研究	刘劲松、冯立强	广东省（重点团队项目）	2015	300	2015
36	大气细颗粒物导致气道重塑的非编码核酸调控机理研究	冉丕鑫	广东省自然科学基金重点项目	2015	30	2015
37	分子水平诊断技术解决广东地区呼吸道变应性疾病常见过敏原组分的交叉反应	孙宝清	广东省科技厅	2015	10	2015
38	尘螨组分 sIgE 和 sIgG4 在特异性免疫治疗中的免疫调控监测	郑佩燕	广州市医药卫生科技项目	2015	1.5	2015
39	呼吸道变应性疾患者检测食物 sIgE 和 sIgG 抗体的辅助诊断价值及饮食调整治疗疗效评价	黄惠敏	广州市医药卫生科技项目	2015	0	2015
40	2015 广州市健康医疗协同创新重大专项三期	赵金存	广州市	2015	600	2015
41	基于 ELISPOT 及嗜碱性粒细胞激发实验的左氧氟沙星速发型药物过敏检测方法的建立与应用评价	张俊艳	广东省公益研究与能力建设专项资金	2015	5	2015

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序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）	下达年度
42	屋尘螨过敏原 Der p 2 蛋白激活的 TLR4 信号通路对 Th2 型免疫及气道上皮细胞通透性的影响研究	刘兆宇	广东省公益研究与能力建设专项资金	2015	5	2015
43	食物过敏及 Fcγ受体基因多态性与肠易激综合征发病的相关性及其机制研究	王珊	广东省公益研究与能力建设专项资金	2015	5	2015
44	靶向 EGFR 的金葡菌肠毒素 B 的毒性与抗原性弱化及其治疗肺癌的实验研究	刘雪婷	广东省公益研究与能力建设专项资金	2015	5	2015
45	广州市过敏反应临床医学研究与转化中心	赖荷	广州市科技创新委员会	2016	200	2016
46	人腺病毒和流感病毒动物模型的建立及应用研究	李潇	广州市科技计划-科学研究专项	2015	150	2015
47	基于云平台的慢性阻塞性肺疾病急性加重个体化预警系统的建立	陈荣昌	广州市	2016	500	2015
48	新发传染病重症病例临床救治新技术研究	陈荣昌	科技部	2016	4000	2016
49	基于云平台智能管理系统的双水平无创呼吸研发及在慢阻肺中的应用评价	周露茜	广东省科技厅	2015	30	2015
50	应用数据挖掘技术构建慢阻肺疾病内因型分类模型的研究	梁振宇	广州市博士后启动	2015	15	2015
51	Myostatin 与慢阻肺肌肉消耗及无力的关系及其机制研究	巨春蓉	广东省自然	2015	10	2015
52	广东省普通高校工程技术研究(开发)中心：中药抗病毒评价及新药研发中心	王新华	广东省教育厅	2015	100	2015
53	尼古丁调节肺动脉平滑肌细胞 Ca2+浓度的作用机制研究	陈豫钦	广州市卫生局医药卫生科技项目	2015	3	2015
54	microRNA19b 对机械牵张引起的小气道上皮细胞凋亡的调控作用	刘晓青	广东省自然科学基金	2015	10	2015
55	中期因子介导机械牵张诱导肺上皮细胞 EMT 的机制研究	黎毅敏	广东省自然科学基金	2015	10	2015
56	重症肺炎诊疗技术的标准化、规范化及推广	黎毅敏	广州市科技计划	2014	50	2015

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序号	项目名称	负责人	项目来源	项目起始年限	资助金额（万元）	下达年度
57	化学物诱导肺癌发生中 circRNA 的功能研究	蒋义国	广州高校“羊城学者”首席科学家科研项目	2016	60	2015
58	循环长链非编码 RNA 在化学物诱导肺癌发生中的作用和标志物意义	蒋义国	广东省自然科学基金重点项目	2015	30	2015

（二）实验室重大科研成果

本年度实验室获得的重大科研成果包括国家科学技术进步奖二等奖、广东省科学技术进步奖二等奖、ISEE 最佳环境流行病学论文奖等三项科技奖项。

1. 慢性阻塞性肺疾病发病与综合防治——国家科学技术进步奖二等奖（冉丕鑫）

慢性阻塞性肺疾病（慢阻肺）是一种严重危害民众身体健康的常见病，从 1965 年至 1998 年间，全美冠心病、中风、其它心脏病和所有其它疾病的患病率分别下降 59%、64%、35%和 7%，而慢阻肺则上升 163%。然而，我国慢阻肺的患病状况不甚清楚，而且缺乏有效的防治措施，使我国的慢阻肺防治水平处于较低水平，造成了较大的经济负担和社会影响。在我国城市人口十大死因中，呼吸疾病（主要是慢阻肺）居第四位，在农村居第三位，全国每年因慢阻肺死亡的人数达 100 万，致残人数 500-1000 万。因此，加强慢阻肺研究以提高其防治水平不仅十分迫切，而且意义重大。本项目历时 16 年，对慢阻肺发病与综合防治等进行了系列研究。

1、首次准确揭示了我国慢阻肺的患病状况和主要发病因素，发现我国 40 岁以上人群慢阻肺患病率为 8.2%，吸烟是我国人群罹患慢阻肺的主要原因，烟草烟雾中主要有害成尼古丁通过致气道上皮细胞转分化和促进气道平滑肌细胞增殖而致气道结构重塑；生物燃料、低体重指数、职业粉尘接触等均是致慢阻肺的重要原因。

2、首次证实生物燃料是慢阻肺发病的重要危险因素，生物燃料不仅增加吸烟致慢阻肺发病的风险，它还能够引起肺内氧化-抗氧化失衡和促进气道上皮细

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胞转分化；首次发现减少生物燃料烟雾暴露可以明显降低慢阻肺患病率。

3、研制出用于评价呼吸中枢驱动及膈肌功能的电极管和老年人股四头肌功能正常值预计公式，发现慢阻肺患者呼吸中枢驱动储备功能下降和外周肌肉功能障碍，其是慢阻肺呼吸衰竭的重要原因之一。

4、发现内皮收缩因子-舒张因子失衡是慢阻肺并发肺动脉高压的重要原因之一；低氧通过低氧诱导因子-1－骨形成蛋白 4－经典瞬时受体电位蛋白通路促进肺血管平滑肌细胞内钙离子浓度增加；首次发现丹参酮ⅡA 对肺动脉高压具有治疗作用。

5、最早在社区采用呼气峰流速仪筛查气流受限人群；制定我国慢阻肺早期筛查问卷和慢阻肺病情初步判别系统；首次构建针对慢阻肺患者、高危人群、普通人群的三级综合防治模式，该防治模式可有效减缓肺功能的年递减率。

6、首次发现羧甲司坦能有效预防慢阻肺急性发作；小剂量茶碱和呼吸道细菌提取物均能减少慢阻肺患者急性加重次数；证实吸入噻托溴铵、沙美特罗/氟替卡松、布地奈德/福莫特罗能持续改善慢阻肺患者的肺功能和生活质量，减少症状；罗氟司特能够改善重度及极重度慢阻肺患者的肺功能。

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国家科学技术奖励工作办公室公告第79号

2015年度国家科学技术奖初评工作已经结束。根据《国家科学技术奖励条例实施细则》的规定，现将初评通过的46项国家自然科学奖项目、50项国家技术发明奖通用项目和141项国家科学技术进步奖通用项目（含3个创新团队）在科技部网站（http://www.most.gov.cn）和奖励办网站（http://www.nosta.gov.cn）公布。初评通过的17项国家技术发明奖专用项目和45项国家科学技术进步奖专用项目在委托管理单位、推荐单位及项目完成单位等进行内部公布。

自公布之日起30日内，任何单位或者个人对公布项目和项目主要完成人、主要完成单位持有异议的，应当以书面方式向我办提出，并提供必要的证明材料。为便于核实查证，确保客观公正处理异议，提出异议的单位或者个人应当表明真实身份，并提供有效联系电话和地址。以单位名义提出异议的，须在书面异议材料上加盖本单位公章；个人提出异议的，须签署真实姓名。超出期限的异议不予受理。

特此公告。

联系方式：国家科学技术奖励工作办公室政策研究处（督查处），北京市西城区三里河路54号，邮政编码100045。

附件：

3、2015年度国家科学技术进步奖初评通过通用项目（含创新团队）

序号	评审组	项目名称	主要完成人	主要完成单位	推荐单位	初评建议等级
1	作物遗传育种与园艺组	CIMMYT小麦引进、研究与创新利用	何中虎，夏先春，陈新民，雷振生，吴振录，庄巧生，于亚雄，魏汉民，杨文雄，李梅芳	中国农业科学院作物科学研究所，四川省农业科学院作物研究所，新疆农业科学院核技术生物技术研究所，云南省农业科学院粮食作物研究所，宁夏农林科学院，甘肃省农业科学院小麦研究所，湖北省农业科学院粮食作物研究所	北京市	二等奖
91	内科二组	慢性乙型肝炎诊疗体系的创新及关键技术推广应用	侯金林，王福生，戴立忠，孙剑，廖家杰，鲁凤民，王战会，陈香梅，孙嘉全，汪艳	南方医科大学，中国人民解放军第三〇二医院，湖南圣湘生物科技有限公司，天下仁心有限公司，北京大学，正大天晴药业集团股份有限公司	中华医学会	二等奖
92	内科二组	我国艾滋病流行新形势下的综合防控策略及应用研究	尚红，吴昊，徐俊驰，汪宁，陈[illegible]，刘[illegible]，王[illegible]，[illegible]	中国医科大学附属第一医院，首都医科大学附属北京佑安医院，清华大学，中国疾病预防控制中心性病艾滋病预防控制中心，云南省疾病预防控制中心，河南省疾病预防控制中心，中国医学科学院基础医学研究所	辽宁省	二等奖
93	内科二组	慢性阻塞性肺疾病发病与防治	冉丕鑫，周玉民，王健，钟南山，郑劲平，陈荣昌，罗远明，卢文菊，唐健，吕春雷	广州医科大学附属第一医院，中国医科大学附属第一医院	广东省	二等奖
94	内科二组	鼻咽癌诊疗关键策略研究与应用	马骏，赵充，李海清，张力，卢泰祥，李宇红，谢方云，胡伟汉，刘孟忠，孙颖	中山大学肿瘤防治中心（中山大学附属肿瘤医院、中山大学肿瘤研究所）	中华医学会	二等奖

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2. 呼吸肌功能检测与应用项目—广东省科学技术进步奖二等奖 罗远明（已通过学科评审）

这一成果获得了五项发明专利授权（包括一项国际发明专利）及六项实用新型专利授权。研发出具有自主知识产权的检测呼吸肌功能与呼吸中枢驱动等一系列产品，包括多导食道电极导管、呼吸信号检测管、多功能呼吸信号检测管，特别是创新地研发出了可用于检测危重病人呼吸肌功能的多功能呼吸信号检测管，这一导管既可代替传统的胃管，又可检测膈肌肌电、呼吸压力及呼吸中枢驱动。通过采用上述呼吸信号检测导管，并引入小波分析法、滤波、均方根等方法提取

纯膈肌肌电信号，研发出呼吸肌功能及呼吸中枢驱动检测系统。这一系统在国际上首次实现了呼吸肌功能及呼吸中枢驱动的自动分析，并可作为常规睡眠多导图检测诊断睡眠呼吸疾病。

通过采用具有自主知识产权的产品及技术开展基础与应用研究，发现呼吸中枢驱动与呼吸困难相关，在国际上首次提出呼吸中枢驱动有效性这一概念，并提出 COPD 患者的运动受限与呼吸中枢驱动有效性下降有关这一新的学术观点。发现单纯 COPD 患者睡眠相关的低通气和呼吸衰竭主要是由于呼吸中枢驱动下降，而不是传统观点所认为的上气道阻力增高。 这些重要新发现对合理管理 COPD 患者有重大价值。发现阻塞性睡眠呼吸暂停事件发生与呼吸中枢驱动不稳定有关，无论是持续恒定正压还是呼气压力释放治疗模式都具有稳定呼吸中枢驱动的作用。微觉醒是阻塞性睡眠呼吸暂停发生发展的重要因素，我们在国际上首次提出与传统学术观点不同的理论，发现睡眠呼吸暂停相关的微觉醒并不是由于呼吸努力增高所致。这些有关睡眠呼吸暂停的创新观点对进一步探究阻塞性睡眠呼吸暂停的发病机制及寻找新的治疗方法有重要价值。在国际上首次建立了以膈肌肌电鉴别阻塞性与中枢性睡眠呼吸暂停事件的新方法，这一方法已逐渐成为临床上鉴别阻塞性与中枢性睡眠呼吸暂停的“金标准”。

这一成果通过产学研有机结合实现了从基础研究到临床应用的成功转化。成果相关的产品已在国内外得到越来越广泛的应用，并被许多发达国家的著名大学、研究机构及其国家重点实验室采用。英国、德国、澳大利亚、加拿大曾派出学者到课题组学习并引进这一成果的相关技术、方法和产品。国内外学者以我们的技术或产品为研究方法，在著名 SCI 期刊如 Am J Respir Crit Care Med（影响因子 12.9），Thorax（影响因子 8.2）等杂志上发表了大量论著。这一成果在国际学术界引起了广泛关注，课题组成员被国

内外众多大型学术组织如中华医学会呼吸分会、亚太呼吸协会（APSR）、亚洲睡眠学会、欧洲呼吸协会(ERS)和美国胸科协会(ATS)等特邀在相关大型的国内外学术会议上做有关呼吸肌功能的专题学术演讲。在 2013 美国费城举行的美国国际呼吸年会（ATS）上，会议组织为课题负责人特设一个专场（60 分钟）介绍膈肌肌电新进展。由上可见，这一成果达到国际领先水平，大大提高了我国在呼吸领域的国际影响力，并产生了一定的经济效益和重要的社会效益

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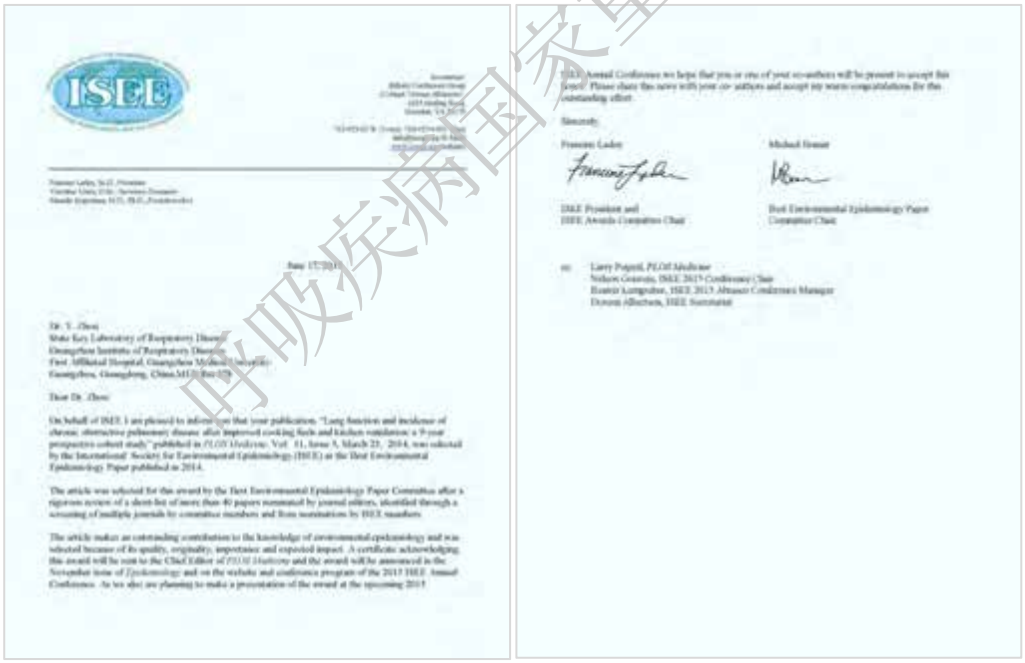
3. “厨房烹饪（生物）燃料和通风状况改善对肺功能 FEV1 和慢阻肺发病率的影响：为期 9 年的前瞻性队列研究”---首次荣获“ISEE 最佳环境流行病学论文奖”

2015 年 6 月 17 日，呼吸疾病国家重点实验室冉丕鑫教授课题组周玉民博士收到国际环境流行病学会(International Society of Environmental Epidemiology, ISEE)主席、ISEE 奖委员会主席 Francine Laden 教授以及 ISEE 委员会主席 Michael Brauer 教授的联名贺信，祝贺其 2014 年度在《PLoS Medicine》杂志发表的题为《厨房烹饪（生物）燃料和通风状况改善对肺功能 FEV1 和慢阻肺发病率的影响：为期 9 年的前瞻性队列研究》（Lung function and incidence of chronic obstructive pulmonary disease after improved cooking fuels and kitchen ventilation: a 9-year prospective cohort study. PLoS Med. 2014; 11(3): e1001621）入选国际环境流行病学会(ISEE) 2014 年度“最佳环境流行病学论文”（每年度仅 1 篇）。此为自 ISEE 最佳环境流行病学论文奖 2008 年设立以来，我国学者首次荣获得该奖项。



国际环境流行病学会（ISEE）为国际环境与健康领域的著名学术团体，学会成员来源于欧洲、美洲、中东及东亚等 60 多个国家和地区，主要致力于健康与环境领域的问题研讨与合作。ISEE 官方刊物为流行病学（Epidemiology）及环境健康展望（Environmental Health Perspectives），影响因子分别高达 5.738 和 7.260，均为公共卫生和环境健康领域顶级杂志。ISEE 最佳环境流行病学论文

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奖则是 ISEE 为鼓励和奖励学者在国际高影响力杂志上发表环境与健康领域原创性、高质量、杰出研究论文而设立的奖项。该奖项经由作者、杂志编辑以及读者推荐报（提）名，经 ISEE 最佳环境流行病学论文奖委员会挑选评审、ISEE 委员会审核通过才能获奖。获奖论文发表杂志（编辑）、论文作者将会收到 ISEE 正式获奖通知及特别的获奖证书，并将受邀参加 ISEE 年会领奖。

生物燃料即常见的柴草、庄稼杆、木炭、干燥的动物大便块等，它是第三世界国家和广大农村地区家庭主要的能源，目前，全世界约有 30 亿人口暴露于生物燃料。冉丕鑫课题组前期首次从现场流行学证实生物燃料烟雾暴露是引起慢性阻塞性肺疾病（简称慢阻肺）的重要原因之一，厨房通风条件差和接触生物燃料烟雾时间长等因素明显增加慢阻肺的患病危险性（Thorax，2007，62：889－897）。在此基础上，该课题组进行了严格的前瞻性大样本人群研究，通过长达 9 年的连续观察，发现使用沼气等清洁燃料和改善厨房通风以减少生物燃料烟雾暴露能够延缓肺功能 FEV1 的下降，减缓 COPD 发病危险。文章于 2014 年 3 月在世界一流综合医学期刊《PLos Medicine》发表，该杂志同期发表编辑部综述文章称“该研究结果显示，以清洁燃料替代生物燃料和改善厨房通风状况，能够减少全球与生物燃料相关的慢阻肺的疾病负担”。同时期出版的世界一流医学杂志《美国医学会会刊》摘要转载了该研究结果（JAMA，2014，311（19）：1958）。这是第一个关于通过减少危险因素暴露而降低慢阻肺发病率的研究报道，为农村推广清洁燃料保护肺功能提供直接证据，对慢阻肺的预防及诊治具有积极的指导意义。

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（三）新获专利

2015 年，实验室新获授权专利共 11 项，其中发明专利 4 项，实用专利 5 项，申请专利 19 项。

授权专利列表

序号	名称	类型（发明专利/实用新型专利/计算机软件著作权）	专利号/申请号	发明人	授权时间
1	一种控制室内环境中的螨的方法	发明专利	ZL201210198068.6	刘志刚	2015-1-14
2	一种免疫印迹检测反应装置	实用新型	ZL201420592921.7	吴善东、沈华浩	2015-2-11
3	一种重组杆状病毒载体及病毒痒颗粒及制备方法和用途	发明专利	ZL201310697541.X	王弋、彭涛、许煜华、马书智、安鸿、尹海滨	2015-3-18
4	一种借助支持向量机建立过敏原家族特征肽的过敏原的预测方法	发明专利	ZL201110302532.7	陶爱林、张利达、邹泽红、黄于艺	2015-3-25
5	一种无创正压通气面罩	实用新型	ZL201320564289.0	郑则广、郑乃乔、何峰、胡俊雄、陈荣昌、钟南山	2015-4-22
6	一种保证压力触发敏感的无创呼吸机通气鼻或面罩	实用新型	ZL201420163634.4	郑则广	2015-5-20
7	一种用于高效构建无抗性标记重组分枝杆菌的抗性表达盒	发明专利	ZL201310386264.0	张天宇，杨峰，邹文英	2015-9-23

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8	穿透型 TALEN 蛋白敲除细胞内源性 CCR5 基因的方法与应用	国家发明专利	ZL201310124191.8	陈小平等	2015-10-28
9	运动小球隔离排气阀	实用新型	ZL2015.2.0410584.X	朱卫华、陈荣昌、戴中华、罗群	2015-11-25
10	一种引流鼻腔分泌物的装置	实用新型	ZL201520100770.3	郑则广	2015-12-2
11	用于抗变异流感病毒的新型环烷胺类化合物	发明专利	CN201310499915.7	胡文辉赵昕曾少高崔巍	2015-11-18

申请专利列表

序号	名称	类型（发明专利/实用新型专利/计算机软件著作权）	专利号/申请号	发明人	申请公布时间
1	一种带数据统计及上传功能的口腔给药装置	实用新型	201520633174.1	周露茜、陈荣昌、崔冬、黎晓莹	2015-11-18
2	一种带数据统计及上传功能的口腔给药装置	发明专利	201510515615.2	周露茜、陈荣昌、崔冬、黎晓莹	2015-11-18
3	构建无选择标记的自主发光脓肿分枝杆菌的方法及建立相应体外高通量筛药模型	发明专利	ZL201510104936.3	张天宇，曹元元，伍甜，谭守勇，谭耀驹，蔡杏珊，刘春平	2015-7-8

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4	脐带间充质干细胞在制备治疗肺间质纤维化的药物制剂中的应用	发明专利	ZL201510091984.3	徐军，刘明，汪劲松，胡祥	2015-6-3
5	间充质干细胞外泌体在制备治疗肺纤维化的药物制剂中的应用	发明专利	ZL201510091820.0	徐军，刘明，汪劲松，胡祥	2015-6-3
6	吲哚[3,2-c]喹啉类化合物或其药学上可接受的盐及其制备方法和应用	发明专利	ZL201310385431.X	朱强，张天宇，刘兰英，鲁明辉，毛婷婷，黄金波	2014-2-5
7	一种新型呼吸道归巢 siRNA 雾化纳米给药系统	发明专利	ZL201110040542.8	徐军、罗永峰、刘文广、翟欣昀、孙鹏、	2011-9-12
8	CCR5 缺失型的造血干细胞及其制备方法与应用	发明专利	ZL201110115680.8	陈小平、姚永超、秦莉、那顺巴雅尔、赵思婷、覃丽梅、何正祥	2011-5-6
9	通过 MAPKAPK2（MK2）基因检测肺癌易感性和判断肺癌预后的试剂盒及其用途	发明专利	ZL201010538875.9	吕嘉春、刘斌	2011-2-6
10	通过 MAP2K4（MKK4）基因检测肺癌易感性的试剂盒及其用途	发明专利	ZL201010538851.3	吕嘉春、刘斌	2011-2-16
11	一种高尔基蛋白 GP73 的夹心 ELISA 定量检测方法及其检测试剂盒	发明专利	ZL200910041621.3	彭涛、古艳丽	2011-3-23
12	联合使用痘病毒载体 HIV 疫苗与腺病毒载体 HIV 疫苗的	发明专利	ZL200910192351.6	陈凌、陈志伟、张林琦、孙彩军	2010-3-17

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	方法及其应用				
13	吡唑并[1,5-a]吡啶类化合物及其应用	发明专利	PCT (CN2015/086852)	陆小云，汤健，丁克，张天宇，涂正超，伍甜，万军庭，曹元元	申请中
14	一种带数据统计及上传功能的噻托溴胺口腔给药装置	实用新型	201520633177.2	周露茜、陈荣昌、崔冬、黎晓莹、梁振宇	申请中
15	一种带数据统计及上传功能的舒利迭口腔给药装置	实用新型	201520633175.6	周露茜、陈荣昌、崔冬、黎晓莹、梁振宇	申请中
16	一种带数据统计及上传功能的都保口腔给药装置	实用新型	201520633173.7	陈荣昌、周露茜、崔冬、黎晓莹、邓葵淼	申请中
17	一种带数据统计及上传功能的硫酸沙丁胺醇口腔给药装置	实用新型	2015063301.8	周露茜、陈荣昌、崔冬、黎晓莹、陈妙	申请中
18	Reactivation of latent virus by STAT3	发明专利	US	周国瑛,Te Du,Bernard Roizman	申请中
19	Suppression of HSV reactivation from latency by Curcurmin	发明专利	US	Te Du, 周国瑛,Bernard Roizman	申请中

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（四）专著

2015 年度，重点实验室 PI 主编或参编出版了五部论著/专著。

序号	论、专著名称	论、专著出版社	出版年份	实验室参编人员	贡献（主编/副主编/参编）
1	《Lung Cancer》	ASVIDE	2015	何建行	主编
2	《肺癌》	中南大学出版社	2015	何建行	主编
3	Allergy Bioinformatics	Springer Netherlands	2015	陶爱林	主编
4	《中医学》（英文版）	科学出版社	2015	王新华	主编
5	军团菌和军团菌病	科学出版社	2015	莫自耀	参编

（五）发表文章

2015 年共发表 SCI 文章 249 篇，其中影响因子大于或等于 20 的有 3 篇，大于或等于 10 的有 23 篇，大于或等于 5 的有 71 篇，大于或等于 3 的有 125 篇，平均影响因子为 4.9797 。

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2015年发表的SCI论文列表

序号	题名	作者	PI通讯作者	期刊名称	出版年	卷期页	影响因子
1	Sputum matrix metalloproteinase-8 and-9 and tissue inhibitor of metalloproteinase-1 in bronchiectasis: Clinical correlates and prognostic implications	Guan, Wei-jie; Gao, Yong-hua; Xu, Gang; Lin, Zhi-ya; Tang, Yan; Gu, Ying-ying; Liu, Gui-hong; Li, Hui-min; Chen, Rong-chang; Zhong, Nan-shan	Chen, RC	RESPIROLOGY	2015	20(7),1073-1081	2.856
2	HLA class I deficiency as an additional cause of bronchiectasis Reply	Guan, Wei-jie; Gao, Yong-hua; Chen, Rong-chang; Zhong, Nan-shan	Guan, W J	RESPIROLOGY	2015	20(7),1145-1146	2.856
3	Will Nonasthmatic Eosinophilic Bronchitis Develop Into Chronic Airway Obstruction? A Prospective, Observational Study	Lai, Kefang; Liu, Baojuan; Xu, Danyuan; Han, Lina; Lin, Ling; Xi, Yin; Wang, Faxia; Chen, Ruchong; Luo, Wei; Chen, Qiaoli; Zhong, Nanshan	Lai, KF	CHEST	2015	148(4),887-894	6.823
4	The Impact of Visceral Pleural Invasion in Node-Negative Non-small Cell Lung Cancer A Systematic Review and Meta-analysis	Jiang, Long; Liang, Wenhua; Shen, Jiantei; Chen, Xiaofang; Shi, Xiaoshun; He, Jiaxi; Yang, Chenglin; He, Jianxing	He, J X	CHEST	2015	148(4),903-911	6.823
5	Identification and Application of Neutralizing Epitopes of Human Adenovirus Type 55 Hexon Protein	Tian, Xingui; Ma, Qiang; Jiang, Zaixue; Huang, Junfeng; Liu, Qian; Lu, Xiaomei; Luo, Qingming; Zhou, Rong	Luo, Q M	Viruses-Basel	2015	7(10),5632-5642	3.437
6	Spirometric Reference Values for Healthy Han Children Aged 5-15 Years in Guangzhou, Southern China	Jiang, Mei; Gao, Yi; Zhong, Nan-Shan; Chen, Wei-Qing; Guan, Wei-Jie; Zheng, Jin-Ping	Zheng, JP	PEDIATRIC PULMONOLOGY	2015	50(10),1009-1016	2.664
7	Post-transcriptional regulation tends to attenuate the mRNA noise and to increase the mRNA gain	Shi, Changhong; Wang, Shuqiang; Zhou, Tianshou; Jiang, Yiguo	Shi, C H	PHYSICAL BIOLOGY	2015	12(5)	2.399
8	2,4-Diarylamino-pyrimidines as kinase inhibitors co-targeting IGF1R and EGFR(L858R/T790M)	Chan, Shingpan; Han, Kun; Qu, Rong; Tong, Linjiang; Li, Yingjun; Zhang, Zhang; Cheng, Huimin; Lu, Xiaoyun; Patterson, Adam; Smaill, Jeff; Ren, Xiaomei; Ding, Jian; Xie, Hua; Ding, Ke	Xie, H	BIOORGANIC & MEDICINAL CHEMISTRY	2015	25(19),4277-4281	2.303

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9	Molecular cloning and characterization of gloverin from the diamondback moth, Plutella xylostella L. and its interaction with bacterial membrane	Xu, X. X.; Jin, F. L.; Wang, Y. S.; Freed, Shoaib; Hu, Q. B.; Ren, S. X.	Jin, F L	WORLD JOURNAL OF MICROBIOLOGY & BIOTECHNOLOGY	2015	31(10),1529-1541	1.655
10	New Epidemiological and Clinical Signatures of 18 Pathogens from Respiratory Tract Infections Based on a 5-Year Study	Liao, Xiaohong; Hu, Zhengbo; Liu, Wenkuan; Lu, Yan; Chen, Dehui; Chen, Meixin; Qiu, Shuyan; Zeng, Zhiqi; Tian, Xingui; Cui, Hong; Zhou, Rong	Zhou, R	PLoS One	2015	10(9)	3.535
11	Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis	Zheng, Xue-yan; Ding, Hong; Jiang, Li-na; Chen, Shao-wei; Zheng, Jin-ping; Qiu, Min; Zhou, Ying-xue; Chen, Qing; Guan, Wei-jie	Chen, Q	PLoS One	2015	10(9)	3.535
12	Impacts of Co-Existing Chronic Rhinosinusitis on Disease Severity and Risks of Exacerbations in Chinese Adults with Bronchiectasis	Guan, Wei-jie; Gao, Yong-hua; Li, Hui-min; Yuan, Jing-jing; Chen, Rong-chang; Zhong, Nan-shan	Chen, RC	PLoS One	2015	10(9)	3.535
13	The Functional Copy Number Variation-67048 in WWOX Contributes to Increased Risk of COPD in Southern and Eastern Chinese	Yang, Lei; Qiu, Fuman; Fang, Wenxiang; Zhang, Lisha; Xie, Chenli; Lu, Xiaoxiao; Huang, Dongsheng; Guo, Yuan; Pan, Mingan; Zhang, Haibo; Zhou, Yifeng; Lu, Jiachun	Lu, JC	COPD-Journal of Chronic Obstructive Pulmonary Disease	2015	12(5),494-501	2.494
14	LincRNA-uc002yug.2 involves in alternative splicing of RUNX1 and serves as a predictor for esophageal cancer and prognosis	Wu, H.; Zheng, J.; Deng, J.; Zhang, L.; Li, N.; Li, W.; Li, F.; Lu, J.; Zhou, Y.	Zhou, Y	ONCOGENE	2015	34(36),4723-4734	7.401
15	CXC195 Induce Apoptosis and Endoplasmic	Zhang, Jiexia; Liang, Ying; Lin, Yongbin; Liu, Yuanbin; Yin,	--		2015	10(9),S7	4.932

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	Reticulum Stress in Human Non-Small Cell Lung Cancer Cells via IRE1 alpha-Dependent Pathway	Weiqiang; You, You				77-S778	
16	Vitamin D level and the correlation with IgE in children with allergic respiratory diseases in Guangzhou China	Huang, H.; Chen, Y.; Zheng, P.; Wei, N.; Luo, W.; Sun, B.	--	ALLERGY	2015	70,303-303	5.746
17	Survey of cognitive situation in parents' knowledge of allergic disease	Jiaying, L.; Baoqing, S.	--	ALLERGY	2015	70,427-428	5.746
18	The relationship between environment and the prevalence of allergy rhinitis and asthma in pre-school children in Guangzhou city	Jiaying, L.; Huimin, H.; Manning, Z.; Nili, W.; Baoqing, S.	--	ALLERGY	2015	70,541-541	5.746
19	Modified IDSA/ATS Minor Criteria for Severe Community-Acquired Pneumonia Best Predicted Mortality	Li, Hai-yan; Guo, Qi; Song, Wei-dong; Zhou, Yi-ping; Li, Ming; Chen, Xiao-ke; Liu, Hui; Peng, Hong-lin; Yu, Hai-qiong; Chen, Xia; Liu, Nian; Lu, Zhong-dong; Liang, Li-hua; Zhao, Qing-zhou; Jiang, Mei	Guo, Q	MEDICINE	2015	94(36)	3.195
20	Mortality among severe community-acquired pneumonia patients depends on combinations of 2007 IDSA/ATS minor criteria	Li, Hai-yan; Guo, Qi; Song, Wei-dong; Zhou, Yi-ping; Li, Ming; Chen, Xiao-ke; Liu, Hui; Peng, Hong-lin; Yu, Hai-qiong; Chen, Xia; Liu, Nian; Lu, Zhong-dong; Liang, Li-hua; Zhao, Qing-zhou; Jiang, Mei	Guo, Q	INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES	2015	38,141-145	2.435
21	Role of folP1 and folP2 Genes in the Action of Sulfamethoxazole and Trimethoprim Against Mycobacteria	Liu, Tianzhou; Wang, Bangxing; Guo, Jintao; Zhou, Yang; Julius, Mugweru; Njire, Moses; Cao, Yuanyuan; Wu, Tian; Liu, Zhiyong; Wang, Changwei; Xu, Yong; Zhang, Tianyu	Zhang, TY	JOURNAL OF MICROBIOLOGY AND BIOTECHNOLOGY	2015	25(9),1559-1567	1.705
22	Correlation between epidermal growth factor receptor	He, Qihua; Zhang, Mingzhe; Zhang, Jianrong; Chen, Ying; He,	Liang, W H	Journal of	2015	7(9),158	#N/A

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	mutations and nuclear expression of female hormone receptors in non-small cell lung cancer: a meta-analysis	Jiaxi; Shen, Jianfei; Liu, Yang; Zhong, Shengyi; Jiang, Long; Yang, Chenglin; Zeng, Yuan; Guo, Minzhang; Chen, Xuewei; He, Jianxing; Liang, Wenhua		Thoracic Disease		8-1594	
23	CUR-65 Score for Community-Acquired Pneumonia Predicted Mortality Better Than CURB-65 Score in Low-Mortality Rate Settings	Li, Hai-yan; Guo, Qi; Song, Wei-dong; Zhou, Yi-ping; Li, Ming; Chen, Xiao-ke; Liu, Hui; Peng, Hong-lin; Yu, Hai-qiong; Chen, Xia; Liu, Nian; Lu, Zhong-dong; Liang, Li-hua; Zhao, Qing-zhou; Jiang, Mei	Guo, Q	AMERICAN JOURNAL OF THE MEDICAL SCIENCES	2015	350(3),186-190	1.418
24	Prevention and management of lung cancer in China	Hong, Qun-Ying; Wu, Guo-Ming; Qian, Gui-Sheng; Hu, Cheng-Ping; Zhou, Jian-Ying; Chen, Liang-An; Li, Wei-Min; Li, Shi-Yue; Wang, Kai; Wang, Qi; Zhang, Xiao-Ju; Li, Jing; Gong, Xin; Bai, Chun-Xue	Bai, C X	CANCER	2015	121,3080-3088	5.434
25	Role of a serum-based biomarker panel in the early diagnosis of lung cancer for a cohort of high-risk patients	Yang, Da-Wei; Zhang, Yong; Hong, Qun-Ying; Hu, Jie; Li, Chun; Pan, Bai-Shen; Wang, Qun; Ding, Fei-Hong; Ou, Jia-Xian; Liu, Fang-Lei; Zhang, Dan; Zhou, Jie-Bai; Song, Yuan-Lin; Bai, Chun-Xue	Bai, C X	CANCER	2015	121,3113-3121	5.434
26	Chinese consensus on early diagnosis of primary lung cancer (2014 version)	Hu, Jie; Qian, Gui-Sheng; Bai, Chun-Xue	Bai, C X	CANCER	2015	121,3157-3164	5.434
27	Quality Assessment of Clinical Practice Guidelines for Respiratory Diseases in China A Systematic Appraisal	Jiang, Mei; Liao, Li-yue; Liu, Xiao-qing; He, Wei-qun; Guan, Wei-jie; Chen, Hao; Li, Yi-min	Li, YM	CHEST	2015	148(3),759-766	6.823
28	NAADP Mediates Calcium Ion Concentration via Two Pore Channels in Pulmonary Artery Smooth Muscle Cells	Jiang, Y. L.; Zhou, Y. M.; Pan, D.; Peng, G. Y.; Liu, L.; Hu, R. C.; Ran, P. X.; Dai, A. G.	--	JOURNAL OF THE AMERICAN GERIATRICS SOCIETY	2015	63,S400-S400	4.867
29	Ceftaroline fosamil for community-acquired	Zhong, Nan Shan; Sun, Tieying; Wilson, David; Melnick, David	Zhong, NS	LANCET	2015	15(9),99	19.29

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	pneumonia Reply			INFECTIOUS DISEASES		9-1000	7
30	Chronic Hypoxia Increases Intracellular Ca2+ Concentration via Enhanced Ca2+ Entry Through Receptor-Operated Ca2+ Channels in Pulmonary Venous Smooth Muscle Cells	Peng, Gongyong; Li, Shaoxing; Hong, Wei; Hu, Jinxing; Jiang, Yongliang; Hu, Guoping; Zou, Yimin; Zhou, Yumin; Xu, Juan; Ran, Pixin	Ran, PX	CIRCULATION JOURNAL	2015	79(9),2058-U232	3.374
31	Drug exposure in a metastatic human lung adenocarcinoma cell line gives rise to cells with differing adhesion, proliferation, and gene expression: Implications for cancer chemotherapy	Li, Huiling; He, Jianxing; Zhong, Nanshan; Hoffman, Robert M.	Zhong, NS	Molecular Medicine Reports	2015	12(3),3236-3242	1.617
32	Hybrid pyrimidine alkynyls inhibit the clinically resistance related Bcr-Abl(T315I) mutant	Lu, Xiaoyun; Zhang, Zhang; Ren, Xiaomei; Pan, Xiaofeng; Wang, Deping; Zhuang, Xiaoxi; Luo, Jingfeng; Yu, Rongmin; Ding, Ke	Ding, Ke	Bioorganic & Medicinal Chemistry Letters	2015	25(17),3458-3463	2.303
33	A Multicenter Retrospective Review of Prone Position Ventilation (PPV) in Treatment of Severe Human H7N9 Avian Flu	Xu, Yuanda; Deng, Xilong; Han, Yun; Zhou, Lixin; He, Weiqun; Chen, Sibei; Nong, Lingbo; Huang, Huang; Zhang, Yan; Yu, Tieou; Li, Yimin; Liu, Xiaoqing	Li, YM	PLoS One	2015	10(8)	3.535
34	Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus	Corti, Davide; Zhao, Jincun; Pedotti, Mattia; Simonelli, Luca; Agnihothram, Sudhakar; Fett, Craig; Fernandez-Rodriguez, Blanca; Foglierini, Mathilde; Agatic, Gloria; Vanzetta, Fabrizia; Gopal, Robin; Langrish, Christopher J.; Barrettg, Nicholas A.; Sallusto, Federica; Baric, Ralph S.;etc	Lanzavecchia, A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	2015	112(33),10473-10478	10.285

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35	Evaluation of spiropiperidine hydantoins as a novel class of antimalarial agents	Meyers, Marvin J.; Anderson, Elizabeth J.; McNitt, Sarah A.; Krenning, Thomas M.; Singh, Megh; Xu, Jing; Zeng, Wentian; Qin, Limei; Xu, Wanwan; Zhao, Siting; Qin, Li; Eickhoff, Christopher S.; Oliva, Jonathan; Campbell, Mary A.; Arnett, Stacy D.;etc	Meyers, M J	BIOORGANIC & MEDICINAL CHEMISTRY	2015	23(16),5144-5150	2.869
36	Synthesis and biological evaluation of 3,5-disubstituted-4-alkynylisoxozales as a novel class of HSP90 inhibitors	Sun, Jian; Lin, Cai; Qin, Xiaochu; Dong, Xiaoping; Tu, Zhengchao; Tang, Fei; Chen, Chaonan; Zhang, Jiancun	Chen, C N	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS	2015	25(16),3129-3134	2.303
37	Organocatalytic Enantioselective Michael Reaction of Malononitrile with beta,beta-Disubstituted Nitroalkenes	Chen, Shengwei; Lou, Qinxin; Ding, Yuyang; Zhang, Shasha; Hu, Wenhui; Zhao, Junling	Hu, WH	ADVANCED SYNTHESIS & CATALYSIS	2015	357(11),2437-2441	5.852
38	Inflammatory Responses, Spirometry, and Quality of Life in Subjects With Bronchiectasis Exacerbations	Guan, Wei-jie; Gao, Yong-hua; Xu, Gang; Lin, Zhi-ya; Tang, Yan; Li, Hui-min; Lin, Zhi-min; Jiang, Mei; Zheng, Jin-ping; Chen, Rong-chang; Zhong, Nan-shan	Guan, W J	Respiratory Care	2015	60(8),1180-1189	2.057
39	Prevalence of 7 virulence genes of Legionella strains isolated from environmental water sources of public facilities and sequence types diversity of L. pneumopila strains in Macau	Xiong, Lina; Zhao, Hongbo; Mo, Ziyao; Shi, Lei	Mo, Z Y	BioScience Trends	2015	9(4),214-220	1.460
40	Sleep apnoea: a major and under-recognised public health concern	McNicholas, Walter T.; Luo, Yuanming; Zhong, Nanshan	McNicholas, W T	Journal of Thoracic Disease	2015	7(8),1269-1272	#N/A
41	Functional residual capacity in beagle dogs with and without acute respiratory distress syndrome	Liu, Qi; Gao, Yong-Hua; Hua, Dong-Ming; Li, Wen; Cheng, Zhe; Zheng, Hui; Chen, Rong-Chang	Chen, R C	Journal of Thoracic Disease	2015	7(8),1459-1466	#N/A

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42	Refractory Hyperlactatemia with Organ Insufficiency in Lipid Storage Myopathy	Xu, Yuanda; Zhou, Li; Liang, Weibo; He, Weiqun; Liu, Xiaoqing; Liang, Xiuling; Zhong, Nanshan; Li, Yimin	Li, YM	Archives of Iranian Medicine	2015	18(8),545-548	1.105
43	Genetically induced moderate inhibition of 20S proteasomes in cardiomyocytes facilitates heart failure in mice during systolic overload	Ranek, Mark J.; Zheng, Hanqiao; Huang, Wei; Kumarapeli, Asangi R.; Li, Jie; Liu, Jinbao; Wang, Xuejun	Wang, X J	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	2015	85,273-281	4.843
44	Mechanical Stress and the Induction of Lung Fibrosis via the Midkine Signaling Pathway	Zhang, Rang; Pan, Ying; Fanelli, Vito; Wu, Sulong; Luo, Alice Aili; Islam, Diana; Han, Bing; Mao, Pu; Ghazarian, Mirna; Zeng, Wenmei; Spieth, Peter M.; Wang, Dingyan; Khang, Julie; Mo, Hongyin; Liu, Xiaoqing;etc	Li, Y M	AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE	2015	192(3),315-323	11.946
45	tert-Butylhydroquinone mobilizes intracellular-bound zinc to stabilize Nrf2 through inhibiting phosphatase activity	Chen, Yunfang; Wang, Sheng; Fu, Xin; Zhou, Wenqu; Hong, Wei; Zou, Dongting; Li, Xichong; Liu, Jinbao; Ran, Pixin; Li, Bing	Li, B	AMERICAN JOURNAL OF PHYSIOLOGY-CELL PHYSIOLOGY	2015	309(3), C148-C158	3.502
46	Expression, purification and identification of Pla a1 in a codon-optimized Platanus pollen allergen	Liu, Yun; Sun, Xiuzhen; Wang, Guizuo; Tao, Ailin; Wu, Yuanyuan; Li, Manxiang; Shi, Hongyang; Xie, Mei	Sun, X Z	Molecular Medicine	2015	12(2),2197-2202	1.617

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				Reports			
47	Food allergy and related risk factors in 2540 preschool children: an epidemiological survey in Guangdong Province, southern China	Zeng, Guang-Qiao; Luo, Jia-Ying; Huang, Hui-Min; Zheng, Pei-Yan; Luo, Wen-Ting; Wei, Ni-Li; Sun, Bao-Qing	Sun, BQ	World Journal of Pediatrics	2015	11(3),219-225	1.213
48	Palladium-catalyzed intermolecular C-H amidation of indoles with sulfonyl azides	Hu, Ziwei; Luo, Shuang; Zhu, Qiang	Luo, S	Science China-Chemistry	2015	58(8),1349-1353	1.652
49	The Sleep Apnea cardioVascular Endpoints (SAVE) Trial: Rationale, Ethics, Design, and Progress	Antic, Nick A.; Heeley, Emma; Anderson, Craig S.; Luo, Yuanming; Wang, Jiguang; Neal, Bruce; Grunstein, Ron; Barbe, Ferran; Lorenzi-Filho, Geraldo; Huang, Shaoguang; Redline, Susan; Zhong, Nanshan; McEvoy, R. Doug	Antic, N A	SLEEP	2015	38(8),1247-1257	5.532
50	Duplicated copy of CHRNA7 increases risk and worsens prognosis of COPD and lung cancer	Yang, Lei; Lu, Xiaoxiao; Qiu, Fuman; Fang, Wenxiang; Zhang, Lisha; Huang, Dongsheng; Xie, Chenli; Zhong, Nanshan; Ran, Pixin; Zhou, Yifeng; Lu, Jiachun	Lu, JC	EUROPEAN JOURNAL OF HUMAN GENETICS	2015	23(8),1019-1024	4.037
51	Cell death-inducing DFFA-like effector B contributes to assembly of hepatitis C virus (HCV) particles and interacts with HCV NS5A	Cai, H.; Yao, W.; Li, L.; Li, X.; Hu, L.; Peng, T.	Yao, W	JOURNAL OF CLINICAL VIROLOGY	2015	69,228-229	2.882
52	Endoplasmic reticulum stress links hepatitis C virus RNA replication to wild-type PGC-1 alpha/liver-specific PGC-1 alpha upregulation	Yao, W.; Cai, H.; Li, X.; Li, T.; Hu, L.; Peng, T.	Yao, W	JOURNAL OF CLINICAL VIROLOGY	2015	69,228-228	2.882
53	A functional genetic variant in fragile-site gene FATS modulates the risk of breast cancer in triparous women	Song, Fangfang; Zhang, Jun; Qiu, Li; Zhao, Yawen; Xing, Pan; Lu, Jiachun; Chen, Kexin; Li, Zheng	Lu, JC	BMC CANCER	2015	15	3.642
54	Human Infection with a Novel Avian Influenza	Yang, Zi-Feng; Mok, Chris K. P.; Peiris, Joseph S. M.; Zhong,	Yang, ZF	NEW	2015	373(5),4	56.17

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	A(H5N6) Virus	Nan-Shan		ENGLAND JOURNAL OF MEDICINE		87-489	0
55	The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies	Gao, Yong-hua; Zhao, Hua-si; Zhang, Fu-rui; Gao, Yang; Shen, Pamela; Chen, Rong-chang; Zhang, Guo-jun	Chen, RC.	PLoS One	2015	10(7)	3.535
56	The Pneumonia Severity Index as a Predictor of In-Hospital Mortality in Acute Exacerbation of Chronic Obstructive Pulmonary Disease	Hu, Guoping; Zhou, Yumin; Wu, Yankui; Yu, Yan; Liang, Weiqiang; Ran, Pixin	Ran, PX	PLoS One	2015	10(7)	3.535
57	C-Aryl glucoside SGLT2 inhibitors containing a biphenyl motif as potential anti-diabetic agents	Ding, Yuyang; Mao, Liufeng; Xu, Dengfeng; Xie, Hui; Yang, Ling; Xu, Hongjiang; Geng, Wenjun; Gao, Yong; Xia, Chunguang; Zhang, Xiquan; Meng, Qingyi; Wu, Donghai; Zhao, Junling; Hu, Wenhui	Zhao, J L	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS	2015	25(14),2744-2748	2.303
58	Polymorphism in mature microRNA-608 sequence is associated with an increased risk of nasopharyngeal carcinoma	Qiu, Fuman; Yang, Lei; Zhang, Lisha; Yang, Xiaorong; Yang, Rongrong; Fang, Wenxiang; Wu, Di; Chen, Jiansong; Xie, Chenli; Huang, Dongsheng; Zhou, Yifeng; Lu, Jiachun	Lu, JC	GENE	2015	565(2),180-186	2.258
59	Mechanistic studies of a novel C-S lyase in ergothioneine biosynthesis: the involvement of a sulfenic acid intermediate	Song, Heng; Hu, Wen; Naowarojna, Nathchar; Her, Ampon Sae; Wang, Shu; Desai, Rushil; Qin, Li; Chen, Xiaoping; Liu, Pinghua	Liu, P H	Scientific Reports	2015	5	5.525
60	Organocatalytic Enantioselective Aza-Michael Reaction of Benzotriazole to ,-Disubstituted Nitroalkenes	Chen, Sheng-Wei; Zhang, Gui-Cheng; Lou, Qin-Xin; Cui, Wei; Zhang, Sha-Sha; Hu, Wen-Hui; Zhao, Jun-Ling	Hu, WH	ChemCatChem	2015	7(13),1935-1938	5.107
61	Effects of the fusion design and immunization route on the immunogenicity of Ag85A-Mtb32 in adenoviral vectored tuberculosis vaccine	Zhang, Yiling; Feng, Liqiang; Li, Liang; Wang, Dimin; Li, Chufang; Sun, Caijun; Li, Pingchao; Zheng, Xuehua; Liu, Yichu; Yang, Wei; Niu, Xuefeng; Zhong, Nanshan; Chen, Ling	Feng, L Q	Human Vaccines & Immunotherapeutics	2015	11(7),1803-1813	2.295

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62	BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non-Small-Cell Lung Cancer	Zhou, Caicun; Wu, Yi-Long; Chen, Gongyan; Liu, Xiaoqing; Zhu, Yunzhong; Lu, Shun; Feng, Jifeng; He, Jianxing; Han, Baohui; Wang, Jie; Jiang, Guoliang; Hu, Chunhong; Zhang, Hao; Cheng, Gang; Song, Xiangqun;etc	Zhou, C C	JOURNAL OF CLINICAL ONCOLOGY	2015	33(19),2197-U108	18.021
63	The role of SOX-2 on the survival of patients with non-small cell lung cancer	Shao, Wenlong; Chen, Hanzhang; He, Jianxing	He, J X	Journal of Thoracic Disease	2015	7(7),1113-1118	#N/A
64	A modified nebulization modality versus classical ultrasonic nebulization and oxygen-driven nebulization in facilitating airway clearance in patients with acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial	Luo, Qiaoling; Zheng, Zeguang; Cen, Huihong; Jiang, Mei; Chen, Qin	Zheng, ZG	Journal of Thoracic Disease	2015	7(7),1130-1141	#N/A
65	Tumor suppressor miR-145 reverses drug resistance by directly targeting DNA damage-related gene RAD18 in colorectal cancer	Liu, Rui-Lei; Dong, Ye; Deng, Yan-Zhen; Wang, Wen-Jun; Li, Wei-Dong	Li, W D	TUMOR BIOLOGY	2015	36(7),5011-5019	2.904
66	Hypoxia inducible factor-1-dependent up-regulation of BMP4 mediates hypoxia-induced increase of TRPC expression in PASMCs	Wang, Jian; Fu, Xin; Yang, Kai; Jiang, Qian; Chen, Yuqin; Jia, Jing; Duan, Xin; Wang, Elizabeth W.; He, Jianxing; Ran, Pixin; Zhong, Nanshan; Semenza, Gregg L.; Lu, Wenju	Wang, J	CARDIOVASCULAR RESEARCH	2015	107(1),108-118	5.815
67	Design, Synthesis, and Biological Evaluation of Pyrazolo[1,5-a]pyridine-3-carboxamides as Novel Antitubercular Agents	Tang, Jian; Wang, Bangxing; Wu, Tian; Wan, Junting; Tu, Zhengchao; Njire, Moses; Wan, Baojie; Franzblauc, Scott G.; Zhang, Tianyu; Lu, Xiaoyun; Ding, Ke	Zhang, TY	ACS Medicinal Chemistry Letters	2015	6(7),814-818	3.294
68	Aetiology of bronchiectasis in Guangzhou, southern China	Guan, Wei-jie; Gao, Yong-hua; Xu, Gang; Lin, Zhi-ya; Tang, Yan; Li, Hui-min; Lin, Zhi-min; Zheng, Jin-ping; Chen,	Chen, RC	RESPIROLOGY	2015	20(5),739-748	2.856

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		Rong-chang; Zhong, Nan-shan					
69	Exon sequencing identifies a novel CHRNA3-CHRNA5-CHRNB4 variant that increases the risk for chronic obstructive pulmonary disease	Zhao, Zhuxiang; Peng, Fang; Zhou, Yumin; Hu, Guoping; He, Hua; He, Fang; Zou, Weifeng; Zhao, Ziwen; Li, Bing; Ran, Pixin	Ran, PX	RESPIROLOGY	2015	20(5),790-798	2.856
70	1-Benzyl-4-phenyl-1H-1,2,3-triazoles improve the transcriptional functions of estrogen-related receptor gamma and promote the browning of white adipose	Xu, Shilin; Mao, Liufeng; Ding, Ping; Zhuang, Xiaoxi; Zhou, Yang; Yu, Lei; Liu, Yingxue; Nie, Tao; Xu, Tingting; Xu, Yong; Liu, Jinsong; Smaill, Jeff; Ren, Xiaomei; Wu, Donghai; Ding, Ke	Ren, X M	BIOORGANIC & MEDICINAL CHEMISTRY	2015	23(13),3751-3760	2.869
71	Quantitative assessment of single-cell whole genome amplification methods for detecting copy number variation using hippocampal neurons	Ning, Luwen; Li, Zhoufang; Wang, Guan; Hu, Wen; Hou, Qingming; Tong, Yin; Zhang, Meng; Chen, Yao; Qin, Li; Chen, Xiaoping; Man, Heng-Ye; Liu, Pinghua; He, Jiankui	Man, H Y	Scientific Reports	2015	5	5.525
72	Utility of contrast-enhanced ultrasound with SonoVue in biopsy of small subpleural nodules	Wang, Jinlin; Zhou, Dazhi; Xie, Xiaohong; Shen, Panxiao; Zeng, Yunxiang	Man, H Y	Scientific Reports	2015	8(9),15991-15998	1.150
73	Leydig cell tumor with lung metastasis diagnosed by lung biopsy	Lai, Ning; Zeng, Xin; Li, Meichan; Shu, Jiaze	Lai, N	International Journal of Clinical and Experimental Pathology	2015	8(10),12972-12976	1.673
74	Adjuvant Chemotherapy for the Completely Resected Stage IB Nonsmall Cell Lung Cancer	He, Jiaxi; Shen, Jianfei; Yang, Chenglin; Jiang, Long; Liang, Wenhua; Shi, Xiaoshun; Xu, Xin; He, Jianxing	Xu, X	MEDICINE	2015	94(22)	3.195
75	Functional role and mechanism of lncRNA LOC728228 in malignant 16HBE cells transformed by anti-benzopyrene-trans-7,8-dihydrodiol-9,10-epoxide	Hu, Gongcheng; Yang, Ti; Zheng, Jingli; Dai, Jiabing; Nan, Aruo; Lai, Yandong; Zhang, Yajie; Yang, Chengfeng; Jiang, Yiguo	Jiang, Y G	MOLECULAR CARCINOGENESIS	2015	54,E192-E204	3.941
76	Noggin inhibits hypoxia-induced proliferation by targeting store-operated calcium entry and transient	Yang, Kai; Lu, Wenju; Jia, Jing; Zhang, Jie; Zhao, Mingming; Wang, Sabrina; Jiang, Haiyang; Xu, Lei; Wang, Jian	Wang, J	AMERICAN JOURNAL	2015	308(11),C869-C	3.502

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	receptor potential cation channels			OF PHYSIOLOGY-CELL PHYSIOLOGY		878	
77	Efficacy and safety of fluticasone furoate/vilanterol (50/25 mcg; 100/25 mcg; 200/25 mcg) in Asian patients with chronic obstructive pulmonary disease: a randomized placebo-controlled trial	Zheng, Jinping; de Guia, Teresita; Wang-Jairaj, Jie; Lands, Amy H. New; Wang, Changzheng; Crim, Courtney; Zhong, Nanshan	Zhong, NS	CURRENT MEDICAL RESEARCH AND OPINION	2015	31(6),1191-1200	2.386
78	The Role of Viral Infection in Pulmonary Exacerbations of Bronchiectasis in Adults A Prospective Study	Gao, Yong-hua; Guan, Wei-jie; Xu, Gang; Lin, Zhi-ya; Tang, Yan; Lin, Zhi-min; Gao, Yang; Li, Hui-min; Zhong, Nan-shan; Zhang, Guo-jun; Chen, Rong-chang	Chen, RC	CHEST	2015	147(6),1635-1643	6.823
79	Cigarette smoking impairs the response of EGFR-TKIs therapy in lung adenocarcinoma patients by promoting EGFR signaling and epithelial-mesenchymal transition	Liu, Ming; Zhou, Chenzhi; Zheng, Jian	Zheng, J	American Journal of Translational Research	2015	7(10),2026-2035	3.500
80	Acoustic Analysis of Snoring in the Diagnosis of Obstructive Sleep Apnea Syndrome: A Call for More Rigorous Studies	Jin, Hui; Lee, Li-Ang; Song, Lijuan; Li, Yanmei; Peng, Jianxin; Zhong, Nanshan; Li, Hsueh-Yu; Zhang, Xiaowen	Zhang, X W	Journal of Clinical Sleep Medicine	2015	11(7),765-771	3.406
81	Extracellular Adenosine Diphosphate Ribose Mobilizes Intracellular Ca2+ via Purinergic-Dependent Ca2+ Pathways in Rat Pulmonary Artery Smooth Muscle Cells	Huang, Chun; Hu, Jinxing; Subedi, Krishna P.; Lin, Amanda H. Y.; Paudel, Omkar; Ran, Pixin; Sham, James S. K.	Sham, J S K	CELLULAR PHYSIOLOGY AND BIOCHEMISTRY	2015	37(5),2043-2059	3.592
82	Component-Resolved Diagnostic Study of Dermatophagoides Pteronyssinus Major Allergen	Zeng, G.; Luo, W.; Zheng, P.; Wei, N.; Huang, H.; Sun, B.; Zhao, X.	Sun, B	JOURNAL OF	2015	25(5),343-351	2.564

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	Molecules in a Southern Chinese Cohort			INVESTIGATIONAL ALLERGOLOGY AND CLINICAL IMMUNOLOGY			
83	Efficacies and adverse reactions of modified vitamin supplement programs before pemetrexed chemotherapy as a second-line treatment against epidermal growth factor receptor (EGFR) mutant wild-type lung adenocarcinoma	Zhou, Chengzhi; Qin, Yinyin; Ming, Ouyang; Xie, Zhanghong; Zhang, Jiexia; Li, Shiyue; Chen, Rongchang; Zhong, Nanshan	Chen, RC	International Journal of Clinical and Experimental Medicine	2015	8(8),13716-13723	1.150
84	Sepsis and ARDS: The Dark Side of Histones	Xu, Zhiheng; Huang, Yongbo; Mao, Pu; Zhang, Jianrong; Li, Yimin	Li, YM	MEDIATORS OF INFLAMMATION	2015		3.649
85	A Meta-analysis of Carbon Nanoparticles for Identifying Lymph Nodes and Protecting Parathyroid Glands during Surgery	Li, Yin; Jian, Wen-Hua; Guo, Zhu-Ming; Li, Qiu-Li; Lin, Shao-Jian; Huang, Hai-Yan	Guo, Z M	OTOLARYNGOLOGY-HEAD AND NECK SURGERY	2015	152(6),1007-1016	2.089
86	Neural Respiratory Drive and Arousal in Patients with Obstructive Sleep Apnea Hypopnea	Xiao, Si-Chang; He, Bai-Ting; Steier, Joerg; Moxham, John; Polkey, Michael I.; Luo, Yuan-Ming	Luo, YM	SLEEP	2015	38(6),941-U250	5.532
87	The Serum Profile of Hypercytokinemia Factors Identified in H7N9-Infected Patients can Predict Fatal Outcomes	Guo, Jing; Huang, Fengming; Liu, Jun; Chen, Yu; Wang, Wei; Cao, Bin; Zou, Zhen; Liu, Song; Pan, Jingcao; Bao, Changjun; Zeng, Mei; Xiao, Haixia; Gao, Hainv; Yang, Shigui; Zhao, Yan;etc	Jiang, C Y	Scientific Reports	2015	5	5.525

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88	A novel long noncoding RNA AK001796 acts as an oncogene and is involved in cell growth inhibition by resveratrol in lung cancer	Yang, Qiaoyuan; Xu, Enwu; Dai, Jiabin; Liu, Binbin; Han, Zhiyuan; Wu, Jianjun; Zhang, Shaozhu; Peng, Baoying; Zhang, Yajie; Jiang, Yiguo	Jiang, Y G	TOXICOLOGY AND APPLIED PHARMACOLOGY	2015	285(2),79-88	4.010
89	Passive Immunotherapy with Dromedary Immune Serum in an Experimental Animal Model for Middle East Respiratory Syndrome Coronavirus Infection	Zhao, Jincun; Perera, Ranawaka A. P. M.; Kayali, Ghazi; Meyerholz, David; Perlman, Stanley; Peiris, Malik	Perlman, S	JOURNAL OF VIROLOGY	2015	89(11),6117-6120	4.428
90	gamma Secretase Inhibitor BMS-708163 Reverses Resistance to EGFR Inhibitor via the PI3K/Akt Pathway in Lung Cancer	Xie, Mian; He, Jianxing; He, Chaosheng; Wei, Shenhai	Xie, M	JOURNAL OF CELLULAR BIOCHEMISTRY	2015	116(6),1019-1027	3.155
91	Polo-like kinase 2 acting as a promoter in human tumor cells with an abundance of TAp73	Hu, ZhengBo; Xu, ZunYing; Liao, XiaoHong; Yang, Xiao; Dong, Cao; Luk, KuaDi; Jin, AnMin; Lu, Hai	Lu, H	OncoTargets and Therapy	2015	8,3475-3488	2.235
92	Surface-enhanced resonance Raman scattering (SERRS) simulates PCR for sensitive DNA detection	Zhou, Haibo; Lin, Shenyu; Nie, Yichu; Yang, Danting; Wang, Qiqin; Chen, Weijia; Huang, Ning; Jiang, Zhengjin; Chen, Shanze	Jiang, Z J	ANALYST	2015	140(22),7518-7521	4.092
93	Efficacy and safety of once-daily inhaled umeclidinium/vilanterol in Asian patients with COPD: results from a randomized, placebo-controlled study	Zheng, Jinping; Zhong, Nanshan; Newlands, Amy; Church, Alison; Goh, Aik H.	Zheng, JP	International Journal of Chronic Obstructive Pulmonary Disease	2015	10,1753-1767	#N/A
94	C5-substituted pyrido[2,3-d]pyrimidin-7-ones as highly specific kinase inhibitors targeting the clinical resistance-related EGFR(T790M) mutant	Xu, Tianfeng; Peng, Ting; Ren, Xiaomei; Zhang, Lianwen; Yu, Lei; Luo, Jinfeng; Zhang, Zhang; Tu, Zhengchao; Tong, Linjiang; Huang, Zhaoru; Lu, Xiaoyun; Geng, Meiyu; Xie, Hua;	Xie, H	MedChemComm	2015	6(9),1693-1697	2.467

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		Ding, Jian; Ding, Ke					
95	Early quantitative CT analysis of oleic acid induced acute respiratory distress syndrome in a canine model	Chen, Huai; Zeng, Qing-Si; Chen, Rong-Chang; Li, Wen; Zhou, Jia-Xuan; Qin-Liu; Dai, Wang-Chun	Zeng, Q S	International Journal of Clinical and Experimental Medicine	2015	8(5),7015-U3262	1.150
96	3,4-dihydroxyphenylethanol suppresses irradiation-induced pulmonary fibrosis in adult rats	Liu, Zhao-Hui; Fan, Wei; Chen, Rong-Chang	Wei Fan, Rong-Chang Chen	Int J Clin Exp Pathol	2015	8(4),3441-3450	1.673
97	miR-497 and miR-34a retard lung cancer growth by co-inhibiting cyclin E1 (CCNE1)	Han, Zhiyuan; Zhang, Yanbin; Yang, Qiaoyuan; Liu, Binbin; Wu, Jianjun; Zhang, Yajie; Yang, Chengfeng; Jiang, Yiguo	Jiang, YG	Oncotarget	2015	6(15),13149-13163	5.415
98	Quantitative evaluation of the immunodeficiency of a mouse strain by tumor engraftments	Ye, Wei; Jiang, Zhiwu; Li, Guan-Xiong; Xiao, Yiren; Lin, Simiao; Lai, Yunxin; Wang, Suna; Li, Baiheng; Jia, Bei; Li, Yin; Huang, Zhi-liang; Li, Jin; Feng, Fenglan; Li, Shuhua; Yao, Huihui;etc	Pei, D Q	Journal of Hematology & Oncology	2015	8	5.384
99	Correlation between EGFR mutations and expression of female hormone receptors in NSCLC: A meta-analysis.	He, Qihua; Liang, Wenhua; Zhang, Jianrong; He, Jianxing	Wenhua Liang	JOURNAL OF CLINICAL ONCOLOGY	2015	33(15)	18.021
100	Association of EGFR mutations with ERCC1 expression in non-small cell lung cancer.	Liang, Wenhua; Lin, Ziying; Xu, Yutong; Zhang, Yaxiong; He, Jianxing	Jianxing He	JOURNAL OF CLINICAL ONCOLOGY	2015	33(15)	18.021
101	Predictive value of BRCA1 expression on the efficacy of chemotherapy based on anti-microtube agents: a pooled analysis across different	Liang, Wenhua; He, Qihua; Zhang, Jianrong; Shen, Jianfei; He, Jiaxi; Yang, Chenglin; He, Jianxing	Jianxing He	JOURNAL OF CLINICAL	2015	33(15)	18.021

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	malignancies and agents.			ONCOLOGY			
102	Copper-Catalyzed Trifluoromethylalkynylation of Isocyanides	Lei, Jian; Wu, Xiaoxing; Zhu, Qiang	Wu, X X	ORGANIC LETTERS	2015	17(10),2322-2325	6.033
103	Polymorphisms of NF kappa B1 and I kappa B alpha and Their Synergistic Effect on Nasopharyngeal Carcinoma Susceptibility	Liu, Yehua; Qiu, Fuman; Yang, Lei; Yang, Rongrong; Yang, Xiaorong; Huang, Dongsheng; Fang, Wenxiang; Zhang, Lisha; Jiang, Qingping; Zhang, Lan; Zhou, Yifeng; Lu, Jiachun	Lu, JC	Biomed Research International	2015		2.149
104	Effects of Schisandra chinensis extracts on cough and pulmonary inflammation in a cough hypersensitivity guinea pig model induced by cigarette smoke exposure	Zhong, Shan; Nie, Yi-chu; Gan, Zhen-yong; Liu, Xiao-dong; Fang, Zhang-fu; Zhong, Bo-nian; Tian, Jin; Huang, Chu-qin; Lai, Ke-fang; Zhong, Nan-shan	Lai, KF	JOURNAL OF ETHNOPHARMACOLOGY	2015	165,73-82	3.333
105	Comprehensive analysis of the T-cell receptor beta chain gene in rhesus monkey by high throughput sequencing	Li, Zhoufang; Liu, Guangjie; Tong, Yin; Zhang, Meng; Xu, Ying; Qin, Li; Wang, Zhanhui; Chen, Xiaoping; He, Jiankui	Chen, XP	Scientific Reports	2015	5	5.525
106	Three decomposition products of valepotriates from Valeriana jatamansi and their cytotoxic activity	Lin, Sheng; Chen, Tao; Fu, Peng; Ye, Ji; Yang, Xian-Wen; Shan, Lei; Li, Hui-Liang; Liu, Run-Hui; Shen, Yun-Heng; Xu, Xi-Ke; Zhang, Wei-Dong	Zhang, W D	JOURNAL OF ASIAN NATURAL PRODUCTS RESEARCH	2015	17(5),455-461	1.028
107	Screening for pectus excavatum among primary students and establishment of a pectus excavatum screening program in Dongguan, China	Zou, Xusen; Lin, Yanqing; Jin, Hui; Cai, Sumei; Xu, Xin; Yin, Weiqiang; Geng, Qingshan; Chen, Jiuhao; Liang, Bing; He, Jianxing; Li, Wei	He, J X	Journal of Thoracic Disease	2015	7(5),868-874	#N/A
108	N-(3-Ethynyl-2,4-difluorophenyl)sulfonamide Derivatives as Selective Raf Inhibitors	Li, Yingjun; Cheng, Huimin; Zhang, Zhang; Zhuang, Xiaoxi; Luo, Jinfeng; Long, Huoyou; Zhou, Yang; Xu, Yong; Taghipouran, Rana; Li, Dan; Patterson, Adam; Smaill, Jeff; Tu, Zhengchao; Wu, Donghai; Ren, Xiaomei;etc	Ren, X M	ACS Medicinal Chemistry Letters	2015	6(5),543-547	3.294

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109	Effectiveness of digital infrared thermal imaging in detecting lower extremity deep venous thrombosis	Deng, Fangge; Tang, Qing; Zeng, Guangqiao; Wu, Hua; Zhang, Nuofu; Zhong, Nanshan	Zhong, NS	MEDICAL PHYSICS	2015	42(5),2242-2248	2.889
110	Sputum bacteriology in steady-state bronchiectasis in Guangzhou, China	Guan, W-J.; Gao, Y-H; Xu, G.; Lin, Z-Y.; Tang, Y.; Li, H-M.; Lin, Z-M.; Zheng, J-P.; Chen, R-C.; Zhong, N-S.	Zhong, NS	INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE	2015	19(5),610-619	2.161
111	Ovarian cancer transformation from adenocarcinoma to undifferentiated small cell carcinoma: A case report	Huang, Zuo Ping; Liu, Xing Jing; Zou, Bin Xin; Shen, Qian; Liu, Ying; Zhou, Tao	Zou, B X	Oncology Letters	2015	9(5),2230-2232	1.448
112	The cystic fibrosis transmembrane conductance regulator as a biomarker in non-small cell lung cancer	Li, Jin; Zhang, Jie Ting; Jiang, Xiaohua; Shi, Xiaoshun; Shen, Jianfei; Feng, Fenglan; Chen, Jingyi; Liu, Guihong; He, Ping; Jiang, Juhong; Tsang, Lai Ling; Wang, Yan; Rosell, Rafael; Jiang, Long; He, Jianxing;etc	He, JX	INTERNATIONAL JOURNAL OF ONCOLOGY	2015	46(5),2107-2115	2.990
113	Radical resection of right upper lung cancer using uniportal video-assisted thoracic surgery with non-intubated anesthesia	Wang, Wei; Peng, Guilin; Guo, Zhihua; Liang, Lixia; Dong, Qinglong; He, Jianxing; Yin, Weiqiang	He, JX	Journal of Thoracic Disease	2015	7(12),2362-2365	#N/A
114	Innovations in bronchoscopic techniques will go a long way for diagnosis of early-stage lung cancers	Chen, Kangni; Zeng, Guangqiao	Zeng, G Q	TRANSLATIONAL CANCER RESEARCH	2015	4(6),688-691	1.633
115	Early screening of lung cancers: an effort arduous but worthwhile	Pei, Chu; Grouse, Lawrence; Zeng, Guangqiao	Zeng, G Q	Chinese Journal of	2015	27(6),617-618	1.834

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				Cancer Research			
116	Natural products against hematological malignancies and identification of their targets	Xu Ying; Liu JinBao; Wu YingLi; Guo QingLong; Sun HanDong; Chen GuoQiang	Chen, G Q	Science China-Life Sciences	2015	58(12),1191-1201	1.772
117	Peroxisome Proliferator-Activated Receptor gamma-Mediated Inhibition on Hypoxia-Triggered Store-Operated Calcium Entry A Caveolin-1-Dependent Mechanism	Yang, Kai; Lu, Wenju; Jiang, Qian; Yun, Xin; Zhao, Mingming; Jiang, Haiyang; Wang, Jian	Wang, J	AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY	2015	53(6),882-892	4.052
118	Structure of product-bound SMG1 lipase: active site gating implications	Guo, Shaohua; Xu, Jinxin; Pavlidis, Ioannis V.; Lan, Dongming; Bornscheuer, Uwe T.; Liu, Jinsong; Wang, Yonghua	Wang, Y H	FEBS Journal	2015	282(23),4538-4547	4.082
119	Upregulation of canonical transient receptor potential channel in the pulmonary arterial smooth muscle of a chronic thromboembolic pulmonary hypertension rat model	Yun, Xin; Chen, Yuqin; Yang, Kai; Wang, Sabrina; Lu, Wenju; Wang, Jian	Lu, WJ	HYPERTENSION RESEARCH	2015	38(12),821-828	2.731
120	Frequent alterations in cytoskeleton remodelling genes in primary and metastatic lung adenocarcinomas	Wu, Kui; Zhang, Xin; Li, Fuqiang; Xiao, Dakai; Hou, Yong; Zhu, Shida; Liu, Dongbing; Ye, Xiaofei; Ye, Mingzhi; Yang, Jie; Shao, Libin; Pan, Hui; Lu, Na; Yu, Yuan; Liu, Liping;etc	Wang, J	Nature Communications	2015	6	12.001
121	Cough and environmental air pollution in China	Zhang, Qingling; Qiu, Minzhi; Lai, Kefang; Zhong, Nanshan	Zhang, Q L	PULMONARY PHARMACOLOGY	2015	35,132-136	2.676

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				&THERAPEUTICS			
122	Adult and paediatric cough guidelines: Ready for an overhaul?	Birring, Surinder S.; Kavanagh, Joanne; Lai, Kefang; Chang, Anne B.	Kavanagh, J	PULMONARY PHARMACOLOGY & THERAPEUTICS	2015	35,137-144	2.676
123	INHALED SALMETEROL/FLUTICASONE PROPIONATE IS MORE EFFECTIVE THAN FLUTICASONE PROPIONATE ALONE AT ACHIEVING WELL-CONTROLLED ASTHMA IN ASIAN PATIENTS: A POST HOC ANALYSIS OF THE GOAL STUDY	Bousquet, Jean; Barnes, Neil; Gibbs, Michael; Gul, Nadeem; Kellam, Lynda; Zhou, Xin; Zhong, Nanshan; Cho, Young-Joo; Park, Hae-Sim		RESPIROLOGY	2015	20,13-13	2.856
124	INHALED SALMETEROL/FLUTICASONE PROPIONATE IS MORE EFFECTIVE THAN FLUTICASONE PROPIONATE ALONE AT ACHIEVING TOTAL ASTHMA CONTROL IN ASIAN PATIENTS: A POST HOC ANALYSIS OF THE GOAL STUDY	Zhong, Nanshan; Barnes, Neil; Gibbs, Michael; Gul, Nadeem; Kellam, Lynda; Zhou, Xin; Cho, Young-Joo; Park, Hae-Sim; Bousquet, Jean		RESPIROLOGY	2015	20,13-13	2.856
125	DER P1 AND DER P2 SIGE CURATIVE EFFECT EVALUATION FOR SPECIFIC IMMUNOTHERAPY	Zheng, Peiyan; Sun, Baoqing; Zeng, Guangqiao; Wei, Nili; Huang, Huimin		RESPIROLOGY	2015	20,63-63	2.856
126	ASSOCIATION STUDY OF NICOTINIC ACETYLCHOLINE RECEPTOR AND CYP2A6 GENE POLYMORPHISMS WITH THE SUSCEPTIBILITY OF LUNG CANCER AMONG	Zhang, Yalei; Jiang, Mei		RESPIROLOGY	2015	20,103-103	2.856

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	CHINESE SOUTHERN MALE POPULATIONIN						
127	COUGH CLINICAL PRACTICE GUIDELINES: A CRITICAL REVIEW OF SCIENTIFIC EVIDENCE AND RECOMMENDATIONS	Mei, Jiang	--	RESPIROLOGY	2015	20,105-105	2.856
128	SURVEY AND ANALYSIS ON CLINICAL NURSES' KNOWLEDGE OF TOBACCO CONTROL, SITUATION OF TRAINING AND ATTITUDE TOWARDS TOBACCO CONTROL FROM RESPIRATORY DEPARTMENT AND GENERAL MEDICINE DEPARTMENT OF TERTIARY HOSPITALS IN GUANGZHOU, CHINA	Su, Yueming; Chen, Shujun; Xin, Lijie; He, Wei; Gong, Yucui; Jiang, Mei	--	RESPIROLOGY	2015	20,118-118	2.856
129	ASSOCIATION BETWEEN PSEUDOMONAS AERUGINOSA INFECTION AND AIRWAY MATRIX METALLOPROTEINASES IN BRONCHIECTASIS	Guan, Wei-Jie	--	RESPIROLOGY	2015	20,126-126	2.856
130	IMPACTS OF CO-EXISTING CHRONIC RHINOSINUSITIS ON DISEASE SEVERITY AND RISKS OF EXACERBATIONS IN CHINESE ADULTS WITH BRONCHIECTASIS	Guan, Wei-Jie	Chen, R C	PLoS One	2015	20,127-127	2.856
131	Genetic Characterization of Highly Pathogenic Avian Influenza A(H5N6) Virus, Guangdong, China	Mok, Chris Ka Pun; Guan, Wen Da; Liu, Xiao Qing; Lamers, Mart Matthias; Li, Xiao Bo; Wang, Ming; Zhang, Tami Jing Shu; Zhang, Qing Ling; Li, Zheng Tu; Huang, Ji Cheng; Lin, Jin Yan; Zhang, Yong Hui; Zhao, Ping; Lee, Horace Hok Yeung; Chen, Ling;etc	Yang, ZF	EMERGING INFECTIOUS DISEASES	2015	21(12),2268-2271	6.591
132	Characteristics of Traveler with Middle East Respiratory Syndrome, China, 2015	Guan, Wen Da; Mok, Chris Ka Pun; Chen, Zi Lin; Feng, Li Qiang; Li, Zheng Tu; Huang, Ji Cheng; Ke, Chang Wen; Deng,	Chen, L	EMERGING INFECTIOUS	2015	21(12),2278-228	6.591

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		Xilong; Ling, Yun; Wu, Shi Guan; Niu, Xue Feng; Perera, Ranawaka A.; Xu, Yuan Da; Zhao, Jincun; Zhang, Lin Qi;etc		DISEASES		0	
133	Magnetic resonance angiography manifestations and prognostic significance in HIV-negative tuberculosis meningitis	Lu, T-T.; Lin, X-Q.; Zhang, L.; Cai, W.; Dai, Y-Q.; Lu, Z-Z.; Wu, A-M.; Bao, J.; Yang, Y.; Hu, X-Q.; Lu, Z-Q.	Lu, Z Q	INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE	2015	19(12),1448-1454	2.161
134	Frequency of food group consumption and risk of allergic disease and sensitization in schoolchildren in urban and rural China	Yang, Z.; Zheng, W.; Yung, E.; Zhong, N.; Wong, G. W. K.; Li, J.	Li, J	CLINICAL AND EXPERIMENTAL ALLERGY	2015	45(12),1823-1832	4.658
135	Dichotomous role of protein kinase A type I (PKAI) in the tumor microenvironment: A potential target for 'two-in-one' cancer chemoimmunotherapeutics	Hussain, Muzammal; Tang, Fei; Liu, Jinsong; Zhang, Jiancun; Javeed, Aqeel	Zhang, J C	CANCER LETTERS	2015	369(1),9-19	5.174
136	Neutralizing epitopes mapping of human adenovirus type 14 hexon	Ma, Qiang; Tian, Xingui; Jiang, Zaixue; Huang, Junfeng; Liu, Qian; Lu, Xiaomei; Luo, Qingming; Zhou, Rong	Zhou, R	VACCINE	2015	33(48),6659-6665	3.338
137	Acute MUS81 depletion leads to replication fork slowing and a constitutive DNA damage response	Xing, Meichun; Wang, Xiaohui; Palmai-Pallag, Timea; Shen, Huahao; Helleday, Thomas; Hickson, Ian D.; Ying, Songmin	Ying, S M	Oncotarget	2015	6(35),37385-37393	5.415
138	The effect of statins on chronic obstructive pulmonary disease exacerbation and mortality: a systematic review and meta-analysis of observational	Cao, Chao; Wu, Yinfang; Xu, Zhiwei; Lv, Dan; Zhang, Chao; Lai, Tianwen; Li, Wen; Shen, Huahao	Shen, H H	Scientific Reports	2015	5	5.525

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	research						
139	Approaches for the generation of active papain-like cysteine proteases from inclusion bodies of Escherichia coli	Ling, Chunfang; Zhang, Junyan; Lin, Deqiu; Tao, Ailin	Lin, D Q	WORLD JOURNAL OF MICROBIOLOGY & BIOTECHNOLOGY	2015	31(5),681-690	1.655
140	COP9 Signalosome Controls the Degradation of Cytosolic Misfolded Proteins and Protects Against Cardiac Proteotoxicity	Su, Huabo; Li, Jie; Zhang, Hanming; Ma, Wenxia; Wei, Ning; Liu, Jinbao; Wang, Xuejun	Wang, X J	CIRCULATION RESEARCH	2015	117(11),956-966	11.218
141	Sodium tanshinone IIA sulfonate inhibits cigarette smoke-induced airway inflammation via regulating cystic fibrosis transmembrane conductance regulator-mediated pathway	Lu, Wenju; Li, Defu; Gong, Xuefang; Wang, Jian; Zhong, Nanshan	Chest	Wang, Jian	2015	194	5.287
142	Copper-Promoted Cycloaddition of alpha-Methylenyl Isocyanides with Benzothiazoles: Tunable Access to Benzo[d]imidazothiazoles	Wang, Jian; Li, Jing; Zhu, Qiang	Zhu, Q	ORGANIC LETTERS	2015	17(21),5336-5339	6.033
143	Expression and refolding of mite allergen pro-Der f1 from inclusion bodies in Escherichia coli	Ling, Chunfang; Zhang, Junyan; Chen, Huifang; Zou, Zehong; Lai, He; Zhang, Jianguo; Lin, Deqiu; Tao, Ailin	Lin, D Q	PROTEIN EXPRESSION AND PURIFICATION	2015	109,93-98	1.401
144	(Z)3,4,5,4 '-trans-tetramethoxystilbene, a new analogue of resveratrol, inhibits gefitinb-resistant non-small cell lung cancer via selectively elevating intracellular calcium level	Fan, Xing-Xing; Yao, Xiao-Jun; Xu, Su Wei; Wong, Vincent Kam-Wai; He, Jian-Xing; Ding, Jian; Xue, Wei-Wei; Mujtaba, Tahira; Michelangeli, Francesco; Huang, Min; Huang, Jun; Xiao, Da-Kai; Jiang, Ze-Bo; Zhou, Yan-Ling; Kam, Richard	Liu, L	Scientific Reports	2015	5	5.525

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		Kin-Ting;etc					
145	Small Molecule Discoidin Domain Receptor Kinase Inhibitors and Potential Medical Applications	Li, Yupeng; Lu, Xiaoyun; Ren, Xiaomei; Ding, Ke	Ren, X M	JOURNAL OF MEDICINAL CHEMISTRY	2015	58(8),3287-3301	5.624
146	Lariciresinol-4-O-beta-D-glucopyranoside from the root of Isatis indigotica inhibits influenza A virus-induced pro-inflammatory response	Li, Jing; Zhou, Beixian; Li, Chufang; Chen, QiaoYan; Wang, Yutao; Li, Zhengtu; Chen, Tingting; Yang, Chunguang; Jiang, Zhihong; Zhong, Nanshan; Yang, Zifeng; Chen, Rongchang	Yang, Z F	JOURNAL OF ETHNOPHARMACOLOGY	2015	174,379-386	3.333
147	Simian Immunodeficiency Virus Infection Evades Vaccine-Elicited Antibody Responses to V2 Region	Guo, Jia; Zuo, Teng; Cheng, Lin; Wu, Xilin; Tang, Jiansong; Sun, Caijun; Feng, Liqiang; Chen, Ling; Zhang, Linqi; Chen, Zhiwei	Chen, Z W	JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES	2015	68(5),502-510	3.953
148	URGCP promotes non-small cell lung cancer invasiveness by activating the NF-kappa B-MMP-9 pathway	Cai, Junchao; Li, Rong; Xu, Xiaonan; Zhang, Le; Wu, Shanshan; Yang, Tianyou; Fang, Lishan; Wu, Jueheng; Zhu, Xun; Li, Mengfeng; Huang, Yongbo	Huang, Y B	Oncotarget	2015	6(34),36489-36504	5.415
149	Expression of Human Tissue Factor Pathway Inhibitor on Vascular Smooth Muscle Cells Inhibits Secretion of Macrophage Migration Inhibitory Factor and Attenuates Atherosclerosis in ApoE(-/-) Mice	Chen, Daxin; Xia, Min; Hayford, Claudia; Tham, El-Li; Semik, Vikki; Hurst, Stuart; Chen, Ying; Tam, Henry H.; Pan, Jun; Wang, Yucheng; Tan, Xiaojin; Lan, Hui-Yao; Shen, Huahao; Kakkar, Vijay V.; Xu, Qingbo;etc	Dorling, A	CIRCULATION	2015	131(15),1350-U101	16.252
150	Para-toluenesulfonamide induces tongue squamous cell carcinoma cell death through disturbing	Liu, Zhe; Liang, Chenyuan; Zhang, Zhuoyuan; Pan, Jian; Xia, Hui; Zhong, Nanshan; Li, Longjiang	Li, L J	ANTI-CANCER DRUGS	2015	26(10),1026-103	2.009

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	lysosomal stability					3	
151	Surveillance for Seasonal Influenza Virus Prevalence in Hospitalized Children with Lower Respiratory Tract Infection in Guangzhou, China during the Post-Pandemic Era	Da Guan, Wen; Gong, Xiao Yan; Mok, Chris Ka Pun; Chen, Ting Ting; Wu, Shi Guan; Pan, Si Hua; Cowling, Benjamin John; Yang, Zi Feng; Chen, De Hui	Yang, ZF	PLoS One	2015	10(4)	3.535
152	Prognosis and status of lymph node involvement in patients with adenocarcinoma in situ and minimally invasive adenocarcinoma-a systematic literature review and pooled-data analysis	Jiang, Long; Yin, Weiqiang; Peng, Guilin; Wang, Wei; Zhang, Jianrong; Liu, Yang; Zhong, Shengyi; He, Qihua; Liang, Wenhua; He, Jianxing	He, J X	Journal of Thoracic Disease	2015	7(11),2003-2009	#N/A
153	A gloves-associated outbreak of imipenem-resistant Acinetobacter baumannii in an intensive care unit in Guangdong, China	Ye, Dan; Shan, Jinglan; Huang, Yongbo; Li, Jianchun; Li, Changan; Liu, Xiaoqing; He, Weiqun; Li, Yimin; Mao, Pu	Li, YM	BMC INFECTIOUS DISEASES	2015	15	2.864
154	A Genetic Variant in Pre-miR-146a (rs2910164 C > G) Is Associated with the Decreased Risk of Acute Coronary Syndrome in a Chinese Population	Huang, Suli; Lv, Ziquan; Deng, Qifei; Li, Lu; Yang, Binyao; Feng, Jing; Wu, Tangchun; Zhang, Xiaomin; Cheng, Jinquan	Cheng, J Q	TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE	2015	237(3),227-233	1.454
155	A humanized neutralizing antibody against MERS-CoV targeting the receptor-binding domain of the spike protein	Li, Yan; Wan, Yuhua; Liu, Peipei; Zhao, Jincun; Lu, Guangwen; Qi, Jianxun; Wang, Qihui; Lu, Xuancheng; Wu, Ying; Liu, Wenjun; Zhang, Buchang; Yuen, Kwok-Yung; Perlman, Stanley; Gao, George F.; Yan, Jinghua	Yan, J H	CELL RESEARCH	2015	25(11),1237-1249	12.393
156	Gambogic acid induces apoptosis in diffuse large B-cell lymphoma cells via inducing proteasome inhibition	Shi, Xianping; Lan, Xiaoying; Chen, Xin; Zhao, Chong; Li, Xiaofen; Liu, Shouting; Huang, Hongbiao; Liu, Ningning; Zang, Dan; Liao, Yuning; Zhang, Peiquan; Wang, Xuejun; Liu, Jinbao	Liu, JB	Scientific Reports	2015	5	5.525
157	Effect of airway Pseudomonas aeruginosa isolation and infection on steady-state bronchiectasis in	Guan, Wei-Jie; Gao, Yong-Hua; Xu, Gang; Lin, Zhi-Ya; Tang, Yan; Li, Hui-Min; Li, Zhi-Min; Zheng, Jin-Ping; Chen,	Zhong, NS	Journal of Thoracic	2015	7(4),625-636	#N/A

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	Guangzhou, China	Rong-Chang; Zhong, Nan-Shan		Disease			
158	Validation of human small airway measurements using endobronchial optical coherence tomography	Chen, Yu; Ding, Ming; Guan, Wei-jie; Wang, Wei; Luo, Wei-zhan; Zhong, Chang-hao; Jiang, Mei; Jiang, Ju-hong; Gu, Ying-ying; Li, Shi-yue; Zhong, Nan-shan	Zhong, NS	RESPIRATORY MEDICINE	2015	109(11), 1446-1453	3.213
159	Study on risk factors and phenotypes of acute exacerbations of chronic obstructive pulmonary disease in Guangzhou, China - design and baseline characteristics	Zhou, Yumin; Bruijnzeel, Piet L. B.; McCrae, Christopher; Zheng, Jinping; Nihlen, Ulf; Zhou, Rong; Van Geest, Marleen; Nilsson, Anna; Hadzovic, Sinela; Huhn, Monika; Taib, Ziad; Gu, Yi; Xie, Jiaxing; Ran, Pixin; Chen, Rongchang;etc	Zhong, NS	Journal of Thoracic Disease	2015	7(4),720-+	#N/A
160	MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation	Bousquet, J.; Schunemann, H. J.; Fonseca, J.; Samolinski, B.; Bachert, C.; Canonica, G. W.; Casale, T.; Cruz, A. A.; Demoly, P.; Hellings, P.; Valiulis, A.; Wickman, M.; Zuberbier, T.; Bosnic-Anticevitch, S.; Bedbrook, A.;etc	Bousquet, J	ALLERGY	2015	70(11),1372-1392	5.746
161	Nonintubated Video-Assisted Thoracoscopic Surgery Under Epidural Anesthesia Compared With Conventional Anesthetic Option: A Randomized Control Study	Liu, Jun; Cui, Fei; Li, Shuben; Chen, Hanzhang; Shao, Wenlong; Liang, Lixia; Yin, Weiqiang; Lin, Yongping; He, Jianxing	He, J X	Surgical Innovation	2015	22(2),123-130	1.326
162	Skp1 in lung cancer: clinical significance and therapeutic efficacy of its small molecule inhibitors	Liu, Yong-Qiang; Wang, Xiao-Lu; Cheng, Xin; Lu, Yong-Zhi; Wang, Gui-Zhen; Li, Xin-Chun; Zhang, Jian; Wen, Zhe-Sheng; Huang, Zhi-Liang; Gao, Qin-Lei; Yang, Li-Na; Cheng, Yong-Xian; Tao, Sheng-Ce; Liu, Jinsong; Zhou, Guang-Biao	Zhou, G B	Oncotarget	2015	6(33),34953-34967	5.415
163	Residue Asn277 Affects the Stability and Substrate Specificity of the SMG1 Lipase from Malassezia globosa	Lan, Dongming; Wang, Qian; Xu, Jinxin; Zhou, Pengfei; Yang, Bo; Wang, Yonghua	Yang, B	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	2015	16(4),7273-7288	3.213
164	Breathlessness or Health Status in Chronic	Han, Jiangna; Dai, Lu; Zhong, Nanshan; Young, David	Han, J N	COPD-Journa	2015	12(2),11	2.494

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	Obstructive Pulmonary Disease: The Impact of Different Definitions			l of Chronic Obstructive Pulmonary Disease		5-125	
165	IL-13 receptor ' 2 is a negative prognostic factor in human lung cancer and stimulates lung cancer growth in mice	Xie, Mian; Wu, Xiao-jun; Zhang, Jin-jun; He, Chao-sheng	Xie, M	Oncotarget	2015	6(32),32902-32913	5.415
166	Exogenous Interleukin-17A Inhibits Eosinophil Differentiation and Alleviates Allergic Airway Inflammation	Tian, Bao-ping; Hua, Wen; Xia, Li-xia; Jin, Yan; Lan, Fen; Lee, James J.; Lee, Nancy A.; Li, Wen; Ying, Song-min; Chen, Zhi-hua; Shen, Hua-hao	Shen, H H	AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY	2015	52(4),459-470	4.052
167	Overexpression of CHD1L is positively associated with metastasis of lung adenocarcinoma and predicts patients poor survival	He, Li-Ru; Ma, Ning-Fang; Chen, Jie-Wei; Li, Bin-Kui; Guan, Xin-Yuan; Liu, Meng-Zhong; Xie, Dan	Xie, D	Oncotarget	2015	6(31),31181-31190	5.415
168	Sequence Variation in Mature MicroRNA-499 Confers Unfavorable Prognosis of Lung Cancer Patients Treated with Platinum-Based Chemotherapy	Qiu, Fuman; Yang, Lei; Ling, Xiaoxuan; Yang, Rongrong; Yang, Xiaorong; Zhang, Lisha; Fang, Wenxiang; Xie, Chenli; Huang, Dongsheng; Zhou, Yifeng; Lu, Jiachun	Lu, JC	CLINICAL CANCER RESEARCH	2015	21(7),1602-1613	8.751
169	The p.Ser267Phe Variant in SLC10A1 Is Associated With Resistance to Chronic Hepatitis B	Peng, Liang; Zhao, Qiang; Li, Qibin; Li, Miaoxin; Li, Caixia; Xu, Tingting; Jing, Xiangyi; Zhu, Xiang; Wang, Ye; Li, Fucheng; Liu, Ruihong; Zhong, Cheng; Pan, Qihao; Zeng, Binghui; Liao, Qijun;etc	Wang, Y M	HEPATOLOGY	2015	61(4),1251-1260	11.854
170	Deubiquitinases (DUBs) and DUB inhibitors: a patent review	Farshi, Pershang; Deshmukh, Rahul R.; Nwankwo, Joseph O.; Arkwright, Richard T.; Cvek, Boris; Liu, Jinbao; Dou, Q. Ping	Dou, Q P	EXPERT OPINION ON	2015	25(10),1191-120	3.592

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				THERAPEUTIC PATENTS		8	
171	Ritonavir-boosted indinavir but not lopinavir inhibits erythrocytic stage Plasmodium knowlesi malaria in rhesus macaques	Qin, Li; Qin, Limei; Xu, Wanwan; Zhao, Siting; Chen, Xiaoping	Chen, XP	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS	2015	25(7),1538-1540	2.303
172	Mapping the epitope of neutralizing monoclonal antibodies against human adenovirus type 3	Tian, Xingui; Liu, Minglong; Su, Xiaobo; Jiang, Zaixue; Ma, Qiang; Liao, Xiaohong; Li, Xiao; Zhou, Zhichao; Li, Chenyang; Zhou, Rong	Li, C Y	VIRUS RESEARCH	2015	208,66-72	2.611
173	Six-minute walk test in Chinese adults with clinically stable bronchiectasis: association with clinical indices and determinants	Guan, Wei-jie; Gao, Yong-hua; Xu, Gang; Lin, Zhi-ya; Tang, Yan; Li, Hui-min; Lin, Zhi-min; Zheng, Jin-ping; Chen, Rong-chang; Zhong, Nan-shan	Chen, RC	CURRENT MEDICAL RESEARCH AND OPINION	2015	31(4),843-852	2.386
174	Indoor Allergen Levels and Household Distributions in Nine Cities Across China	Zheng Yi Wu; Lai Xu Xin; Zhao De Yu; Zhang Chun Qing; Chen Jian Jun; Zhang Luo; Wei Qing Yu; Chen Shi; Liu En Mei; Norback, Dan; Gjesing, Birgitte; Zhong Nan Shan; Spangfort, D. Michael	Zhong, NS	BIOMEDICAL AND ENVIRONMENTAL SCIENCES	2015	28(10),709-717	1.751
175	Group IIE Secretory Phospholipase A(2) Regulates Lipolysis in Adipocytes	Zhi, Hui; Qu, Linbing; Wu, Fang; Chen, Ling; Tao, Jun	Chen, L	Obesity	2015	23(4),760-768	4.181
176	Lower airway inflammation and hyperresponsiveness in nonasthmatic patients with non-allergic rhinitis	Wang, Qiuping; Ji, Junfeng; Xie, Yanqing; Guan, Weijie; Zhang, Yong; Wang, Zhiyi; Wu, Kunmin; Zhong, Nanshan	Zhong, NS	Journal of Thoracic Disease	2015	7(10),1756-1764	#N/A
177	Prognostic value of ERCC1, RRM1, and TS proteins in patients with resected non-small cell lung cancer	He, Yu-Wen; Zhao, Mei-Ling; Yang, Xin-Yun; Zeng, Jun; Deng, Qiu-Hua; He, Jian-Xing	He, JX	CANCER CHEMOTHE	2015	75(4),861-867	2.731

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				RAPY AND PHARMACOLOGY			
178	A comparative analysis of lung cancer patients treated with lobectomy via three-dimensional video-assisted thoracoscopic surgery versus two-dimensional resection	Yang, Chengliang; Mo, Lili; Ma, Yegang; Peng, Guilin; Ren, Yi; Wang, Wei; Liu, Yongyu; He, Jianxing	He, J X	Journal of Thoracic Disease	2015	7(10),1798-1805	#N/A
179	Tc17 cells are associated with cigarette smoke-induced lung inflammation and emphysema	Zhou, Hongbin; Hua, Wen; Jin, Yan; Zhang, Chao; Che, Luanqing; Xia, Lixia; Zhou, Jiesen; Chen, Zhihua; Li, Wen; Shen, Huahao	Shen, H H	RESPIROLOGY	2015	20(3),426-433	2.856
180	Establishment of a mathematic model for predicting malignancy in solitary pulmonary nodules	Zhang, Man; Zhuo, Na; Guo, Zhanlin; Zhang, Xingguang; Liang, Wenhua; Zhao, Sheng; He, Jianxing	He, J X	Journal of Thoracic Disease	2015	7(10),1833-1841	#N/A
181	Efficacy and safety of Ban-Lan-Gen granules in the treatment of seasonal influenza: study protocol for a randomized controlled trial	Li, Zheng-tu; Li, Li; Chen, Ting-ting; Li, Chu-yuan; Wang, De-qin; Yang, Zi-feng; Zhong, Nan-shan	Zhong, N S	Trials	2015	16	2.193
182	Surface Confined Retro Diels-Alder Reaction Driven by the Swelling of Weak Polyelectrolytes	Lyu, Beier; Cha, Wenli; Mao, Tingting; Wu, Yuanzi; Qian, Hujun; Zhou, Yitian; Chen, Xiuli; Zhang, Shen; Liu, Lanying; Yang, Guang; Lu, Zhongyuan; Zhu, Qiang; Ma, Hongwei	Ma, H W	ACS Applied Materials & Interfaces	2015	7(11),6254-6259	7.332
183	Characterization of a new subtype of allergen in dermatophagoides farinae-Der f 28	Lin, Jian-Li; Wang, Yuan-Yuan; Xiao, Xiao-Jun; Wu, Yu-Lan; Sun, Bao-Qing; Gao, An-Jian; Liu, Zhi-Gang; Li, Jing; Yang, Ping-Chang; Liu, Xiao-Yu	Liu, X Y	Journal of Thoracic Disease	2015	7(10),1842-1849	#N/A
184	Aminopalladation-Triggered Carbene Insertion Reaction: Synthesis of 2-(1H-Indol-3-yl)acetates	Hu, Ziwei; Luo, Shuang; Zhu, Qiang	Luo, S	ADVANCED SYNTHESIS & CATALYSIS	2015	357(5),1060-1064	5.852
185	Circular RNA ITCH has inhibitory effect on ESCC	Li, Fang; Zhang, Liyuan; Li, Wei; Deng, Jieqiong; Zheng, Jian;	Zhou, Y F	Oncotarget	2015	6(8),600	5.415

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	by suppressing the Wnt/beta-catenin pathway	An, Mingxing; Lu, Jiachun; Zhou, Yifeng				1-6013	
186	Engineering More Stable, Selectable Marker-Free Autoluminescent Mycobacteria by One Step	Yang, Feng; Njire, Moses M.; Liu, Jia; Wu, Tian; Wang, Bangxing; Liu, Tianzhou; Cao, Yuanyuan; Liu, Zhiyong; Wan, Junting; Tu, Zhengchao; Tan, Yaoju; Tan, Shouyong; Zhang, Tianyu	Zhang, TY	PLoS One	2015	10(3)	3.535
187	Cationic nanoparticles directly bind angiotensin-converting enzyme 2 and induce acute lung injury in mice	Sun, Yang; Guo, Feng; Zou, Zhen; Li, Chenggang; Hong, Xiaoxu; Zhao, Yan; Wang, Chenxuan; Wang, Hongliang; Liu, Haolin; Yang, Peng; Han, Zongsheng; Liu, Kangtai; Kuba, Keiji; Song, Bin; Gao, Jinming;etc	Penninger, J M	Particle and Fibre Toxicology	2015	12	9.618
188	NPTX1 is a novel epigenetic regulation gene and associated with prognosis in lung cancer	Zhou, Chengzhi; Qin, Yinyin; Xie, Zhanhong; Zhang, Jiexia; Yang, Mingou; Li, Shiyue; Chen, Rongchang	Shiyue Li,Rongchang Chen	Biochem Biophys Res Commun	2015	458(2),381-386	2.392
189	Evaluation of the efficacy and safety of anti-PD-1 and anti-PD-L1 antibody in the treatment of non-small cell lung cancer (NSCLC): a meta-analysis	Jia, Minghan; Feng, Weijiao; Kang, Shiyang; Zhang, Yaxiong; Shen, Jianfei; He, Jiaxi; Jiang, Long; Wang, Wei; Guo, Zhihua; Peng, Guilin; Chen, Gang; He, Jianxing; Liang, Wenhua	Liang, W H	Journal of Thoracic Disease	2015	7(3),455-461	#N/A
190	The rural-urban enigma of allergy: What can we learn from studies around the world?	Schroeder, Paul C.; Li, Jing; Wong, Gary W. K.; Schaub, Bianca	Schaub, B	PEDIATRIC ALLERGY AND IMMUNOLOGY	2015	26(2),95-102	3.262
191	Prognosis of synchronous and metachronous multiple primary lung cancers: Systematic review and meta-analysis	Jiang, Long; He, Jiaxi; Shi, Xiaoshun; Shen, Jianfei; Liang, Wenhua; Yang, Chenglin; He, Jianxing	He, J X	LUNG CANCER	2015	87(3),303-310	3.760
192	Erlotinib in combination with pemetrexed/cisplatin for leptomeningeal metastases and cerebrospinal fluid drug concentrations in lung adenocarcinoma patients after gefitinib faliure	Yang, Haihong; Yang, Xinyun; Zhang, Yalei; Liu, Xin; Deng, Qiuhua; Zhao, Meiling; Xu, Xin; He, Jianxing	He, J X	Targeted Oncology	2015	10(1),135-140	3.019

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193	GP73 was upregulated in PBMC stimulated with ConA but failed to promote lymphocyte proliferation	Wang, Fang; Li, Zhaotao; Li, Leike; Hu, Longbo; Xiao, Jing; Su, Zhong; Peng, Tao	Peng, T	CELL BIOLOGY INTERNATIONAL	2015	39(3),334-340	1.607
194	Peroxisome proliferator-activated receptor gamma inhibits pulmonary hypertension targeting store-operated calcium entry	Wang, Yingfeng; Lu, Wenju; Yang, Kai; Wang, Yan; Zhang, Jie; Jia, Jing; Yun, Xin; Tian, Lichun; Chen, Yuqin; Jiang, Qian; Zhang, Bo; Chen, Xiuqing; Wang, Jian	Lu, W J	JOURNAL OF MOLECULAR MEDICINE-JMM	2015	93(3),327-342	4.440
195	Clinical, Virological and Immunological Features from Patients Infected with Re-Emergent Avian-Origin Human H7N9 Influenza Disease of Varying Severity in Guangdong Province	Yang, Zi Feng; Mok, Chris Ka Pun; Liu, Xiao Qing; Li, Xiao Bo; He, Jian Feng; Da Guan, Wen; Xu, Yong Hao; Pan, Wei Qi; Chen, Li Yan; Lin, Yong Ping; Wu, Shi Guan; Pan, Si Hua; Huang, Ji Cheng; Ding, Guo Yun; Zheng, Kui;etc	Chen, R C	PLoS One	2015	10(2)	3.535
196	c-MYB regulates cell growth and DNA damage repair through modulating MiR-143	Wang, Wenjun; Wu, Sipei; Shi, Yongsheng; Miao, Yong; Luo, Xiaojun; Ji, Mei; Yao, Kaitai; He, Jianxing	He, JX	FEBS LETTERS	2015	589(5),555-564	3.478
197	Neural respiratory drive and symptoms that limit exercise in chronic obstructive pulmonary disease	Jolley, Caroline; Luo, Yuanming; Steier, Joerg; Sylvester, Karl; Man, William; Rafferty, Gerrard; Polkey, Michael; Moxham, John	Jolley, Caroline	LANCET	2015	385,51-51	46.119
198	Resveratrol induces cell apoptosis in adipocytes via AMPK activation	Chen, Sifan; Zhou, Niman; Zhang, Zili; Li, Wenxue; Zhu, Wei	Chen, S F	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS	2015	457(4),608-613	2.392
199	Chiral Phosphoric Acid Catalyzed Highly	Bi, Bo; Lou, Qin-Xin; Ding, Yu-Yang; Chen, Sheng-Wei; Zhang,	Hu, WH	ORGANIC	2015	17(3),54	6.033

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	Enantioselective Friedel-Crafts Alkylation Reaction of C3-Substituted Indoles to beta,gamma-Unsaturated alpha-Ketimino Esters	Sha-Sha; Hu, Wen-Hui; Zhao, Jun-Ling		LETTERS		0-543	
200	Selective killing of lung cancer cells by miRNA-506 molecule through inhibiting NF-kappa B p65 to evoke reactive oxygen species generation and p53 activation	Yin, M.; Ren, X.; Zhang, X.; Luo, Y.; Wang, G.; Huang, K.; Feng, S.; Bao, X.; Huang, K.; He, X.; Liang, P.; Wang, Z.; Tang, H.; He, J.; Zhang, B.	Zhang, B	ONCOGENE	2015	34(6),691-703	7.401
201	Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis	Lai, Tianwen; Wang, Shaobin; Xu, Zhiwei; Zhang, Chao; Zhao, Yun; Hu, Yue; Cao, Chao; Ying, Songmin; Chen, Zhihua; Li, Wen; Wu, Bin; Shen, Huahao	Shen, H H	Scientific Reports	2015	5	5.525
202	High Incidence of EGFR Mutations in Pneumonic-Type Non-Small Cell Lung Cancer	Liu, Jun; Shen, Jianfei; Yang, Chenglin; He, Ping; Guan, Yubao; Liang, Wenhua; He, Jianxing	He, J X	MEDICINE	2015	94(8)	3.195
203	Effect of tiotropium on neural respiratory drive during exercise in severe COPD	Qin, Yin-Yin; Li, Rui-Fa; Wu, Guo-Feng; Zhu, Zheng; Liu, Jie; Zhou, Cheng-Zhi; Guan, Wei-Jie; Luo, Jia-Ying; Yu, Xin-Xin; Ou, Yang-Ming; Jiang, Mei; Zhong, Nan-Shan; Luo, Yuan-Ming	Luo, YM	PULMONARY PHARMACOLOGY & THERAPEUTICS	2015	30,51-56	2.676
204	Carbocisteine attenuates hydrogen peroxide-induced inflammatory injury in A549 cells via NF-kappa B and ERK1/2 MAPK pathways	Wang Wei; Zheng Jin-ping; Zhu Shao-xuan; Guan Wei-jie; Chen Mao; Zhong Nan-Shan	Zheng, JP	INTERNATIONAL IMMUNOPHARMACOLOGY	2015	24(2),306-313	2.752
205	Prognostic Significance of Programmed Cell Death 1 (PD-1) or PD-1 Ligand 1 (PD-L1) Expression in Epithelial-Originated Cancer A Meta-Analysis	Zhang, Yaxiong; Kang, Shiyang; Shen, Jianfei; He, Jiaxi; Jiang, Long; Wang, Wei; Guo, Zhihua; Peng, Guilin; Chen, Gang; He, Jianxing; Liang, Wenhua	Liang, W H	MEDICINE	2015	94(6)	3.195
206	Neural respiratory drive and breathlessness in COPD	Jolley, Caroline J.; Luo, Yuanming M.; Steier, Joerg; Rafferty,	Jolley, C J	EUROPEAN	2015	45(2),35	7.284

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207	The draft genome, transcriptome, and microbiome of Dermatophagoides farinae reveal a broad spectrum of dust mite allergens	Chan, Ting-Fung; Ji, Kun-Mei; Yim, Aldrin Kay-Yuen; Liu, Xiao-Yu; Zhou, Jun-Wei; Li, Rui-Qi; Yang, Kevin Yi; Li, Jing; Li, Meng; Law, Patrick Tik-Wan; Wu, Yu-Lan; Cai, Ze-Lang; Qin, Hao; Bao, Ying; Leung, Ross Ka-Kit;etc	Zhong, NS	JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY	2015	135(2),539-548	11.476
208	Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial	Zhong, Nan Shan; Sun, Tieying; Zhuo, Chao; D'Souza, George; Lee, Sang Haak; Nguyen Huu Lan; Chiang, Chi-Huei; Wilson, David; Sun, Fang; Iaconis, Joseph; Melnick, David	Zhong, NS	LANCET INFECTIOUS DISEASES	2015	15(2),161-171	19.297
209	FLUOROFENIDONE ATTENUATES TGF-beta(1)-INDUCED LUNG FIBROBLAST ACTIVATION VIA RESTORING THE EXPRESSION OF CAVEOLIN-1	Liu, Jingjing; Song, Cheng; Xiao, Qiming; Hu, Gaoyun; Tao, Lijian; Meng, Jie	Meng, J	SHOCK	2015	43(2),201-207	2.810
210	Glycomic Signatures on Serum IgGs for Prediction of Postvaccination Response	Wang, Jing-Rong; Guan, Wen-Da; Yau, Lee-Fong; Gao, Wei-Na; Zhan, Yang-Qing; Liu, Liang; Yang, Zi-Feng; Jiang, Zhi-Hong	Yang, ZF	Scientific Reports	2015	5	5.525
211	Developing influenza treatments using traditional Chinese medicine	Yang, Zi Feng; Leung, Elaine Lai-Han; Liu, Liang; Jiang, Zhi-Hong; Zhong, Nanshan	Zhong, N	SCIENCE	2015	347(6219),S35-S37	34.921
212	Utility Of Contrast-Enhanced Ultrasound With Sonovue In Biopsy Of Small Subpleural Nodules	Wang, J.	Zeng, Y X	International Journal of Clinical and	2015	191	11.946

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				Experimental Medicine			
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56	重视鲍曼不动杆菌院内感染	谭守勇	2015	其他	广东医学	(12)1797-1798
57	吡嗪酰胺敏感性检测结果应该运用到对结核病治疗	谭耀驹	2015	其他	广东医学	36 (10): 1509-1511
58	糖尿病合并菌阴肺结核诊断评分系统的建立	谭守勇	2015	其他	实用医学杂志	2015 年 06 期 922-924 页
59	Kartagener 综合征误诊为肺结核 1 例	陈品儒	2015	其他	实用医学杂志	2015 年 31 卷 03 期 519-520 页
60	结核专科肺结核合并下呼吸道感染病原菌分布与耐药	谭守勇	2015	其他	实用医学杂志	2015 年 31 卷 01 期 135-136 页
61	重症监护病房耐碳青霉烯类抗生素鲍曼不动杆菌耐药机制研究	黎毅敏	2015	其他	中国感染与化疗杂志	15(3):253-256
62	俯卧位通气的呼吸力学变化趋势	徐远达	2015	其他	国际呼吸杂志	10:791-795
63	中国利福平耐药结核分枝杆菌株 rpoB 基因耐药决定区基因突变的分子特征	刘志辉	2015	其他	实用医学杂志	31(14)2372-2375
64	广州市越秀区及海珠区非结核分枝杆菌流行状况	谭守勇	2015	其他	实用医学杂志	(13)2211-2213

呼吸疾病国家重点实验室

65	护肝药物预防抗结核药物所致肝损伤的作用	谭守勇	2015	其他	实用医学杂志	(13)2194-2196.
66	臭灵丹乙醇提取物体外抑制甲 1 型流感病毒实验研究	王新华	2015	其他	昆明医科大学学报	36（2）：4-6.
67	臭灵丹抗甲 1 型流感病毒 FM1 株感染小鼠的药效学研究	王新华	2015	其他	广州中医药大学学报	32(2）：291-294.
68	白藜芦醇对常见肠道病毒抑制作用的实验研究	王新华	2015	其他	新中医	47(2):222-224
69	Human alveolar epithelial type II cells in primary culture.	黎毅敏	2015	其他	Physiol Rep.	2015 Feb 12;3(2). pii: e12288.
70	ICU 患者血流感染耐碳青霉烯类鲍曼不动杆菌同源性分析	黎毅敏	2015	其他	中国感染控制杂志	14（9）577-581
71	改良的自主呼吸实验在机械通气的老年慢性阻塞性肺疾病患者撤机过程中的应用	桑岭	2015	其他	实用医学杂志	31（13）
72	重组大肠杆菌表达的 Ber e 1 纯化工艺中内毒素的去除	陶爱林	2015	其他	热带医学	15(5):14-17
73	H7N9 流感病毒 HA、NA 蛋白的抗原表位预测及其 HLA-II 类等位基因的相关性分析	何颖	2015	其他	中国免疫学杂志	31(1):16-21
74	俯卧位通气的呼吸力学变化趋势	徐远达	2015	其他	国际呼吸杂志	(10):791-795

呼吸疾病国家重点实验室

75	脓毒症预后影响因素分析及预后价值评估	黎毅敏	2015	其他	中国中西医结合急救杂志	22(2):118-123
76	结核病院呼吸道分离鲍曼不动杆菌构成比及耐药趋势分析	覃红娟	2015	其他	广东医学	第 36 卷第 12 期
77	结核重症监护室鲍曼不动杆菌感染及耐药产生原因分析	李德宪	2015	其他	广东医学	第 36 卷第 12 期
78	医院感染不动杆菌属控制进展	谭守勇	2015	其他	广东医学	第 36 卷第 12 期
79	重视鲍曼不动杆菌院内感染	谭守勇	2015	其他	广东医学	第 36 卷第 12 期
80	Human alveolar epithelial type II cells in primary culture	黎毅敏	2015	其他	Physiol Rep	3(2)
81	AKT 信号转导途径在尼古丁促进大鼠气道平滑肌细胞增殖中的作用		2015	其他	广东医学	2015 年 06 期 846-849
82	肺炎链球菌表面黏附素 A（PsaA）蛋白抗原表位的预测、筛选及确定	袁竹青（周国瑛组）	2015	其他	中山大学学报（医学科学版）	36:55-64
83	重组大肠杆菌表达的 Ber e 1 纯化工艺中内毒素的去除	陶爱林	2015	其他	热带医学	15(5):14-17
84	H7N9 流感病毒 HA、NA 蛋白的抗原表位预测及其 HLA-II 类等位基因的相关性分析	何颖	2015	其他	中国免疫学杂志	31(1): 16-21

呼吸疾病国家重点实验室

85	新一代纳米复合骨填充材料在 60 例胸腰椎结核手术中的应用	张强	2015	其他	中国防痨杂志	37(03)249-255
86	体外γ-干扰素释放试验在儿童结核病密切接触者筛查结核病的作用	谭守勇	2015	其他	实用医学杂志	31(15)2463-2466

呼吸疾病国家重点实验室

（六）访问学者

本着“请进来，走出去”的人才培养原则，本实验室在积极引进人才和邀请国内外知名专家来室讲学交流的同事，也逐步增加自我造血功能，着意加大年轻专业人才的培训力度，为实验室的可持续发展提供人才保证。本年度共新派出 8 位青年学术骨干到国外进行培训学习，目前已有 7 位同志学成归来，在岗位上作出贡献。

学者姓名	赴外研究时间	访问机构	研究课题名称
陈如冲	2014.02-至今	加拿大 Firestone 研究所	固有免疫 2 群淋巴细胞（ILC2）在支气管哮喘中的作用机制
江　倩	2014.10-2015.10	美国约翰霍普金斯大学	肺静脉平滑肌钙通道调控机制研究
陈　愉	2015.01-2016.01	美国 Henry Ford Health System	支气管镜的学习与交流
杨子峰	2015.03-2015.06	美国 Saint Jude 儿童研究医院	树鼩和雪貂流感动物模型的比较研究
巨春蓉	2015.01-2016.10	加拿大多伦多综合医院	肺移植患者术后内科并发症的诊治
陈莉延	2015.04-2015.10	英国赫尔大学/赫尔东约克郡医学院	慢性咳嗽的临床诊疗和科研
桑　岭	2015.01-2016.06	加拿大多伦多综合医院	肺移植与 ICU 相关的临床与科研
徐　鑫	2015.01-2016.06	加拿大多伦多综合医院	肺移植相关的外科技术

呼吸疾病国家重点实验室

杨子峰

江倩与导师们

陈莉延

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（七）学术交流与开放共享

1. 举办会议、学习班

2015 年实验室主办学术会议共 12 个，其中国际级会议 4 个，国家级会议 8 个；举办继续教育培训班 18 个，其中具有国家级学分的培训班共 5 个。

实验室主办国际学术会议一览表

序号	会议名称	会议类型	举办时间	举办地点
1	肺血管国际学术会议	国际级	1 月 14-18 日	广州
2	2015 中美日新国际咳嗽高峰论坛		8 月 22 日	杭州

3	冷泉港亚洲•呼吸系统发育与病理生理学会议		11 月 16-20 日	苏州
4	第一届国际无管微创胸外科学术会议		12 月 7-11 日	广州

实验室主办国家级等学术会议一览表

序号	会议名称	会议类型	举办时间	举办地点
1	2015 全国肺功能临床应用与规范化培训学术会议 学习班	国家级	3 月 28 日	广州
2	广东省医学会第一次胸外科学学术会议		5 月 15 日、17 日	广州
3	第一届全国腔镜气管手术隆突研讨会		5 月 16 日、17 日	广州
4	第八届中国咳嗽论坛		8 月 6-9 日	内蒙古
5	食物过敏临床诊治研讨会		11 月 18 日	广州
6	COPD 日活动：名医大讲堂-早防早治，呼吸畅顺		11 月 19 日	广州
7	2015 年第三届（广州）无创通气学术峰会		11 月 19-20 日	广州
8	2015 年呼吸内科肺部肿瘤诊治研讨会		11 月 14-16 日	广州

呼吸疾病国家重点实验室

国内外会议图片

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<tr><td>2015 中美日新国际咳嗽高峰论坛</td><td>冷泉港亚洲•呼吸系统发育与病理生理学会议</td></tr>
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<tr><td>第一届国际无管微创胸外科学术会议</td><td>全国肺功能临床应用与规范化培训学术会议</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>首届静脉血栓栓塞病防治与红外热成像检测技术学习班</td><td>第八届中国咳嗽论坛</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>COPD 日活动：名医大讲堂-早防早治，呼吸畅顺</td><td>2015 年呼吸内科肺部肿瘤诊治研讨会</td></tr>
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呼吸疾病国家重点实验室

实验室举办继续教育学习班一览表

序号	日期	类型	学习班名称	参加人数
1	3 月 27-31 日	国家级	呼吸系统疾病诊疗技术新进展学习班	1035
2	7 月 2-6 日	国家级	全国肺功能检查基础与临床新进展学习班	118
3	8 月 30 日-9 月 3 日	国家级	呼吸和危重症监护医学学习班	145
4	11 月 17-21 日	国家级	胸外科微创伤手术学习班	448
5	8 月 13-17 日	国家级	支气管哮喘诊治新进展	266
6	6 月 5-12 日	省级	变态反应性疾病实验检测技术及临床应用新进展学习班	240
7	9 月 7-14 日	省级	支气管镜护理技术及其新进展	120
8	1 月 19-25 日	市级	全国变态反应性疾病诊疗培训班	96
9	8 月 11-18 日	市级	儿童呼吸系统常见疾病诊治新进展	299
10	3 月 25-31 日	市级	呼吸系统疾病诊疗技术新进展学习班	391
11	9 月 17-20 日	市级	药物临床试验法规与技术学习班	--
12	11 月 20-22 日	市级	2015 年护理肺康复学习班	252

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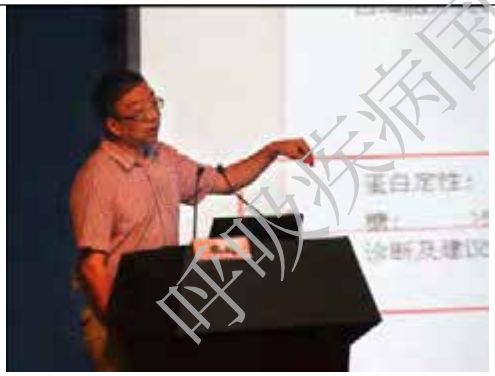
13	11 月 15-22 日	市级	慢性阻塞性肺疾病（COPD）诊疗新进展与管理学习班	354
14	11 月 16-22 日	市级	全国变态反应性疾病诊疗培训班	--
15	7 月 19-26 日	市级	肺功能临床应用与规范化培训学习班	352
16	8 月 26 日-9 月 2 日	市级	体外膜肺氧合（ECMO）技术的临床应用	119
17	12 月 14-21 日	市级	晚期肺癌及其特殊人群的优化治疗与全程管理	95
18	11 月 19 日-26 日	市级	变态反应性（过敏性）疾病实验检测技术新进展学习班	265

呼吸疾病国家重点实验室

学习班图片

	
2015 年过敏性疾病诊治新技术学习班暨全国第十六届标准化变应原特异免疫治疗培训班	2015 呼吸内科肺部肿瘤诊治研讨会暨晚期肺癌及其特殊人群的优化治疗与全程管理学习班

	
2015 呼吸系统疾病诊疗技术新进展学习班	首届体外膜肺（ECMO）在呼吸衰竭临床应用学习班
	
2015 年“支气管哮喘诊治新进展学习班暨“ 儿童呼吸系统常见疾病进展交流会‘通知	国际肺血管病研究院(PVRI)第八届年度肺血管病大会
	
呼吸和危重症监护医学学习班	慢性阻塞性肺疾病进展与呼吸治疗康复学习班

呼吸疾病国家重点实验室

2. 外出交流

2015 年实验室共 60 人次参加国内外各类会议，进行大会发言或壁报交流，其中参加国际会议 49 人次、国内会议 60 人次，参会足迹遍布全球，包括美国、加拿大、欧洲各国、韩国、东南亚以及中国各地包括北京、上海、广州、杭州、苏州、武汉、郑州、成都等。

实验室人员参加国际学术交流一览表

报告人	国际会议名称	参会形式	时间	地点
王健	第八届 PVRI 年度肺血管疾病国际会议	特邀报告	2015 年 1 月	
陈豫钦	八届 PVRI 年度肺血管疾病国际会议	壁报交流	2015 年 1 月	
陈凌	Keystone Symposium 会议	口头报告	2015 年 4 月	美国
王健	美国胸科学会国际会议（ATS）	特邀报告	2015 年 5 月	美国
白春学	美国胸科学会国际会议（ATS）	特邀报告	2015 年 5 月	美国
李靖	EAACI Congress 2015	交流论文	2015 年 6 月	西班牙
杨朝崴	EAACI Congress 2015	特邀报告	2015 年 6 月	西班牙
李靖	学术访问	特邀报告	2015 年 7 月	加拿大
张孝文	2015 佛罗伦萨国际嗓音大会	参会	2015 年 8 月	佛罗伦萨
白春学	ERS（欧洲呼吸协会年会）	特邀报告	2015 年 9 月	荷兰
郑则广	ERS（欧洲呼吸协会年会）	参会	2015 年 9 月	荷兰
冯木林	ERS（欧洲呼吸协会年会）	壁报讨论	2015 年 9 月	荷兰
沈华浩	ERS（欧洲呼吸协会年会）	大会报告、壁报交流	2015 年 9 月	荷兰
胡文辉	第十届中日药物分子设计与开发研讨会	特邀报告	2015 年 9 月	
张孝文	2015 美国耳鼻咽喉头颈外科学年会	参会	2015 年 9 月	美国
白春学	WCLC（世界肺癌大会）	特邀报告	2015 年 9 月	美国
王健	第二十六届长城国际心脏病学会议	特邀报告	2015 年 10 月	中国北京
冯立强	国际疫苗学会第九届年会	壁报交流	2015 年 10 月	韩国
潘蔚绮	国际疫苗学会第九届年会	口头报告	2015 年 10 月	韩国
李楚芳	国际疫苗学会第九届年会	壁报交流	2015 年 10 月	韩国
陈凌	国际疫苗学会第九届年会	特邀报告	2015 年 10 月	韩国
李靖	XXIV World Allergy Congress (WAC 2015)	特邀报告	2015 年 10 月	韩国
杨朝崴	XXIV World Allergy Congress (WAC 2015)	交流论文	2015 年 10 月	韩国
鲜墨	XXIV World Allergy Congress (WAC 2015)	交流论文	2015 年 10 月	韩国

呼吸疾病国家重点实验室

报告人	国际会议名称	参会形式	时间	地点
王万钧	XXIV World Allergy Congress (WAC 2015)	交流论文	2015 年 10 月	韩国
白春学	Annual Academic Sessions of the Sri Lanka College of Pulmonologists	特邀报告	2015 年 10 月	斯里兰卡
白春学	CHEST(美国胸科医师学会年会)	特邀报告	2015 年 10 月	美国
杨一峻	ISEV Therapeutic Workshop 2015 Application of Therapeutic Evs in the Patients	大会报告	2015 年 10 月	新加坡
钟南山	冷泉港亚洲会议-呼吸系统发育生物学	大会主席、特邀报告	2015 年 11 月	中国苏州
陈凌	冷泉港亚洲会议-呼吸系统发育生物学	特邀报告	2015 年 11 月	中国苏州
张必良，任晓帅，尹梦回，刘承丽，熊薇	第三届广州核酸国际论坛	参会	2015 年 11 月	中国广州
赵军岭 赵昕	冷泉港亚洲会议	参会	2015 年 11 月	中国苏州
沈华浩 陈志华	2015 苏州冷泉港亚洲会议	特邀报告、壁报交流	2015 年 11 月	中国苏州
沈华浩 陈志华	2015 首届海峡两岸四地呼吸病高峰论坛	大会主席、大会报告	2015 年 11 月	中国杭州
白春学	APSR（亚太呼吸病协会年会）	特邀报告	2015 年 11 月	马来西亚
陈小平 秦莉 刘权 杨一峻	冷泉港亚洲会议-呼吸道系统的发育与病理生理学	大会报告	2015 年 11 月	中国苏州
丁克	新西兰奥克兰大学莫里斯•威尔金斯研究中心	特邀报告	2015	新西兰
丁克	第十届药物化学亚洲联合会-2015 国际药物化学研讨会	特邀报告	2015	

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实验室人员参加国内学术交流一览表

报告人	国内会议名称	参会形式	时间	地点
白春学	中华医学会呼吸病年会 第十六次全国呼吸病学学术会议	特邀报告	2015/09/03-06	境内
白春学	中国非公立医疗机构协会物联网医疗专业委员 会成立大会暨物联网医疗高峰论坛	特邀报告	2015/11/05-07	境内
白春学	第二届慢性气道疾病管理暨呼吸危重症与疑难疾病 诊治新进展学习班和全国医师定期考核呼吸和危重 症专业教材、题库和考纲审稿会议	特邀报告	2015/10/15-18	境内

报告人	国内会议名称	参会形式	时间	地点
白春学	关于召开提升协会行业服务与管理能力座谈会会议	特邀报告	2015/8/29	境内
冯立强	2015 年全国病毒学学术年会暨武汉现代病毒学国际研讨会	大会发言	11.23-11.25	境内（武汉）
陈凌	海峡医学会会议，国自然基金区域免疫小鼠交流会	特邀报告	11.28-11.30	境内（杭州）
刘权 杨一峻	2015 年细胞治疗大会	参会	2015 年 10 月 18-22 日	四川成都
刘广杰 刘权 杨一峻 肖宏奎	第五届全国免疫学研讨会	大会报告	2015 年 8 月 14-16 日	河南郑州
陈小平，秦莉，覃丽梅，陶铸，李姣姣，	下一代 CAR-T 与免疫细胞治疗研讨会	大会报告	2015 年 11 月 7 日	上海
邓方阁	首届“治未病”发展论坛	邀请报告	2015 年	境内
邓方阁	第二届中国太极血管病学论坛	邀请报告	2015 年	境内
邓方阁	南国代谢与血管病论坛	邀请报告	2015 年	境内
邓方阁	全国第十五届红外加热暨红外医学发展研讨会	邀请报告	2015 年	境内
邓方阁	第四届全国红外成像检测技术中医应用学习班	邀请报告	2015 年	境内
邓方阁	华南肺血管病会议	邀请报告	2015 年	境内
邓方阁	中华医学会第十五届全国呼吸病学学术会议	壁报论文交流	2015 年	境内
沈华浩、李雯、陈志华、应颂敏、楼剑、朱忱、毛园园等	中华医学会呼吸病学年会-2015 第十六次全国呼吸病学学术会议	大会报告、壁报交流	2015.09	境内
李雯、赖天文	2015 全国慢性阻塞性肺疾病学术会议	大会报告、讨论交流	2015.10	境内
陶爱林	2015 中法霍夫曼免疫研究所学术报告会	特邀报告	2015.12.8	境内
邹泽红，王珊，何颖	2015 中法霍夫曼免疫研究所学术报告会	参会	2015.12.8	境内
陶爱林，邹泽红，王珊，何颖，张俊艳，李文，黄于艺，陈惠芳	食物过敏临床诊治研讨会	参会	2015.11.18	境内
任晓帅，尹梦回，刘承丽，周小晓	表观遗传学经验交流会	参会	2015 年 8 月	境内

呼吸疾病国家重点实验室

报告人	国内会议名称	参会形式	时间	地点
李潇、刘文宽、吴宏楷、周志超、田新贵	第十一届全国病毒学学术年会暨第六届武汉现代病毒学国际研讨会	论文交流	2015 年 10 月 23-2015 年 10 月 25	境内
李潇、周志超、田新贵	广东省实验动物学会 2015 年学术年会	参会	2015 年 11 月 15-2015 年 11 月 17	境内

呼吸疾病国家重点实验室

3.受邀来访

本年度，实验室特邀多名国内外知名专家来访并作学术交流讲座、共商合作。此外，实验室重视与国内外各大科研机构的交流合作，先后与加拿大 Firestone、美国阿拉巴马州哈森阿尔法生物技术研究院、英国皇家学院、加拿大湖首大学/雷湾地区研究院等发达国家或发达地区的研究机构进行密切的合作交流，以期促进资源互通、信息共享，进一步推进实验室与国际水平接轨。

实验室来访学者一览表

序号	来访时间	来访学者	单位	讲学题目
1	2015/1/4	张海波和 Arthur S. Slutsky	多伦多大学 St. Michael's 医院	Recent advances in ARDS; Midkine mediates mechanical ventilation-induced lung fibrosis
2	2015/1/13	赵金存		无
3	2015/1/22	白春学	复旦大学中山医院	物联网医学发展计划
4	2015/1/30	吴殿青	耶鲁大学正教授、南京大学特聘教授	New insights into cell migration regulation-leading to potential new therapeutic targets for treating lung fibrosis
5	2015/2/5	苏枭	中国科学院上海巴斯德研究所	α7 nAChR regulates Influenza A Virus-induced Acute Lung Infection and Inflammation

呼吸疾病国家重点实验室

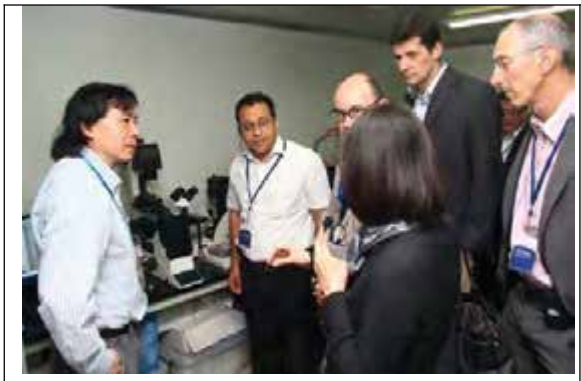
序号	来访时间	来访学者	单位	讲学题目
6	2015/2/11	Dora	法国领事馆科技部	无
7	2015/4/3	董晨	清华大学医学院	Th17 细胞、炎症及肿瘤的关键调节者
8	2015/4/14	代表团	法国科学与技术高等学院	无
9	2015/4/27	王建飞	国际AAALAC认证委员会	AAALAC 在亚洲开展认证的简介，为什么要认证
10	2015/5/6	赵金存	引进人才	呼吸道管状病毒的致病机理及动物模型研究
11	2015/5/21	韩健	美国阿拉巴马州哈森阿尔法生物技术研究院	免疫组库技术在医学研究中的应用
12	2015/5/27	王凯	美国南加州大学 Zilkha 神经遗传所	基因组大数据解读-全基因组测序的生物信息学方法
13	2015/6/15	Dong Lin-Wang	圣-路易斯大学	Update on PAH evaluation and hemodynamic assessment
14	2015/6/19	陈则	上海生物制品研究	流感病毒暨流感疫苗研究
15	2015/6/19	李鹏	中国科学院广州生物医药与健康研究院	人源化小鼠模型的研发与应用
16	2015/6/29	Malik Peiris	英国皇家学院院士，香港大学公共卫生学院	中东呼吸综合征冠状病毒的出现、传播与控制
17	2015/6/30	周国飞	芝加哥伊利诺伊大学儿科系、伊利诺伊大学肿瘤中心	Role of miR-17~92 in Pulmonary Hypertension

呼吸疾病国家重点实验室

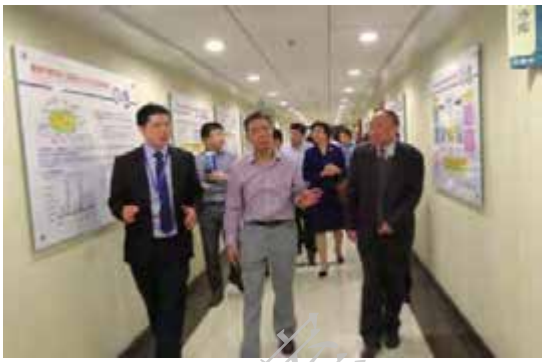
序号	来访时间	来访学者	单位	讲学题目
18	2015/7/7	Mark Inman	McMaster University、Firestone Institute for Respiratory Health	喘的气道高反应性:根本机制及其临床应用
19	2015/8/20	余鹰	中科院上海营养所	PGE2 与哮喘和肺血管重塑
20	2015/9/10	宁璞	北京诺禾致源生物信息科技有限公司	扩增子和宏基因组测序在疾病研究中的应用
21	2015/11/13	赵友阳	芝加哥伊利诺伊大学医学院药理学系	Novel mechanisms of severe pulmonary vascular remodeling and pulmonary arterial hypertension
22	2015/11/19	Mitchell Albert	加拿大湖首大学、雷湾地区研究院	利用超极化惰性气体开展肺的功能性磁共振成像研究
23	2015/11/25	高霞	美国 Duke 大学	肺再生与肺干细胞研究
24	2015/11/26	Kian Fan Chung	英国帝国理工学院	New Treatments for Severe Asthma and Need for New Biomarkers
25	2015/12/4	田志刚	中国科学技术大学生命科学院	肺脏区域免疫与肺部疾病
26	2015/12/10	徐华强	中国科学院上海药物所	Structure and Drug Discovery of Glucocorticoid Receptor for Inflammatory Diseases
27	2015/12/22	付民桂	美国密苏里大学堪萨斯分校	MCPIP1: a Novel Regulator of Inflammation,

呼吸疾病国家重点实验室

序号	来访时间	来访学者	单位	讲学题目
				Anti-virus and Acute Lung Injury



法国科学与技术高等学院代表团到访



出访浙江大学附属第一医院传染病协同创新中心

英国皇家学院院士，香港大学公共卫生学院院长 Malik Peiris 交流访问

美国 Duke 大学高霞博士学术交流

呼吸疾病国家重点实验室

4. 网络平台、期刊

2015 年重点实验室网络工作建设主要集中于实验室网站的改版和实验室微信平台的建设和维护，纸媒方面的进展为常态化出版《通讯》。

（1）网站

实验室旧版网站在 2010-2011 年迎评期间建立，为适合当时实验室工作需要，设立新闻公告、实验室概况、实验室学术队伍人员设置和开放基金、开放课题专栏等一系列丰富内容并使用当时最适合的页面风格展示。经过 5 年的发展，实验室进行了充实的扩展，原版的网站框架难以适应现在实验室现状，因此在

2015 年对实验室网站进行改造升级。2015 年 12 月，改版工作进入冲刺阶段，新网站的框架和板式基本确定，现在正进行资料的整理和上传。新版网站将保留绿色主题背景风格为主，对网页框架进行了改动，主页进行了大幅度的精简，新引进学术活动日历提示部件，精简了主页一部分栏目并将其收于导航栏中，新增了其余一些专题板块等其余一些细节修改。新版网站将于评估前投入使用。

（2）微信公众平台

本年度，实验室新建立微信公众平台，主要面向实验室基础研究人员和临床医生，推送实验室最新科研快报、学术讲座和实验室新闻公告。目前公众号关注人数为 200 余人，有一定的影响力基础，但还需要进一步发展和扩大影响力。

呼吸疾病国家重点实验室

（3）《通讯》

本年度，重点实验室以季刊形式常态化出版《通讯》，本年度已印出三期，前两期已在 8 月中期 PI 大会上进行派发。《通讯》以各个课题组科研秘书/通讯员网络为基础，通过约稿和课题组自觉投稿的形式，将各个课题组的科研进展、技术创新、发表文章、学术交流等新闻动态作出综合报道。同时通讯稿会在实验室网站及微信平台作同步推送。

《通讯》共设置八大模块，包括科研进展、人才引进、亮点文章、创新技术、开放交流、综合报道、研究生园地、产学研合作，全面呈现呼吸疾病国家重点实验室各个领域的发展。

呼吸疾病国家重点实验室

5. 开放课题

2015 年 4 月，实验室完成了 2014 年 12 项开放课题的首期拨款。2015 年度开放课题，经向 PI 公开征集项目，共收到开放课题申请书 23 份，经过专家评审，最终确定资助 21 个项目，资助金额共 111 万。本年度改革开放课题资助方案，采取的资助办法为：评审项目申报书进行前期资助 2-10 万不等，后根据项目中期发展、结题成果的综合评分继续后期奖励性资助 10 万元。

呼吸疾病国家重点实验室（2015-2016 年度）开放课题立项统计表

资助号	项目名称	申请单位	申请人	合作 PI
SKLRD-2016KF-001	外源性线粒体治疗慢性阻塞性肺疾病的实验研究	华中科技大学	胡清华	王健
SKLRD-2016KF002	控制炎症细胞凋亡缓解慢性气道炎症的机制研究	浙江大学	应颂敏	沈华浩
SKLRD-2016KF003	基于组分抗体作为变应性呼吸疾病脱敏疗效临床生物学评估指标的应用研究	苏州大学附属儿童医院	郝创利	孙宝清
SKLRD-2016KF004	CHD1L 基因在肺腺癌恶性进展中的作用和分子机制研究	中山大学-肿瘤防治中心	谢 丹	蒋义国
SKLRD-2016KF005	抗中性粒细胞胞浆抗体活化中性粒细胞在闭塞性细支气管炎发生发展机理与临床应用的研究	广州医科大学第一附属医院儿科	陈德晖	牛学锋
SKLRD-2016KF006	延胡索酸水合酶（FH）通过调节 Notch 信号通路对表观遗传的调控在肺癌发展和转移中的作用	上海交通大学附属第一人民医院	蒋玉辉	李瑾

呼吸疾病国家重点实验室

资助号	项目名称	申请单位	申请人	合作 PI
SKLRD-2016KF007	利用创新糖组学技术研究流感肺炎 IgG 糖基化特征及其对炎症调节机制的研究	澳门科技大学	王静蓉	杨子峰
SKLRD-2016KF008	慢性阻塞性肺疾病合并睡眠呼吸暂停（重叠综合征）患者夜间呼吸中枢驱动	National Heart and Lung Institute, Imperial College, London, UK	Micheal I Polkey	罗远明
SKLRD-2016KF009	Breg 细胞在 COPD 气道炎症中的作用	中山大学孙逸仙纪念医院呼吸内科	陈 瑞	陈荣昌
SKLRD-2016KF010	广州空气污染对呼吸系统健康的急性影响研究	广州市环境监测中心站	曾燕君	赖克方
SKLRD-2016KF011	$P16^{INK4a}$ 基因甲基化对多原发性肺癌早期诊断和预后的研究	广州医科大学第一附属医院科研科	关玉宝	何建行
SKLRD-2016KF012	TPCs 介导 Ca2+在低氧性肺动脉高压肺动脉平滑肌细胞增殖中的作用	湖南省马王堆医院	蒋永亮	冉丕鑫
SKLRD-2016KF013	慢阻肺合并支气管扩张患者气道微生物菌群结构及宿主上皮细胞的适应性变化研究	郑州大学第一附属医院	高永华	陈荣昌
SKLRD-2016KF014	基 于BIPES 法分析气道微生物群落信息与 COPD 急性加重的关系	广州南方医院呼吸与危重症医学科	苏 瑾	陈荣昌
SKLRD-2016KF015	TRPM2 通道对 PM2.5 暴露致慢性咳嗽豚鼠中枢致敏机制的研究	东南大学医学院生理系	董 榕	赖克方

呼吸疾病国家重点实验室

资助号	项目名称	申请单位	申请人	合作 PI
SKLRD-2016KF016	以减毒疟原虫为载体的肺癌疫苗研发	广州中科蓝华生物科技有限公司	童 英	陈小平
SKLRD-2016KF017	我国常见过敏原分子诊断试剂研制及产业化	广州呼研所生物技术有限公司	李晨阳	孙宝清
SKLRD-2016KF018	心跳骤停与心肺复苏后家猪急性肺损伤的呼吸病理生理学改变及超早期氢气对其保护作用研究	中山大学孙逸仙纪念医院	杨正飞	黎毅敏
SKLRD-2016KF019	体表膈肌肌电检测技术在慢性阻塞性肺疾病肺康复临床评估中的应用	南方医科大学珠江医院呼吸内科	陈 新	陈荣昌
SKLRD-2016KF020	外周血重金属含量与肺癌相关性研究	广东省靶向肿瘤干预与防控研究院	张积仁	吕嘉春
SKLRD-2016KF021	循环系统外泌体(exosomes)中 MicroRNA 作为无创肿瘤筛查和诊断标志物的研究	广州洪祥生物医药科技有限公司	王 勇	谭守勇

呼吸疾病国家重点实验室

6.公众开放

遵照科技部《关于开展国家重点实验室公众开放活动的通知》精神，实验室本年度举办了多次对外公众开放活动。本年度，实验室继续参与由市科技局牵头、广州市科学技术协会主办的“广州科普自由行”活动，先后组织了5批市民参观实验室；此外，由实验室主办的院士视频大查房从2013年开始举办至今，已发展成系列活动，与全国各地各级（包括基层医院）医疗机构现场连线会诊疑难病例，更吸引了上百名医疗机构、科研机构的工作人员前来参观。

2015年呼吸疾病国家重点实验室对外开放活动一览表

日期	活动名称
2015/3/18	第二届中国医院协会“拓峰行”活动
2015/3/21	呼吸疾病国家重点实验室科普一日游
2015/4/22	视频大查房
2015/5/5	世界哮喘日义诊活动
2015/5/23	呼吸疾病国家重点实验室科普一日游
2015/6/10	拓峰行活动
2015/6/24	“名院名家面对面：院士大查房”万人网络公开课
2015/7/22	院士视频大查房
2015/7/25	呼吸疾病国家重点实验室科普一日游
2015/7/29	拓峰行活动
2015/8/26	院士视频大查房
2015/9/26	呼吸疾病国家重点实验室科普一日游
2015/11/29	呼吸疾病国家重点实验室科普一日游

呼吸疾病国家重点实验室

	
名院名家面对面院士大查房--国际篇	拓峰行活动
	
“广州科普一日游”市民参观活动	世界哮喘日义诊活动

呼吸疾病国家重点实验室

（八）JTD 编辑部

在医院、呼研所和重点实验室的支持下，在编委会团队的辛勤工作下，JTD 在 2015 年全年出版了诸多热点专题，涵盖雾霾，房颤，胸膜疾病诊疗研究的进展及争议话题，呼吸睡眠及肺通气等。

其中，2015 年 1 月份刊出的“雾霾，健康与疾病”专刊，由 JTD 主编钟南山院士，副主编 Kian Fan Chung 教授(来自英国帝国理工学院国立心肺研究所)，编委 Junfeng (Jim) Zhang 教授（来自美国杜克大学）共同担任客编，本期专刊主要描述环境污染对呼吸系统的潜在危害。专刊中的西方流行病学数据，是室外空气污染对呼吸系统健康影响的优秀报告，对于中国现状及空气污染所致呼吸系统疾病的诊治有着深远意义。

胸腔积液是许多肺部疾病及全身性疾病的常见表现。然而对于胸腔疾病诊疗进展的报告却非常匮乏，远远少于其他常见肺部疾病。故 6 月的专刊报告了胸膜疾病的最新进展及相关的争议话题，以期对临床医生有所启发。

在 2015 年 6 月，JTD 非常荣幸地取得了第一个影响因子 1.783 分（也即 JTD 在 2014 年的影响因子）。此外，JTD 在 PubMed 中月检索次数由 2014 年 11 月的五万上升至了 2015 年 11 月的九万。

呼吸疾病国家重点实验室

（九）产学研平台

经过多年的发展，呼吸疾病国家重点实验室产学研平台建立团队、平台、整合技术，创办了“广东华南联合疫苗开发院有限公司”，5 项疫苗品种研发进展顺利、并已成功新增融资 3500 万元；以多项呼吸道病毒荧光 PCR 试剂技术与阳普医疗等共同出资 3000 万元创立了“广东和信健康科技有限公司”等；建立了“中药质量研究及评价中心”、“生物安全技术和产品评价中心”，将所建立的中药效应物质分离评价技术、病原分离培养鉴定技术对外提供服务，目前已承接相关服务项目超过 10 项、总金额超过 200 万元。郭绍华团队在国内率先研发出中空管状滤膜全新风机及申报相关专利、该成果转由郭绍华领衔的广东风和洁净工程有限公司进行产业化、目前已经量产及进入市场销售并获得用户好评；周荣、吴国庆等联手设计和发明了一系列“单人隔离消杀院感防控技术和产品”获得“广州南山安捷健康产业投资中心”和“广州瑞发一号投资管理中心”的认可和投资、成立了“广州南山安捷健康科技有限公司”进行该成果转化和产业化、预计会创造出很好的社会经济效益、特别是填补国内外院感防控实用技术和产品的空白。

2015 年产学研发展的里程碑，10 月 14 日下午，广州医科大学/广州呼吸疾病研究所/广州呼研所医药科技有限公司联合建设的呼吸疾病国家重点实验室产学研基地园区在广州开发区科学城盛大举行启用仪式。

参会人员有：中国工程院院士、呼吸疾病国家重点实验室主任钟南山教授、广东省科

技厅钟小平副厅长、广州开发区管委会张晖总经济师、广州开发区科技与知识产权局刘石局长、澳门科技大学刘良校长、广州医科大学王新华校长、上海安捷投资集团张晓雷董事长等政企事业单位的领导，以及来自香港、台湾、澳门、北京、上海、广州、深圳、天津、宁波、湖北、山东、江苏、佛山、珠海、东莞等全国各地的政府部门、医疗机构、大学院校、研究院所、银行、企业、媒体等单位累计近 500 人参加。

广州呼研所医药公司是一个依托于广州呼吸疾病研究所、呼吸疾病国家重点实验室和广州医科大学的医药健康孵化器企业，也是响应党和国家“大众创业，万众创新”号召的积极先行者，在医药领域产学研结合与成果转化上具有创新性。

入园企业揭牌仪式上，首批入园的 30 多家企业和机构集体崭新亮相并签署多项重要合作协议。其中，广州开发区科技与知识产权局与广东省南山医药创新研究院签订了进一步支持钟院士团队创业的协议。上海安捷集团与钟南山院士团队及广州医大完成了产学研全方位战略合作协议签约。澳门科技大学中药质量研究国家重点实验室与广州医科大学中西医结合研究所、广东省南山医药创新研究院就设立“粤澳中药质量检测评价中心”进行了共同签约。山东乐康电器科技有限公司与广州呼研所医药科技有限公司签订了关于空气净化产品开发的合作协议。广东省南山医药创新研究院等 11 家机构联合倡议发起成立“南山健康呼吸技术创新和产业化联盟”。此外，广州呼吸疾病研究所、广东出入境检验检疫局检验检疫技术中心、广东省南山医药创新研究院联合共建“生物安全产品测试中心”揭牌仪式，共同打造华南生物安全的坚固城墙。

呼吸疾病国家重点实验室

三、实验室队伍建设

（一）引进人才

赵金存

2015 年 5 月 6 日，呼吸疾病国家重点实验室新引进赵金存博士

赵金存博士，1978 年 8 月出生于天津。2002 年本科毕业于北京大学医学部基础医学系，2007 年获北京大学医学部免疫学系免疫学博士；2007 年 8 月至 2012 年 8 月于美国爱荷华大学微生物系开展博士后研究；2012 年 9 月任美国爱荷华大学微生物系助理研究科学家（Assistant Research Scientist）。赵金存主要研究呼吸道病毒及其发病

机制，近年来在 J Clin Invest、J Exp Med、Proc Natl Acad Sci U S A、PLoS Pathog、J Immunol、J Virol 等著名杂志以第一或通讯作者发表论文近 30 篇。

赵金存于 11 年前在北京参与了 SARS 冠状病毒（SARS-CoV）的研究和防控，2007 赴美国后，继续呼吸道冠状病毒和甲型流感病毒研究（IAV）研究，近年又投入到中东地区新发 MERS 冠状病毒（MERS-CoV）的研究。赵金存将于 2015 年下半年回国，全职加入广州医科大学/广州呼吸疾病研究所/呼吸疾病国家重点实验室工作。

金方

研究员、博士生导师，1987 年毕业于中国药科大学药剂学专业，曾在上海医药工业研究院长期从事药物新制剂的研究，期间曾赴美国 Virginia Commonwealth University 师从 Peter Byron 教授进行吸入制剂的博士后研究，曾任“创新药物与制药工艺国家重点实验室”副主任、上海呼吸系统药物工程技术研究中心主任。现为广州医科大学特聘教授、呼吸疾病国家重点实验室 PI、广州健康元呼吸药物工程技术有限公司总经理、健康元药业集团首席科学家、第九、十届国家药典委员会委员、中国药学会药剂专业委员会委员。

呼吸疾病国家重点实验室

（二）研究生教学情况

2015 年实验室毕业硕士研究生 46，博士研究生 23。新招硕士研究生 54，博士研究生 20。出站博士后 3 人，在站博士后 13 人。。

	毕业	新招	在读	硕转博
硕士研究生	38+8	40+14	109+37	7
博士研究生	18+5	18+2	36+35	

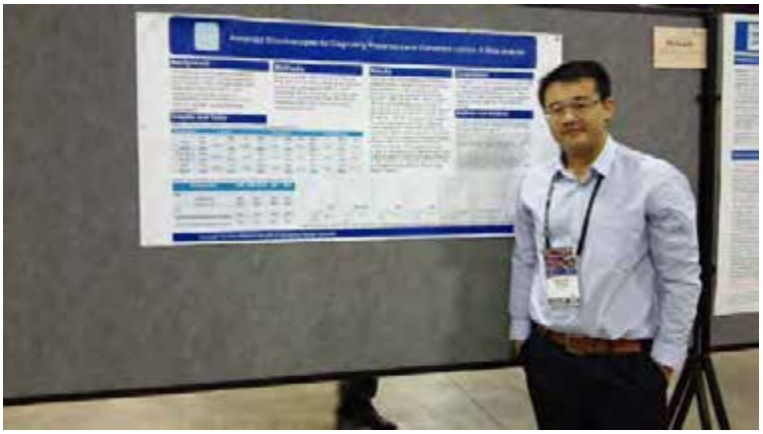
（三）研究生参会情况

序号	时间	会议名称	参会形式	论文名称	姓名
1	2015 年 12 月 3-6 日	APSR	口头	Correlation of hyperresponsiveness between the upper and lower airways in patients with allergic rhinitis and asthma	朱政
2	2015 年 12 月 3-6 日	APSR	口头	Comparison of the effects of leukotriene D4 and histamine nasal challenges on airway responsiveness and inflammation in allergic rhinitis" has been approved for Oral presentation	朱政
3	2015 年 12 月 3-6 日	APSR	口头	Effects of LTD4 nasal provocation on bronchial responsiveness and inflammation in patients with allergic rhinitis and asthma	朱政
4	2015 年 1 月	第八届世界肺血管病大会	壁报	Effects of chronic exposure to cigarette smoke on canonical transient receptor potential expression in rat pulmonary arterial smooth muscle	陈豫钦
5	2015 年	ATS	壁报	The better sample for avian influenza A (H7N9) virus - infected patient rapidly screening via rapid point-of-care test	李征途

呼吸疾病国家重点实验室

6	2015 年	WCLC	壁报	Advanced bronchoscopies for diagnosing precancerous or cancerous lesions: a meta-analysis	张剑嵘
7	2015 年 12 月	ESMO Asia 2015 Congress	壁报	Direct comparison of diagnostic accuracy between autofluorescence bronchoscopy (AFB) and AFB combined with white light bronchoscopy (AFB+WLB) for lung cancer and precancerous lesions: a systematic review and meta-analysis	张剑嵘
8	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	大会发言	Capparilоside A 体外抗流感病毒以及抑制流感病毒介导的炎症反应药效研究	李征途
9	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	大会发言	痰嗜酸粒细胞增高在 COPD 疾病严重程度评估中的意义	易芳
10	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	大会发言	定量 CT 评价支气管哮喘气道重塑、空气潴留的应用研究	赖政道
11	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	大会发言	机动车尾气体内暴露诱导豚鼠非特异性气道炎症初探	方章福
12	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	大会发言	机动车尾气诱导豚鼠咳嗽高敏感性及其机制探讨	方章福
13	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	大会发言	变应性鼻炎合并哮喘患者上下气道反应性的相关性研究	朱政
14	2015 年 9 月 3-6 日	第十六次全国呼吸病学年会	壁报/书面交流		37 人次

呼吸疾病国家重点实验室



张剑嵘参加 2015WCLC 会议

李征途参加 2015 年 ATS 会议

朱政参加 2015 年 APSR 会议

呼吸疾病国家重点实验室

（四）研究生获奖情况

实验室重视人才队伍建设，培养研究生人才辈出，参与国际学术会议交流，获得了国内国际多个奖项，其中包括优秀壁报、国家奖学金、企业奖学金等。

序号	奖励明细	学生姓名
1	2015ATS-ISRD Travel Award	李征途
2	第八届世界肺血管病大会暨中华医学会第七届全国肺栓塞与肺血管疾病学术会议优秀壁报奖	陈豫钦
3	2015 年广东省励志成长优秀学生典型	李征途
4	2015 年国家奖学金	刘宝娟
5	2015 年国家奖学金	朱政
6	2015 年国家奖学金	许志恒
7	2015 年国家奖学金	李梦溪
8	企业奖学金-红日奖学金	何嘉曦
9	企业奖学金-红日奖学金	陈豫钦
10	企业奖学金-金域奖学金	段林立
11	广州教育基地报告会一等奖	汤健

呼吸疾病国家重点实验室

（五）研究生学术沙龙

为活跃研究生之间的学习氛围，促进跨学组之间的合作，培养研究生跨学科的科研创

新能力，研究所在今年举行了两次研究生学术沙龙活动。具体参加报告学生和报告题目如下。

序号	报告题目	学生姓名	指导老师
1	呼吸道病毒的检测与治疗	陈婷婷	杨子峰
2	间质性肺疾病	邓葵淼	陈荣昌

陈婷婷同学进行报告

邓葵淼同学进行报告

呼吸疾病国家重点实验室

（六）实验室大学生夏令营

为了加强呼吸疾病国家重点实验室的对外开放；为提供广大热爱呼吸病学及生物医学研究的学子了解呼吸疾病国家重点实验室、深入了解呼吸系统疾病科学研究机会；同时基于实验室“吸引有志于从事呼吸系统疾病研究学子、培养新世纪呼吸系统疾病防诊治创新人才”人才培养战略，实验室计划在今年暑期开展夏令营（推免生接收）活动。

本次夏令营为期 4 天，收到全国各地共 27 名大学生的申请，最后共邀请 14 名学生进营。该次夏令营邀请到钟南山院士、陈凌主任、刘金保院长等知名教授与各位学生进行面对面授课，各位教授分别从人生理想，、重点实验室情况，实验室研究生教育政策（招生、培养政策）等方面与学生们进行分享。另外更安排了丰富多彩的参观行程，如院士大查房、中国科学院广州生物医药与健康研究院、爱国主义教育基地-黄埔军校旧址等地的参观活动。经过 4 天密锣紧鼓的行程后，同学们均表示获益良多，对自己的人生和学习有了新的规划和目标。而呼吸疾病国家重点实验室/广州呼吸疾病研究所和谐融洽的氛围和凝聚力，更加坚定了同学们报考呼吸疾病国家重点实验室/广州呼吸疾病研究所的决心。

呼吸疾病国家重点实验室

广州医科大学（番禺校区）参观

广医附一院（海印院区）
基础研究部 参观

中国科学院广州生物医药与健康
研究院 参观

黄埔军校 参观

珠江夜游

圣心石室大教堂 参观

呼吸疾病国家重点实验室

四、2015 年大事记

1 月份			
1 月 4 日	张海波教授及多伦多大学 St. Michael's 医院副院长 Arthur S. Slutsky 来访并作学术讲座：Recent advances in ARDS；Midkine mediates mechanical ventilation-induced lung fibrosis	8 楼会议室	学术交流
1 月 13 日	赵金存博士来访	学校	队伍建设
1 月 14-18 日	肺血管国际学术会议	东方宾馆	学术交流、会务
1 月 15 日	结构化电子病历上线培训	30 楼会议厅	呼研所建设
1 月 22 日	白春学来访洽谈物联网医学发展计划		呼研所建设
1 月 30 日	耶鲁大学正教授、南京大学特聘教授吴殿青教授来访作学术讲座：New insights into cell migration regulation-leading to potential new therapeutic targets for treating lung fibrosis	30 楼会议厅	学术交流
2 月份			
2 月 2 日	“粤澳呼吸道病原体新药联合研究中心”第二次理事会暨板蓝根抗流感病毒研究研讨会	8 楼会议室	对外开放、合作
2 月 5 日	中国科学院上海巴斯德研究所苏枭研究员来访作学术讲座：α7 nAChR regulates Influenza A Virus-induced Acute Lung Infection and Inflammation	30 楼东厅	
2 月 7 日	抗非经验与新发突发重大呼吸道传染病临床防控专家研讨会	8 楼会议室	学术交流、合作
2 月 11 日	法国领事馆科技部 Dora 女士来访参观实验室	海印	对外开放、合作交流
2 月 12 日	上海肺科医院费苛院长一行来访参观交流		学术交流、合作
3 月份			
3 月 13 日	博士研究生复试	30 楼	教学、人才培养
3 月 16 日	国家自然科学基金重大项目“肺气血屏障损伤与修复的调控机制”启动会	8 楼会议室	呼研所建设、学术交流

呼吸疾病国家重点实验室

3 月 18 日	第二届中国医院协会“拓峰行”活动	30 楼会议厅	学术交流、对外开放
3 月 21 日	科普一日游	30 楼东厅	对外开放
3 月 24 日	上海市瑞金医院来访	30 楼东厅	学术交流、合作
3 月 25 日-27 日	呼吸系统疾病诊疗技术新进展学习班	30 楼会议厅	人才培养、继续教育
3 月 27 日	中国医师协会人文医学专业委员会常委扩大会暨中国医学人文杂志工作会议	30 楼会议厅	人才培养、党委、团委
3 月 28 日	2015 全国肺功能临床应用与规范化培训学术会议	30 楼会议厅	人才培养、继续教育
4 月份			
4 月 3 日	清华大学医学院董晨教授来访作学术讲座“Th17 细胞、炎症及肿瘤的关键调节者”	30 楼东厅	人才培养、学术交流
4 月 14 日	法国科学与技术高等学院代表团来访参观	海印	学术交流、对外开放
4 月 13 日-17 日	飞利浦无创通气短期学习班		人才培养
4 月 17 日-19 日	钟院士、陈所一行到浙大参观学习	浙大	学术交流、合作、实验室建设
4 月 22 日	视频大查房	30 楼会议厅	学术交流、人才培养、对外开放
4 月 27 日	国际 AAALAC 认证委员会常务理事王建飞博士作“AAALAC 在亚洲开展认证的简介，为什么要认证”的学术报告	中科院	学术交流、人才培养
4 月 29 日	研究生学术沙龙	30 楼西厅	人才培养
5 月份			
5 月 5 日	世界哮喘日义诊活动		对外开放
5 月 6 日	实验室赵金存博士作“呼吸道管状病毒的致病机理及动物模型研究”学术报告	30 楼东厅	学术交流、人才培养
5 月 15 日	东莞市第六人民医院副院长一行来访		学术交流
5 月 21 日	实验室邀请美国阿拉巴马州哈森阿尔法生物技术研究院研究员韩健博士做题为“免疫组库技术在医学研究中的应用”学术讲座	30 楼东厅	学术交流
5 月 27 日	实验室邀请美国南加州大学 Zilkha 神经遗传所助理教授王凯博士做题为“基因组大数据解读-全基因组测序的生物信息学方法”的学术讲座	30 楼东厅	学术交流

呼吸疾病国家重点实验室

6月份			
6月10日	拓峰行活动	30楼会议厅	学术交流、人才培养、对外开放
6月12日	广东省医师协会人文医学主委换届会议	广东大厦	会务
6月13日	首届静脉血栓栓塞病防治与红外热成像检测技术学习班	8楼会议室	人才培养、会务
6月15日	圣-路易斯大学博士后兼助理教授Dong Lin-Wang 教授来访并作“Update on PAH evaluation and hemodynamic assessment”学术讲座	30楼东厅	学术交流、人才培养
6月19日	实验室邀请上海生物制品研究所研究员，首席科学家陈则教授做题为“流感病毒暨流感疫苗研究”的学术讲座	科学城健研院	学术交流
6月19日	实验室邀请中国科学院广州生物医药与健康研究院研究员李鹏博士做题为“人源化小鼠模型的研发与应用”学术讲座	30楼东厅	学术交流
6月24日	“名院名家面对面：院士大查房”万人网络公开课	30楼会议厅	学术交流、人才培养、对外开放
6月29日	实验室邀请英国Malik Peiris院士做题为“中东呼吸综合征冠状病毒的出现、传播与控制”学术讲座	30楼东厅	学术交流
6月30日	实验室邀请芝加哥伊利诺伊大学儿科系、伊利诺伊大学肿瘤中心助理教授周国飞做题为“Role of miR-17~92 in Pulmonary Hypertension”学术讲座	30楼东厅	学术交流
7月份			
7月7日	实验室邀请McMaster University内科学教授 Firestone Institute for Respiratory Health学术主任Mark Inman做题为“哮喘的气道高反应性：根本机制及其临床应用”学术报告	30楼东厅	学术交流
7月18-19日	第十三届脓毒症高峰论坛	白云国际	会务、学术交流、人才培养
7月20-23日	重点实验室第一期暑假大学生夏令营活动		对外开放
7月21-23日	ACCP专家团来访	东风宾馆	学术交流、交流合作
7月22日	院士视频大查房	30楼会议厅	学术交流、人才培养、对外开放

呼吸疾病国家重点实验室

7 月 29 日	拓峰行活动	30 会议厅	学术交流、人才培养、对外开放
8 月份			
8 月 1 日	重点实验室中期汇报会	南沙大酒店	实验室建设
8 月 6-9 日	第九届全国慢性咳嗽与疑难少见病学习班暨第八届中国咳嗽论坛会议成功举办	内蒙古	会务、学术交流、人才培养、继续教育
8 月 14-16 日	广东省医学会呼吸病学分会血管学组正式成立，我所为副组长单位	江门	实验室建设
8 月 16 日	王新华赴美国约翰.霍普金斯大学医学院访问交流，看望我所留学生		学术交流、人才培养
8 月 20 日	实验室邀请中科院上海营养所研究员余鹰博士做题为“PGE2 与哮喘和肺血管重塑”学术讲座	30 楼东厅	学术交流
8 月 21 日	实验室邀请英国帝国理工研究员张幼明博士做题为“哮喘的遗传学和基因组学研究：现状和进展”学术讲座	29 楼会议室	学术交流
8 月 24-26 日	飞利浦无创通气短期学习班		人才培养
8 月 26 日	院士视频大查房	30 楼会议厅	学术交流、人才培养、对外开放
9 月份			
9 月 8 日	2015 年研究生入学培训系列——实验室安全管理培训		人才培养
9 月 9 日	拓峰行活动	30 楼会议厅	学术交流、人才培养、对外开放
9 月 10 日	北京诺禾致源生物信息科技有限公司宁璞进行“扩增子和宏基因组测序在疾病研究中的应用”讲座	29 楼会议室	交流合作
9 月 11-12 日	儿童呼吸学习班	30 楼会议厅	会务、学术交流、人才培养、继续教育
10 月份			
10 月 14 日	重点实验室产学研基地园区启动仪式	开发区	实验室建设
10 月 16-17 日	首届体外膜肺(ECMO)在呼吸衰竭临床应用学习班	30 楼会议厅	人才培养、继续教育

呼吸疾病国家重点实验室

11 月份			
11 月 13 日	实验室邀请芝加哥伊利诺伊大学医学院药理学系赵友阳教授做题为“Novel mechanisms of severe pulmonary vascular remodeling and pulmonary arterial hypertension”学术讲座	30 楼西厅	学术交流
11 月 19 日	实验室邀请Mitchell Albert 教授进行题为“利用超极化惰性气体开展肺的功能性磁共振成像研究”的学术讲座	30 楼西厅	学术交流 技术合作
11 月 25 日	实验室邀请美国 Duke 大学高霞博士进行题为“肺再生与肺干细胞研究”的学术讲座	30 楼东厅	学术交流
11 月 26 日	英国帝国理工学院 Kian Fan Chung 教授进行题为“New Treatments for Severe Asthma and Need for New Biomarkers”学术讲座	30 楼西厅	学术交流
12 月份			
12 月 4 日	实验室邀请中国科学技术大学生命科学院田志刚教授进行题为“肺脏区域免疫与肺部疾病”学术讲座	30 楼东厅	学术交流
12 月 7 日	“大气污染的急性健康风险”重点专项项目申请启动会	30 楼西厅	技术交流
12 月 11 日	2015 年“过敏性疾病诊治新技术学习班”暨“全国第十六届标准化变应原特异性免疫治疗培训班”	30 楼会议厅	学术交流
12 月 19 日	实验室学术委员会	8 楼会议室	年度会议
12 月 20 日	国自然重大项目“肺气血屏障损伤与修复的调控机制”年度汇报会	8 楼会议室	年度会议

呼吸疾病国家重点实验室

五、依托单位年度考核

关于2015年度呼吸疾病国家重点实验室年度考核意见：

2015年实验室在承担国家级、省部级等各级部门的科研项目方面整体稳定发展，并取得突破性的科研成果。

2015年，实验室新获国家级课题27项，国家自然科学基金项目重大项目2项，国际合作1项，面上项目11项，资助金额为1762万元；承担国家级项目31项，资助金额为1335万元；省部级、市级项目58项，资助金额为76905万元。实验室承担科研项目数量整体稳步发展，其中李靖教授的“尘螨免疫治疗对呼吸道上皮细胞HBD-2和树突状细胞的调节作用”和朱强教授的“过渡金属催化烯烃的氧化官能化新反应研究”获得了国家自然科学基金重大项目资助，王新华教授的“滇药臭灵丹靶向流感病毒和宿主免疫调节的新型活性成分药效机制及构效关系研究”获得云南-联合基金资助，卢文菊教授的“MUC1对慢性阻塞性肺疾病气道炎症和重构的调节作用与机制研究”获得国际(地区)合作与交流项目资助，资助力度有较大进步，有利于开展科学研究。

在成果方面，本年度实验室获得的重大科研成果包括国家科学技术进步奖二等奖、广东省科学技术进步奖二等奖、ISEE最佳环境流行病学论文奖等三项科技奖项。实验室新获授权专利共11项，其中发明专利4项，实用专利5项，申请专利19项。2015年共发表SCI文章249篇，其中影响因子大于或等于20的有3篇，大于或等于10的有23篇，大于或等于5的有71篇，大于或等于3的有125篇，平均影响因子为4.9797 。

2015年实验室主办学术会议共12个，其中国际级会议4个，国家级会议8个；举办继续教育培训班18个，其中具有国家级学分的培训班共5个。实验室共60人次参加国内外各类会议，进行大会发言或壁报交流，其中参加国际会议

呼吸疾病国家重点实验室

49 人次、国内会议 60 人次，参会足迹遍布全球，包括美国、加拿大、欧洲各国、韩国、东南亚以及中国各地包括北京、上海、广州、杭州、苏州、武汉、郑州、成都等。

在人才培养方面，2015 年实验室毕业硕士研究生 46，博士研究生 23。新招硕士研究生 54，博士研究生 20。出站博士后 3 人，在站博士后 13 人。

通过年度考核。

广州医科大学

2015 年 12 月 22 日

呼吸疾病国家重点实验室

六、本年度发表文章首页

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呼吸疾病国家重点实验室

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1-Benzyl-4-phenyl-1*H*-1,2,3-triazoles improve the transcriptional functions of estrogen-related receptor γ and promote the browning of white adipose

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ABSTRACT

The estrogen-related receptor γ (ERRγ) is a potential molecular target for the development of small molecules to stimulate the adipose browning process, which may represent a novel attractive strategy to treat obesity related disorders. The receptor possesses a very small ligand binding cavity and therefore identification of small molecule ERRγ modulators is a considerable challenge. We have successfully designed and synthesized a series of 1-benzyl-4-phenyl-1*H*-1,2,3-triazoles and demonstrated that they improve the transcriptional functions of ERRγ, potently elevating both the mRNA levels and the protein levels of ERRγ downstream targets. One of the most promising compounds, 4-(1-(4-iso-propylbenzyl)-1*H*-1,2,3-triazol-4-yl)benzene-1,2-diol (**2e**) was further shown to directly bind with the ERRγ ligand binding domain (ERRγ-LBD) in an isothermal calorimetric (ITC) assay and to thermally stabilize ERRγ-LBD protein by increasing its melting temperature (T_m) as demonstrated by circular dichroism (CD) spectroscopy. Furthermore, **2e** potently stimulates the adipocyte browning process and induces mitochondrial biogenesis both in vitro and in vivo, suggesting the considerable therapeutic potential of this compound for the treatment of obesity and related disorders.

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1. Introduction

Two types of adipose tissues have been identified in mammals, that is, white adipose tissue (WAT) and brown adipose tissue (BAT).[1] WAT is located predominantly in the subcutaneous and visceral organs where it stores excess energy in the form of triglycerides. Excessive accumulation of WAT is the primary cause of obesity and can eventually lead to type 2 diabetes, cardiovascular disease and other metabolic disorders.[2] BAT, on the other hand, stores lipids in a multilocular droplet morphology and possesses much higher mitochondrial content than WAT. The key functions of BAT are to burn fat for body heat production (adaptive thermogenesis) and to promote weight loss by increasing energy expenditure.[3] Although controversy had been associated with the occurrence of BAT in adult humans, recent data derived from a positron-emission-tomography (PET) study convincingly demonstrated the existence of active BAT in adults.[4] Different reports have shown that exposure to cold temperatures or expression of several endogenous ligands (e.g., Irisin,[5] FGF21[6]) can induce the presence of brown-like adipocytes (also known as beige cells) in WAT tissue and cause the weight loss of animals.[7] The WAT → BAT transition has been termed biologically as adipose browning. Promoting the browning process in white adipose tissue and/or activation of the function of BAT by small molecules becomes a highly attractive strategy to treat obesity and its related

Abbreviations: ERR, estrogen-related receptor; WAT, white adipose tissue; BAT, brown adipose tissue; PET, positron-emission-tomography; FGF21, fibroblast growth factor 21; MOA, mechanisms of action; UCP1, uncoupling protein 1; SHP, small heterodimer partner; ATP5b, ATP synthase 5b; MCAD, medium-chain acyl-coenzyme A dehydrogenase; MEF, mouse embryonic fibroblasts; Prdm16, PR domain containing 16; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; CS, citrate synthase; CPT1, carnitine palmitoyltransferase-1; COXII, cytochrome c oxidase subunit II; SDH, succinate dehydrogenase; ITC, isothermal titration calorimetry; CD, circular dichroism; LBD, ligand binding domain; T_m, melting temperature.

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2,4-Diarylamino-pyrimidines as kinase inhibitors co-targeting IGF1R and EGFR$^{L858R/T790M}$

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ABSTRACT

IGF1R amplification was recently implied to be related to the secondary acquired resistance against the 2nd or 3rd generation EGFR inhibitor therapies. We have successfully identified a series of 2,4-diarylamino-pyrimidines as new IGF1R/EGFR$^{L858R/T790M}$ co-targeting agents. One of the most promising compounds **8g** potently inhibits both kinases with low nanomolar IC_{50} values, but is significantly less potent in inhibiting the wild type EGFR. The compound also displays a good kinase selectivity profile against a panel of 468 kinases. Moreover, **8g** strongly suppresses the proliferation of CO-1686-resistant H1975-IGF1R cancer cells, suggesting its promising potential as a new lead compound for future anticancer drug discovery.

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The first generation epidermal growth factor receptor (EGFR) inhibitors (e.g., gefitinib and erlotinib) have shown remarkable benefits for non-small-cell lung cancer (NSCLC) patients carrying EGFR activating mutations (L858R and exon-19 deletion).[1,2] However, an acquired threonine^{790} → methionine^{790} (T790M) mutation of EGFR contributes greatly to the clinical resistance against current drugs.[3] The cysteine^{797} reactive second-generation inhibitors afatinib, neratinib and dacomitinib were subsequently developed and demonstrated a promising resistance-overcoming capability in preclinical studies. However, they display strong, non-selective suppression on wild-type EGFR which causes unacceptably low Maximum-Tolerated-Dose (MTD) in resistant patients.[4] Recently, several 3rd generation wild-type sparing EGFR^{T790M} inhibitors, such as CO-1686 (**1**),[5] AZD9291 (**2**),[6] compound **3**[7] and WZ4002 (**4**),[8] were discovered. Both **1** and **2** have demonstrated significant clinical benefit for resistant NSCLC patients and were granted 'Breakthrough Therapy' designations by the US FDA in 2014.[9]

Most recently, EGFR^{C797S} mutation has been reported to mediate a secondary acquired resistance against drug **2** in EGFR^{T790M} mutated NSCLC patients.[10] Tyrosine Kinase Inhibitor dose-escalation investigations also suggested that sustained activation of Akt could induce insensitivity against drugs **1** and **2** in H1975 NSCLC cells.[5,11] A similar independent study demonstrated that amplification of Insulin-like Growth Factor 1 Receptor (IGF1R) was involved in over-activation of Akt. A selective IGF1R inhibitor BMS536924 (**5**) successfully restored the drug sensitivity to **4** in the WZ4002-Resistant (WZR) NSCLC cells, and a combination of **4** with **5** completely prevented the emergence of drug-resistant clones in the experimental system.[12]

IGF1R is another tyrosine kinase whose overexpression is closely correlated to malignant transformation and acquired resistance of various human cancers.[13] Although most IGF1R based therapies displayed relatively disappointing clinical outcomes with metabolic side effects (e.g., hyperglycemia) when utilized as a single agent in non-selected patients,[14,15] combinations of IGF1R inhibitors with other drugs were recently demonstrated synergistic therapeutic benefits in metastatic pancreatic cancer and lung cancer patients.[16,17] There results collectively imply that co-targeting EGFR^{T790M} and IGF1R may be a tractable strategy to overcome potential resistance against the 2nd or 3rd generation EGFR inhibitors. Encouragingly, several AZD9291 derivatives were recently reported to strongly inhibit both EGFR^{T790M} and IGF1R and display promising in vivo antitumor efficacy.[6,18]

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A 50-year-old woman with haemoptysis, cough and tachypnea: cholesterol pneumonia accompanying with pulmonary artery hypertension

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Abstract

Lipoid pneumonia is an uncommon disease caused by the presence of lipid in the alveoli. Here we described a case of a 50-year-old woman with haemoptysis, cough and tachypnea, who was diagnosed with cholesterol pneumonia accompanying with pulmonary artery hypertension. The extremely high pulmonary artery pressure achieved, in this case, is alarming and should alert the physicians that the cholesterol pneumonia may be one of the underlying causes of pulmonary artery hypertension. After a treatment of methylprednisolone, her clinical symptoms were significantly improved, which suggested that steroid might be a promising therapeutic for patients with cholesterol pneumonia.

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*Mengxi Li and Nuofu Zhang are equal contributors.

This article was selected as a poster in the international institute of pulmonary vascular disease (PVRI) the eighth annual world conference on lung vascular disease and the Chinese medical association the 7th national conference on pulmonary embolism and pulmonary vascular disease academic conference.

Key words

cholesterol pneumonia – endogenous lipoid pneumonia – pulmonary artery hypertension – right heart catheterization – transbronchial lung biopsy

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Authorship and contributorship

Mengxi Li, Chunli Liu, Jian Wang designed study, Nuofu Zhang, Ying Zhou, Jinhui Li performed study; Nuofu Zhang and Yingying Gu collected data; Mengxi Li wrote the paper.

Ethics

Patient's informed consent was signed

Conflict of interest

Financial/nonfinancial disclosures: No potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Introduction

Lipoid pneumonia is an uncommon disease caused by the presence of lipid in the alveoli, which was first described by McDonald *et al.* in 1949 as 'obstructive pneumonitis' in patients with lung neoplasms, and can be classified into two major groups, endogenous and exogenous. Endogenous lipoid pneumonia must be distinguished from exogenous lipoid pneumonia, which follows the inhalation of adventitious oils of mineral, animal or vegetable origin. Exogenous lipoid pneumonia is common while cholesterol pneumonia can be rarely seen. Endogenous lipoid pneumonia also called cholesterol pneumonia and chronic pneumonia

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Original Article

A comparative analysis of lung cancer patients treated with lobectomy via three-dimensional video-assisted thoracoscopic surgery versus two-dimensional resection

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Background: Three-dimensional (3D) vision systems are now available for thoracic surgery. It is unclear whether 3D video-assisted thoracic surgery (VATS) is superior to 2D VATS systems. This study aimed to compare the operative and perioperative data between 2D and 3D VATS lobectomy (VTL) and to identify the actual role of 3D VTL in thoracic surgery.

Methods: A two-institutional comparative study was conducted from November 2013 to November 2014 at Liaoning Cancer Hospital & Institute and the First Affiliated Hospital of Guangzhou Medical University, China, of 300 patients with resectable non-small cell lung cancer (NSCLC). Patients were assigned to receive either the 3D VATS (n=150) or 2D VATS (n=150) lobectomy. The operative and perioperative data between 2D VATS and 3D VATS were compared.

Results: Although there was no significant difference between the two groups regarding the incidence of each single complication, a significantly less operative time was found in the 3D VATS group (145 min) than in the 2D VATS group (176 min) (P=0.006). Postoperative mortality rates in 3D VATS and 2D VATS groups were both 0%.No significant difference was found between groups for estimated blood loss (P=0.893), chest drainage tube placement time (P=0.397), length of hospital stay (P=0.199), number of lymph nodes resected (P=0.397), postoperative complications (P=0.882) and cost of care (P=0.913).

Conclusions: Early results of this study demonstrate that the 3D VATS lobectomy procedure can be performed with less operative time. 3D VATS and 2D VATS lobectomy are both safe procedures in first-line surgical treatment of NSCLC.

Keywords: Video-assisted thoracic surgery (VATS); three-dimensional (3D); lobectomy

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ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

Cycloamination

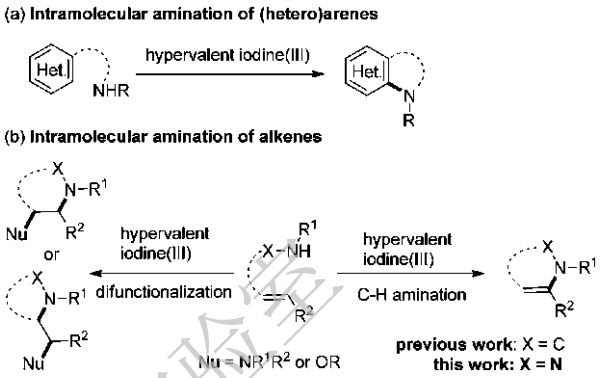
A Facile Synthesis of Pyrazoles through Metal-Free Oxidative C(sp^2)–H Cycloamination of Vinyl Hydrazones

Dongdong Liang and Qiang Zhu*[a]

Abstract: An efficient synthesis of structurally diversified pyrazole derivatives through metal-free oxidative C–H cycloamination of vinyl hydrazones has been developed. The reaction was usually complete within 5 min at ambient temperature in air in good to excellent yields.

Intramolecular C(sp^2)–N bond formation through direct C–H functionalization, featuring step-efficiency and atom-economy, has emerged as an attractive strategy for the synthesis of N-heterocycles in recent years.[1] Transition-metal catalysts such as Pd, Rh, Ru, Cu, etc. predominate the arsenal in achieving this goal.[2–4] However, these reactions normally suffer from using stoichiometric or even excess amount of metal salts as oxidants, harsh reaction conditions, and narrow substrate scope. These disadvantages limit their application in the manufacture of small molecule active pharmaceutical ingredients (APIs) due to cost concerns as well as purification difficulties in removing metal contaminants from final products. As a result, the development of alternative metal-free approaches through C–H oxidative cycloamination under mild conditions would be of great importance in the synthesis of N-heterocycles with biological interests.

Hypervalent iodine(III) reagents have played an increasingly important role in C–C and C-heteroatom bond-forming reactions, which are usually performed under much milder conditions with higher efficiency than transition-metal-catalyzed reactions. In addition, the reaction byproducts, PhI and acetic acid in most cases, are more environmentally benign and readily removable.[5] Hypervalent iodine(III)-mediated/-catalyzed intramolecular oxidative C–H amination of (hetero)arenes has been well documented for the synthesis of fused heterocyclic rings (Scheme 1 a).[6] When alkenes are present in place of (hetero)arenes under similar reaction conditions, non-aromatic heterocycles, as a result of alkene difunctionalization, are normally obtained (left, Scheme 1 b).[7,8] However, substitution of a vinylic



Scheme 1. Hypervalent iodine(III)-promoted intramolecular C(sp^2)–N formation.

C–H bond by an intramolecular nitrogen atom, leading to nitrogen-containing aromatic heterocycles, is much less common (right, Scheme 1 b). Recently, Muñiz et al reported an elegant synthetic approach to indoles starting from 2-vinyl anilines through a PhIO-mediated C–H/N–H oxidative coupling.[9] It was envisaged that the NH moiety in vinyl hydrazones can be used as a N-donor in coupling with the vinylic C–H bond in the presence of the hypervalent iodine(III) reagent to construct five-membered pyrazoles. However, the compatibility of the N–N single bond in hydrazones with hypervalent iodine(III) reagents and the avoidance of alkene difunctionalization as a side reaction are the major challenges facing the hypothesized reaction.

The pyrazole scaffold is an important skeleton in many biological active molecules[10] and commercialized pharmaceutical products, such as Celebrex, Viagra, and Acomplia.[11] Therefore, the synthesis of pyrazole derivatives has attracted much attention.[12] However, traditional methods that are based on the condensation of hydrazines with alkynones or alkenones usually suffer from regioselectivity, high reaction temperatures, and substrate tolerance with the acidic conditions. In recent years, transition-metal-catalyzed intramolecular oxidative C–H amination of vinyl hydrazones has been successfully applied to the regioselective synthesis of pyrazoles.[13] For instance, Jiang and co-workers recently reported a practical synthesis of pyrazoles and indazoles through a copper-catalyzed oxidative C(sp^2)–H amination of vinyl and aryl hydrazones in O_2 at 100 to 120 °C in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as an additive.[13a] Aggarwal and Kumar reported that electron-deficient *N*-substituted hydrazones derived from chalcones were

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BMC Cancer

RESEARCH ARTICLE Open Access

A functional genetic variant in fragile-site gene *FATS* modulates the risk of breast cancer in triparous women

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Abstract

Background: The fragile-site associated tumor suppressor (*FATS*, formerly known as *C10orf90*), a regulator of p53-p21 pathway has been involved in the onset of breast cancer. Recent data support the idea that the crosstalk between FATS and p53 may be of physiological importance for reproduction during evolution. The aim of the current study was to test the hypothesis that *FATS* genetic polymorphism can influence the risk of breast cancer.

Methods: We conducted population-based studies in two independent cohorts comprising 1 532 cases and 1 573 controls in Tianjin of North China, and 804 cases and 835 controls in Guangzhou of South China, coupled with functional validation methods, to investigate the role of *FATS* genetic variant in breast cancer risk.

Results: We identified a functional variant rs11245007 (905C > T, 262D/N) in fragile-site gene *FATS* that modulates p53 activation. FATS-262 N exhibited stronger E3 activity to polyubiquitinate p53 than did FATS-262D, leading to the stronger transcriptional activity of p53 and more pronounced stabilization of p53 protein and its activation in response to DNA damage. Case–control studies found that CT or TT genotype was significantly associated with a protective effect on breast cancer risk in women with parity ≥ 3, which was not affected by family history.

Conclusions: Our findings suggest the role of FATS-p53 signaling cascade in suppressing pregnancy-related carcinogenesis and potential application of *FATS* genotyping in breast cancer prevention.

Keywords: Breast cancer, FATS, Single-nucleotide polymorphism, p53, Parity

Background

Breast cancer is both the most common malignancy and the one causing the highest number of cancer deaths in women worldwide. For most sporadic breast cancers, it has been suggested that genetic polymorphisms, especially single nucleotide polymorphisms (SNPs) in low-penetrance susceptibility genes in concert with environmental exposures may be more important. The p53 tumor suppressor protein, through its downstream target p21, plays a key role in sustaining cell-cycle checkpoints after DNA damage to maintain the genomic stability [1, 2]. The defects in this pathway may result in genomic instability and carcinogenesis. Over the past few years, emerging evidence have revealed a role of p53 in regulating human maternal reproduction [3]. It is well-known that reproductive history represents lifetime exposure to hormones and is a significant risk factor for breast cancer, besides the family history of breast cancer [4–9]. However, whether the modulation of p53 activation may contribute to the genetic basis underlying the effect of reproductive history on the risk of breast cancer remains unknown.

Recently, the fragile-site associated tumor suppressor (*FATS*, aka *C10orf90*), a regulator of p53-p21 pathway, has been identified at a common fragile site (CFS) FRA10F mapped to 10q26, a genomic region susceptible to DNA damage and frequently deleted in tumor genomes [10–13].

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

A gloves-associated outbreak of imipenem-resistant *Acinetobacter baumannii* in an intensive care unit in Guangdong, China

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Abstract

Background: Imipenem-resistant *Acinetobacter baumannii* (IRAB) is an important cause of hospital-acquired infection. We aimed to describe an outbreak of IRAB infection and to investigate its possible source in an intensive care unit.

Methods: An environmental investigation was undertaken. Antimicrobial susceptibility testing was performed by microdilution. These isolates were genotyped by use of repetitive extragenic palindromic polymerase chain reaction (rep-PCR; DiversiLab). The study included 11 patients infected with IRAB and 14 control patients free of IRAB. Case and control patients were compared for possible predisposing factors. A multifaceted intervention was implemented to control the outbreak.

Results: Thirty-nine IRABs were isolated from patients and the environmental surveillance culture in August, November, and December 2011. All isolates were resistant to imipenem. The IRAB strains belonged to seven clones (A–G) by the use of rep-PCR. There were four epidemic clones (D–G) in the outbreak, and Clone D was predominant. For the case–control study, patients with chronic obstructive pulmonary disease were susceptible to infection with IRAB. The hospital mortality of the case group was significantly higher than that of the control group.

Conclusions: The outbreak strains were transmitted among infected patients and equipment by inappropriate use of gloves. A combination of aggressive infection control measures is essential for preventing recurrent nosocomial outbreaks of IRAB.

Keywords: Outbreak, *Acinetobacter baumannii*, ICU, Gloves

呼吸疾病国家重点实验室

Background

Acinetobacter baumannii, a non-fermenting Gram-negative bacterium, is recognized as an important opportunistic pathogen, and is particularly associated with mortality in intensive care units (ICUs) [1]. As a result of the simplicity of its growth requirements and its remarkable capacity for extended survival on environmental surfaces, *A. baumannii* is ubiquitous in the environment [2]. Thus, environmental contamination is an important source of cross-infection [3,4]. The carbapenem group of antimicrobial agents is commonly used for treating nosocomial infections caused by *A. baumannii* [5]. However, carbapenem resistance has been increasingly identified in the past decade [6,7], and imipenem-resistant *A. baumannii* (IRAB) has also been increasingly reported as a cause of nosocomial outbreaks [8-12].

On August 9, 2011, an outbreak of nosocomial infection with IRAB was noted in our medical ICU. In this study, we isolated IRAB from clinical specimens and the hospital environment, using the DiversiLab repetitive extragenic palindromic sequence-based PCR (rep-PCR) to assess the genetic relationship of these resistant isolates.

Methods

The study was approved by the institutional Research Ethical Board of the First Affiliated Hospital

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Original Article

A modified nebulization modality versus classical ultrasonic nebulization and oxygen-driven nebulization in facilitating airway clearance in patients with acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial

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呼吸疾病国家重点实验室

Background: Ultrasonic nebulization (UN) and oxygen-driven nebulization (ON), two commonly used modalities for nebulization inhalation, are not ideally suitable for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods: A total of 91 patients with AECOPD were randomized to three groups given different nebulization modalities: ON, UN, and ultrasonic nebulization with warming and oxygen (UNWO). The sputum clearance, lung function, changes in physiological measures such as peripheral oxygen saturation (SpO_2) and tolerance to these nebulization modalities were recorded and compared among the three groups.

Results: The time to the first expectoration was shorter and the sputum volume was larger after UN and UNWO than after ON (both P<0.01). Compared with pre-nebulization, SpO_2 significantly increased (P<0.01) and the dyspnea decreased significantly (P<0.05) after UNWO. The SpO_2 and dyspnea post-UNWO were significantly better than those post-UN (P<0.01, P<0.05), but not statistically different from those post-ON (both P>0.05). UNWO demonstrated significantly greater comfort and longer duration of nebulization than UN (P<0.01, P<0.05), but no significant differences in these respects from ON (both P>0.05). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF) decreased significantly after UNWO (P<0.05, P<0.01, and P<0.01, respectively).

Conclusions: UNWO may promote expectoration of sputum with fewer adverse reactions and a higher level of comfort than simple UN and ON. Therefore, it can be used as an adjuvant therapy for AECOPD patients.

Keywords: Oxygen-driven nebulization (ON); ultrasonic nebulization (UN); ultrasonic nebulization with warming and oxygen (UNWO); sputum expectoration; chronic obstructive pulmonary disease (COPD); acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

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Introduction

Nebulized inhalation is a common procedure given to patients with respiratory diseases that helps moisten and dilute viscous airway secretions, and thereby facilitates their clearance. Addition of therapeutic agents (such as antibiotics and bronchodilators) to the nebulizing solution can further lead to direct, local effects against airway inflammation,

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PLOS | ONE

RESEARCH ARTICLE

A Multicenter Retrospective Review of Prone Position Ventilation (PPV) in Treatment of Severe Human H7N9 Avian Flu

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background

Patients with H7N9 avian flu concurrent with severe acute respiratory distress syndrome (ARDS) usually have a poor clinical outcome. Prone position ventilation (PPV) has been shown to improve the prognosis of patients with severe ARDS. This study explored the effects of PPV on the respiratory and circulatory mechanics of H7N9-infected patients with severe ARDS.

Methods

Individuals admitted to four hospitals designated for H7N9 patients in Guangdong province were treated with PPV, and their clinical data were recorded before and after receiving PPV.

Results

Six of 20 critically ill patients in the ICU received PPV. After treatment with 35 PPV sessions, the oxygenation index (OI) values of the six patients when measured post-PPV and post-supine position ventilation (SPV) were significantly higher than those measured pre-PPV ($P < 0.05$).The six patients showed no significant differences in their values for respiratory rate (RR), peak inspiratory pressure (PIP), tidal volume (TV) or arterial partial pressure of carbon dioxide ($PaCO_2$) when compared pre-PPV, post-PPV, and post-SPV. Additionally, there were no significant differences in the mean values for arterial pressure (MAP), cardiac index (CI), central venous pressure (CVP), heart rate (HR), lactic acid (LAC) levels or the doses of norepinephrine (NE) administered when compared pre-PPV, post-PPV, and post-SPV.

呼吸疾病国家重点实验室

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A novel long noncoding RNA AK001796 acts as an oncogene and is involved in cell growth inhibition by resveratrol in lung cancer

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ABSTRACT

Lung cancer is the most common form of cancer throughout the world. The specific targeting of long noncoding RNAs (lncRNAs) by resveratrol opened a new avenue for cancer chemoprevention. In this study, we found that 21 lncRNAs were upregulated and 19 lncRNAs were downregulated in lung cancer A549 cells with 25 μmol/L resveratrol treatment determined by microarray analysis. AK001796, the lncRNA with the most clearly altered expression, was overexpressed in lung cancer tissues and cell lines, but its expression was downregulated in resveratrol-treated lung cancer cells. By monitoring cell proliferation and growth in vitro and tumor growth in vivo, we observed a significant reduction in cell viability in lung cancer cells and a slow growth in the tumorigenesis following AK001796 knockdown. We also found that AK001796 knockdown caused a cell-cycle arrest, with significant increases in the percentage of cells in G_0/G_1 in lung cancer cells. By using cell cycle pathway-specific PCR arrays, we detected changes in a number of cell cycle-related genes related to lncRNA AK001796 knockdown. We further investigated whether AK001796 participated in the anticancer effect of resveratrol and the results showed that reduced lncRNA AK001796 level potentially impaired the inhibitory effect of resveratrol on cell proliferation. To our knowledge, this is the first study to report the changes in an lncRNA expression profile induced by resveratrol in lung cancer.

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Introduction

Lung cancer, a leading cause of morbidity and cancer-related mortality throughout the world, remains an important public health burden worldwide, especially in developing countries, including China (Jemal et al., 2011; Oak et al., 2012). In 2008, lung cancer replaced liver cancer as the principal cause of death among people with malignant tumors in China, and imposes an enormous burden on patients, health-care professionals, and society (She et al., 2013; Yang et al., 2004). Despite novel therapies and advances in its early detection, lung cancer is often diagnosed at an advanced stage and has a poor prognosis. Therefore, effective preventive strategies are crucial to the management of lung cancer. Both smoking prevention and cessation are key elements in any overall strategy for lung cancer prevention, but they do not address the problem of the increasing population of former smokers who remain at risk. To address this problem, the focus in basic and clinical lung cancer research has been on chemoprevention.

Resveratrol (trans-3,4′,5-trihydroxystilbene, $C_{14}H_{12}O_3$), a natural polyphenol found in various plants and Chinese herbs, has been proposed as an ideal chemopreventive agent because of its relatively low toxicity and its capacity to target multiple signaling molecules that collectively promote cancer cell survival and tumor growth (Athar et al., 2007; Bishayee, 2009; Kaur et al., 2009). Many in vitro studies have investigated the antiproliferative and proapoptotic effects of resveratrol in human cancer cells and its mechanisms of action (Athar et al., 2009; Cimino et al., 2012; Shih et al., 2004). It has also been shown to exert a strong inhibitory effect on the formation of free radicals by human macrophages, reducing oxidative stress within premalignant cells, and to reduce the production of NO, consequently limiting the growth and spread of prostate cancer (Ratan et al., 2002). Another interesting chemopreventive mechanism related to this compound involves its sensitization effect (Gupta et al., 2011). However, until now, the molecular mechanisms of resveratrol's actions have only been partially understood, despite numerous studies. Several previous studies suggested that the protective properties of resveratrol arise from its modulation of the expression of small, noncoding RNAs (microRNAs [miRNAs]), which implies an emerging role for the modulation of miRNA signatures in cancer chemoprevention (Li et al., 2010; Whyte et al., 2007). For example, Bae et al. reported that resveratrol

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Original Articles

Activation of mucosal mast cells promotes inflammation-related colon cancer development through recruiting and modulating inflammatory CD11b$^+$Gr1$^+$ cells

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ABSTRACT

Mast cells (MCs) have been reported to be one of the important immunoregulatory cells in promoting the development of colitis-related colon cancer (CRC). It is not clear which MC subtypes play critical roles in CRC progression from colitis to cancer because mucosal mast cells (MMCs) are distinct from connective tissue mast cells (CTMCs) in maintaining intestinal barrier function under homeostatic and inflammatory conditions. In the current study, we found that MMC numbers and the gene expressions of MMC-specific proteases increased significantly in an induced CRC murine model. The production of mast cell protease-1 (mMCP-1) after MMC activation not only resulted in the accumulation of CD11b$^+$Gr1$^+$ inflammatory cells in the colon tissues but also modulated the activities of CD11b$^+$Gr1$^+$ cells to support tumor cell growth and to inhibit T cell activation. Blocking the MMC activity in mice that had developed colitis-related epithelium dysplasia, CD11b$^+$Gr1$^+$ infiltration was reduced and CRC development was inhibited. Our results suggest that MMC activation recruited and modulated the CD11b$^+$Gr1$^+$ cells to promote CRC and that MMCs can be potential therapeutic targets for the prevention of CRC development.

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Introduction

Intrinsic genetic lesions are critical in tumor formation; nevertheless, the importance of chronic inflammation in cancer development has been highlighted recently [1–3]. MCs are abundant at sites exposed to the external environment, such as the intestine, and considered to be important sentinel cells for the inflammatory stimuli. Early studies demonstrated that these cells were vital in medicating bacterial clearance at the sites of infection by producing TNF-α and recruiting neutrophils [4,5]. Their immunomodulatory functions have been observed in a variety of inflammatory diseases, including allergy and autoimmune diseases [6].

Innate and adaptive immune cells shape tumor growth [2,7]. The roles of MCs in tumor development have attracted attention in recent years. MC infiltration has been documented in several types of human tumors. However, the role of MCs in the tumor microenvironment is still debated [8–11]. The mechanisms that underline the opposite effect of MCs on cancer are unclear.

Clinical and experimental animal studies suggest that an altered intestinal epithelium creates a tumorigenic microenvironment that boosts tumor progression [12,13]. In fact, different types of MCs are distinct in maintaining the intestinal barrier function under homeostatic and inflammatory conditions [14,15]. Two major MC subtypes, MMCs and CTMCs, have been described so far [16,17]. The MMCs mainly reside within the mucosa of the intestinal and respiratory tracts and contain mouse mast cell protease (mMCP)-1 and mMCP-2 (chymases); they rarely express tryptase. The CTMCs reside in the submucosa of the gastrointestinal tract and dermis and express the chymases mMCP-4 and mMCP-5, and the tryptases mMCP-6, mMCP-7, and carboxypeptidase A (CPA) [18,19]. Under homeostatic conditions, the overall MC numbers are low, with an approximate 1:1 ratio of MMCs to CTMCs. However, the ratio changed to approximately 5:1 MMCs to CTMCs under inflammatory conditions, with the numbers increased approximately 20–25-fold [20]. Consistent with the increased number of MMCs, remarkably increased mMCP-1 levels were observed [14]. In a colitis-related colon (CRC) animal model, it was found that the mice lacking MCs were less susceptible to inflammation-associated colorectal carcinogenesis [21]. However, it is unclear which MC subtype is mainly involved in the progression from colitis to cancer.

Abbreviations: CRC, colitis-related colon cancer; MC, mast cells; MMC, mucosal mast cells; CTMC, connective tissue mast cells; mMCP, mouse mast cell protease; DSS, dextran sodium sulfate; AOM, azoxymethane; DSCG, disodium cromoglycate.

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Adenosine monophosphate is not superior to histamine for bronchial provocation test for assessment of asthma control and symptoms

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Abstract

Background: Adenosine monophosphate (AMP) may reflect airway inflammation and hyperresponsiveness, but relationship between AMP and histamine (His, a conventional stimulus) bronchial provocation test (BPT) in asthma is not fully elucidated.

Objectives: To compare both BPTs and determine their utility in reflecting changes of asthmatic symptoms.

Methods: BPTs were performed in a cross-over fashion, at 2–4 day intervals. Cumulative doses eliciting 20% FEV_1fall ($PD_{20}FEV_1$), diagnostic performance and adverse events (AEs) were compared. Patients with $PD_{20}FEV_1$ lower than geometric mean were defined as responders, otherwise poor responders. Patients with uncontrolled and partly controlled asthma, who maintained their original inhaled corticosteroids therapy, underwent reassessment of airway responsiveness and asthmatic symptoms 3 and 6 months after.

Results: Nineteen uncontrolled, 22 partly controlled and 19 controlled asthmatic patients and 24 healthy subjects were recruited. Lower $PD_{20}FEV_1$ geometric means were associated with poorer asthma control in His-BPT (0.424 μmol vs 1.684 μmol vs 3.757 μmol), but not AMP-BPT (11.810 μmol vs 7.781 μmol vs 10.220 μmol). Both BPTs yielded similar overall diagnostic performance in asthma (area under curve: 0.842 in AMP-BPT vs 0.850 in His-BPT). AEs, including wheezing and tachypnea, were similar and mild. Ten patients with uncontrolled and 10 partly controlled asthma were followed-up. At months 3 and 6, we documented an increase in $PD_{20}FEV_1$-AMP and $PD_{20}FEV_1$-His, which did not correlate with reduction asthmatic symptom scores. This overall applied in responders and poor responders of AMP-BPT and His-BPT.

Conclusion: Despite higher screening capacity of well-controlled asthma, AMP-BPT confers similar diagnostic performance and safety with His-BPT. AMP-BPT might not preferentially reflect changes asthmatic symptoms.

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Clinical trial registry:
www.clinicaltrials.gov, URL: NCT02318043

*Fan Wu and Wei-Jie Guan shared first co-authorship.

Key words
adenosine monophosphate – asthma – bronchial provocation test – histamine – responder

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Ethics
The Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University.

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OPEN

Adjuvant Chemotherapy for the Completely Resected Stage IB Nonsmall Cell Lung Cancer

A Systematic Review and Meta-Analysis

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Abstract: Adjuvant chemotherapy is recommended for postoperative stage II-IIIB nonsmall cell lung cancer patients. However, its effect remains controversial in stage IB patients. We, therefore, performed a meta-analysis to compare the efficacy of adjuvant chemotherapy versus surgery alone in stage IB patients.

Six electronic databases were searched for relevant articles. The primary and secondary outcomes were overall survival (OS) and disease-free survival (DFS). The time-to-event outcomes were compared by hazard ratio using log-rank test.

Sixteen eligible trials were identified. A total of 4656 patients were included and divided into 2 groups: 2338 in the chemotherapy group and 2318 in the control group (surgery only). Patients received platinum-based therapy, uracil-tegafur, or a combination of them. Our results demonstrated that patients can benefit from the adjuvant chemotherapy in terms of OS (HR 0.74 95% CI 0.63–0.88) and DFS (HR 0.64 95% CI 0.46–0.89). Patients who received 6-cycle platinum-based therapy (HR 0.45 95% CI 0.29–0.69), uracil-tegafur (HR 0.71 95% CI 0.56–0.90), or a combination of them (HR 0.51 95% CI 0.36–0.74) had better OS, but patients who received 4 or fewer cycles platinum-based therapy (HR 0.97 95% CI 0.85–1.11) did not. Moreover, 6-cycle platinum-based therapy (HR 0.29 95% CI 0.13–0.63) alone or in combination with uracil-tegafur (HR 0.44 95% CI 0.30–0.66) had advantages in DFS. However, 4 or fewer cycles of platinum-based therapy (HR 0.89 95% CI 0.76–1.04) or uracil-tegafur alone (HR 1.19 95% CI 0.79–1.80) were not beneficial.

Six-cycle platinum-based chemotherapy can improve OS and DFS in stage IB NSCLC patients. Uracil-tegafur alone or in combination with platinum-based therapy is beneficial to the patients in terms of OS, but uracil-tegafur seems to have no advantage in prolonging DFS, unless it is administered with platinum-based therapy.

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Abbreviations: 95% CI = 95% confidence interval, DFS = disease-free survival, HR = hazard ratio, NSCLC = nonsmall cell lung cancer, OS = overall survival.

INTRODUCTION

Roughly 1.5 million new cases of lung cancer are diagnosed worldwide each year[1] with nonsmall cell lung cancers (NSCLCs) accounting for about 85% of all reported cases. Though surgery is regarded as the primary treatment modality for early stage NSCLC, only 20% to 25% of the tumors are suitable for potentially curative resection, and a substantial percentage of these patients eventually develop local recurrence or distant metastases. As a result, more effective treatment strategies to reduce lung cancer mortality and recurrence rates are needed.

Five-year survival improvements of 5% to 10% have been reported with cisplatin-based adjuvant chemotherapy from multiple large randomized clinical trials[2–5] and meta-analyses.[6,7] Most of the randomized clinical trials reported positive results in patients with completely resected stage IB, II, and IIIA NSCLC.[2–5] Only 1 large randomized trial CALGB9633[8] focused on completely resected stage IB (T2N0) patients. However, its final results of overall survival (OS) and disease-free survival (DFS) lacked statistical significance.

Currently, the role of adjuvant cisplatin-based chemotherapy has been established by multiple large randomized phase III trials for resected stage II and IIIA NSCLC, but its role is controversial in stage IB patients. We, therefore, carried out a systematic review and meta-analysis to provide more reliable and up-to-date evidence on the effect of postoperative chemotherapy in stage IB patients through OS and DFS to identify whether the effect varies by patient subgroup. This included trying to verify the effects of different regimens and duration of postoperative chemotherapy.

MATERIALS AND METHODS

Search Strategy

The electronic search was performed using PubMed, Medline, Cochrane Central Register of Controlled Trial, Cochrane Database of Systematic Reviews, ACP Journal Club, and Database of Abstracts of Reviews of Effects from the date of the earliest publication (1962) to October 2014. In order to achieve the maximum sensitivity, we used the following search strategy: ''lung cancer'' [all fields] AND (''chemotherapy, adjuvant'' [MeSH Terms] OR ''postoperative chemotherapy'' [all fields]. All the articles were filtered by inclusion and exclusion criteria. The study did not involve any experiment on humans or animals, thus the ethical approval was not necessary.

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ORIGINAL ARTICLE

Aetiology of bronchiectasis in Guangzhou, southern China

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ABSTRACT

Background and objective: **Aetiologies of bronchiectasis in mainland China and their comparisons with those in western countries are unknown. We aimed to investigate bronchiectasis aetiologies in Guangzhou, southern China, and to determine ethnic or geographic differences with reports from western countries.**

Methods: **Consecutive patients with steady-state bronchiectasis were randomly recruited. Past history was meticulously extracted. Patients underwent physical examination, saccharine test, humoral immunity assays, gastroesophageal reflux scoring and sputum culture. Fiberoptic bronchoscopy, total immunoglobin E (IgE) and *Aspergillus fumigatus*-specific IgE measurement, 24-h gastroesophageal pH monitoring and miscellaneous screening tests were performed, if indicated. This entailed comparisons on aetiologies with literature reports.**

Results: **We enrolled 148 patients (44.6 ± 13.8 years, 92 females), most of whom had mild to moderate bronchiectasis. Idiopathic (46.0%), post-infectious (27.0%) and immunodeficiency (8.8%) were the most common aetiologies. Miscellaneous aetiologies consisted of asthma (5.4%), gastroesophageal reflux (4.1%), aspergillosis (2.7%), congenital lung malformation (2.0%), Kartagener syndrome (1.4%), rheumatoid arthritis (1.4%), chronic obstructive pulmonary disease (0.7%), Young's syndrome (0.7%), yellow nail's syndrome (0.7%), eosinophilic bronchiolitis (0.7%) and foreign bodies (0.7%). No notable differences in clinical characteristics between idiopathic and known aetiologies were found. Ethnic or geographic variations of aetiologies were overall unremarkable.**

Conclusions: **Idiopathic, post-infectious and immunodeficiency constitute major bronchiectasis aetiologies in Guangzhou. Clinical characteristics of patients between known aetiologies and idiopathic bronchiectasis were similar. Ethnicity and geography only account for limited differences in aetiologic spectra. These findings will offer rationales for early diagnosis and management of bronchiectasis in future studies and clinical practice in China.**

SUMMARY AT A GLANCE

This is the first report on bronchiectasis aetiologies in mainland China. Idiopathic, post-infectious and immunodeficiency were the most common aetiologies. No significant differences were found in ethnicity or geography. Our findings will shed light on early diagnosis and management of bronchiectasis in future studies and clinical practice in China.

Key words: aetiology, bronchiectasis, clinical characteristic, diagnostic test, idiopathic.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; MMEF, maximal mid-expiratory flow.

INTRODUCTION

Bronchiectasis is a heterogeneous disease characterized by chronic cough, sputum production, haemoptysis and fever[1–4] that results from various aetiologies. Ethnic or geographic variations were shown to contribute to different aetiologic spectra among different studies, for instance, idiopathic bronchiectasis accounted for around 50% in western countries[5–9] and 80% in Hong Kong, China.[10]

Symptoms, signs, disease severity and prognosis of bronchiectasis differ considerably with different

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Review Article

Air pollution and COPD in China

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Abstract: Recently, many researchers paid more attentions to the association between air pollution and chronic obstructive pulmonary disease (COPD). Haze, a severe form of outdoor air pollution, affected most parts of northern and eastern China in the past winter. In China, studies have been performed to evaluate the impact of outdoor air pollution and biomass smoke exposure on COPD; and most studies have focused on the role of air pollution in acutely triggering symptoms and exacerbations. Few studies have examined the role of air pollution in inducing pathophysiological changes that characterise COPD. Evidence showed that outdoor air pollution affects lung function in both children and adults and triggers exacerbations of COPD symptoms. Hence outdoor air pollution may be considered a risk factor for COPD mortality. However, evidence to date has been suggestive (not conclusive) that chronic exposure to outdoor air pollution increases the prevalence and incidence of COPD. Cross-sectional studies showed biomass smoke exposure is a risk factor for COPD. A long-term retrospective study and a long-term prospective cohort study showed that biomass smoke exposure reductions were associated with a reduced decline in forced expiratory volume in 1 second (FEV_1) and with a decreased risk of COPD. To fully understand the effect of air pollution on COPD, we recommend future studies with longer follow-up periods, more standardized definitions of COPD and more refined and source-specific exposure assessments.

Keywords: Biomass smoke; air pollution; haze; chronic obstructive pulmonary disease (COPD)

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death globally presently, and it is predicted to become the third leading cause by 2030 (1), making this disease one of the major health challenges in the future (2). The best way to reduce the prevalence of COPD is to control its risk factors; and it is general accepted that smoking is an important risk factor for COPD, although there are other aetiologies of COPD (3). Recently, air pollution as a COPD risk factor has been increasingly recognized.

The Chinese haze is a phenomenon caused by the presence of fine particles ($PM_{2.5}$) at high concentration in the atmosphere, resulting in diminished atmospheric visibility. A few regions were seriously affected by the haze such as the Hua Bei Plain in Northern China, the Yangtze River Delta and the Pearl River Delta (4). In these regions, Air Pollution Index reached above 500, the maximum of the scale. Less than 1% of the 500 largest cities in the People's Republic of China can meet the air quality guidelines recommended by the World Health Organization. Seven of these cities were ranked among the ten most polluted cities in the world (5). So far, studies of the health effects of haze have mainly focused on $PM_{2.5}$, as these fine particles can penetrate deeply into the lung, irritate and corrode the alveolar wall, and consequently impair lung function, clinically leading to cough, wheeze, respiratory disorders and other symptoms. $PM_{2.5}$ exposure, hence, increases the risks of COPD, emphysema and other respiratory diseases (6).

Biomass smoke is the main source of indoor air pollution in the developing world. Biomass fuel is the domestic energy source for almost 3 billion people (7), and the

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Case Report

Alveolar proteinosis in extremis: a critical case treated with whole lung lavage without extracorporeal membrane oxygenation

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Abstract: Pulmonary alveolar proteinosis is a rare idiopathic lung disease characterized by the accumulation of lipoproteinaceous material within the alveoli, which impairs gas transfer and decreases the ventilation/perfusion ratio, and can lead to respiratory failure. Whole lung lavage is the most effective therapy for pulmonary alveolar proteinosis, but may not be tolerated by patients with severe respiratory failure. Extracorporeal membrane oxygenation support is advocated for such patients to ensure appropriate oxygenation during lung lavage. We report a case of a 39-year-old patient with pulmonary alveolar proteinosis and severe life-threatening respiratory failure, with an oxygen index of 51 when under mechanical ventilation. The patient was successfully treated with bilateral whole lung lavage without extracorporeal oxygenation. The results suggest that there is improved ventilation and perfusion matching when one lung is ventilated while the other is lavaged, may be the mechanism of which severe respiratory failure patient due to pulmonary alveolar proteinosis can complete whole lung lavage under one lung ventilation.

Keywords: Pulmonary alveolar proteinosis, severe respiratory failure, whole lung lavage, ventilation/perfusion, extracorporeal membrane oxygenation, treatment

Introduction

Pulmonary alveolar proteinosis (PAP) is a syndrome arising from altered surfactant homeostasis. Pathophysiologically, the major changes involve impaired pulmonary diffusion and ventilation/perfusion mismatch, which may result in respiratory failure [1]. Whole lung lavage (WLL) is considered the standard treatment for progressive PAP leading to respiratory compromise [2]. In very rare cases where the patient has developed critical respiratory failure and cannot tolerate single-lung ventilation, extracorporeal membrane oxygenation (ECMO) may be required to facilitate WLL [2, 3]. However, our experience with WLL over the past 15 years suggests that oxygen saturation may be improved rather than significantly reduced during lavage. This may bring up a question whether ECMO or hyperbaric conditions are always essential for WLL in PAP patients with critical respiratory failure. We present a life-threatening case of PAP requiring mechanical ventilation in which the patient was successfully managed by bilateral WLL under single lung ventilation alone. ECMO was nevertheless set up beforehand.

Case description

A 39-year-old man complained of worsening dyspnea over the past one year. He had a > 10-year history of cigarette smoking (20/day) and worked as a cementer during the past 3 years. In April 2011 he was referred to Beijing Hospital with shortness of breath. Open-lung biopsy demonstrated pulmonary alveolar proteinosis and culture of sputum showed growth of Marseille mycobacterium. He was treated with ethambutol, minocycline and azithromycin according to susceptibility testing. However, he did not improve and exacerbation of the lesions was observed on computed tomography (CT) after two months. Therefore, bilateral WLL was

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Supporting Information

Aminopalladation-Triggered Carbene Insertion Reaction: Synthesis of 2-(1*H*-Indol-3-yl)acetates

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An Intratracheal Challenge Murine Model of Asthma: Can Bronchial Inflammation Affect the Nose?

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Purpose: Extensive data support the influence of the upper airway on lower airway inflammation and pathophysiology in allergic disease. However, few studies have focused on allergic inflammation in the nose after an isolated lower airway allergen challenge, a situation that can exist clinically when human subjects breathe primarily through the mouth, as occurs when nasally congested. This study used a mouse model to investigate whether upper airway inflammation and hyperresponsiveness were induced by an isolated lower airway allergen challenge. **Methods:** BALB/c mice were sensitized by systemic intraperitoneal injection of ovalbumin/saline and challenged with intratracheal ovalbumin/saline. Inflammation in the nose and lungs was assessed by cytology and histology of nasal tissues and bronchoalveolar lavage fluid (BALF), while nasal airway resistance and response were measured over 3 days post-challenge. **Results:** Intratracheal application of an allergen in anaesthetized mice resulted in exclusive deposition in the lower airway. Compared to control animals, ovalbumin -sensitized mice after challenge showed bronchial hyperreactivity and increased IL-5 in the serum BALF, as well as eosinophil infiltration in the lungs. However, nasal histology of the ovalbumin-sensitized mice showed no increase in eosinophil infiltration. The nasal lavage fluid revealed no increase in eosinophils or IL-5, and the nasal airway resistance did not increase after challenge either. **Conclusions:** In a mouse allergy model, exclusive allergen challenge of the lower airway can elicit a pulmonary and systemic allergic response, but does not induce upper airway inflammatory or physiological responses.

Key Words: Asthma; rhinitis; mice; inflammation

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INTRODUCTION

Many academics now consider that allergic rhinitis (AR) and asthma reflect the pathology of a common pathologic process in one 'united airway'.[1] Previous studies have indicated an extensive impact of upper airway conditions on the lower airways in airway allergic diseases.[2] The majority of patients with asthma have rhinitis.[1,3] One-third of allergic rhinitis patients suffer from clinically demonstrable asthma[4] and have lower airway inflammation and bronchial hyper responsiveness (BHR).[5] There is a 3-fold increased risk of developing asthma if a patient has AR.[6] Nasal allergen challenge causes sputum eosinophilia and BHR in patients with allergic rhinitis and asthma.[7,8] Asthmatic patients with moderate to severe allergic rhinitis may experience more severe asthma.[9,10] Several studies using murine models to mimic the human condition have shown that isolated upper airway allergen provocation initiates allergic inflammation and BHR in the lower airways.[11-14] This suggests that allergen provocation of the upper airways in animals and humans can exert physiological effects in the distal airways in the absence of a direct allergen challenge.

Contrary to previous results on the effects exerted by the upper airways on the lower airways, few studies have focused on the pathologic consequences in an "upstream" organ (the nose) after an isolated *lower* airway allergen challenge.[15,16] The aim of this study was to determine, in a murine model, if an isolated lower airway allergen provocation was sufficient to induce *upper* airway allergic inflammation and hyperresponsiveness.

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REVIEW

Approaches for the generation of active papain-like cysteine proteases from inclusion bodies of *Escherichia coli*

Chunfang Ling · Junyan Zhang · Deqiu Lin · Ailin Tao

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Abstract Papain-like cysteine proteases are widely expressed, fulfill specific functions in extracellular matrix turnover, antigen presentation and processing events, and may represent viable drug targets for major diseases. In depth and rigorous studies of the potential for these proteins to be targets for drug development require sufficient amounts of protease protein that can be used for both experimental and therapeutic purposes. *Escherichia coli* was widely used to express papain-like cysteine proteases, but most of those proteases are produced in insoluble inclusion bodies that need solubilizing, refolding, purifying and activating. Refolding is the most critical step in the process of generating active cysteine proteases and the current approaches to refolding include dialysis, dilution and chromatography. Purification is mainly achieved by various column chromatography. Finally, the attained refolded proteases are examined regarding their protease structures and activities.

Keywords Papain-like cysteine proteases · *Escherichia coli* · Refolding · Purification · Activation

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Introduction

One of the important protease families found in the prokaryotic, plant, and animal kingdoms is the cysteine protease family, which is involved in diverse aspects of the physiology and development of organisms (Dolinar et al. 1995; Dutta et al. 2010; Joo et al. 2007). Papain-like cysteine proteases, the most numerous subfamily of the cysteine protease class, have been identified as responsible for the key proteolytic activities in invasive, immune system related and degenerative disorders (Lecaille et al. 2002). For instance, cathepsin S regulates MHC class II dependent antigen presentation. Specific inhibition of cathepsin S can attenuate antibody response and, therefore, cathepsin S could be considered as a novel drug target for asthma and certain auto-immune diseases (Riese et al. 1998). Cathepsins are also involved in a variety of disease processes such as glomerulonephritis, arthritis and cancer metastasis (Smith and Gottesman 1989). Group 1 (DerF1 and DerP1) allergens are a contributing factor in atopic disease (perennial rhinitis, asthma, and atopic dermatitis) worldwide (Best et al. 2000; Yasuhara et al. 2001). In addition, parasite derived papain-like cysteine proteases are critical to the life cycle or pathogenicity of many parasites (Sajid and McKerrow 2002).

Sufficient amounts of bioactive papain-like cysteine proteases would be useful for analysis of the relationship between enzymatic activity and pathogenesis as well as for understanding the development of therapeutic inhibitors. Expression of cysteine proteases at high expression rates has been accomplished using recombinant DNA technology. Among the heterologous recombinant DNA expressions systems, the *E. coli* expression system is the most convenient and frequently used, and plays a key role in producing useable amounts of genetically engineered

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RESEARCH ARTICLE

Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis

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Abstract

Background

Air pollution constitutes a significant stimulus of asthma exacerbations; however, the impacts of exposure to major air pollutants on asthma-related hospital admissions and emergency room visits (ERVs) have not been fully determined.

Objective

We sought to quantify the associations between short-term exposure to air pollutants [ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter $\leq$10μm (PM_{10}) and $PM_{2.5}$] and the asthma-related emergency room visits (ERV) and hospitalizations.

Methods

Systematic computerized searches without language limitation were performed. Pooled relative risks (RRs) and 95% confidence intervals (95%CIs) were estimated using the random-effect models. Sensitivity analyses and subgroup analyses were also performed.

Results

After screening of 246 studies, 87 were included in our analyses. Air pollutants were associated with significantly increased risks of asthma ERVs and hospitalizations [O_3: RR(95%

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Original Article

Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications

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Contributions: (I) Conception and design: WJ Guan, YH Gao, RC Chen, NS Zhong; (II) Administrative support: None; (III) Provision of study materials and patients: JP Zheng, RC Chen, NS Zhong; (IV) Collection and assembly of data: WJ Guan, YH Gao, G Xu, JJ Yuan, HM Li; (V) Data analysis and interpretation: WJ Guan, YH Gao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Bronchial dilation testing is an important tool to assess airway reversibility in adults with bronchiectasis. This study aims to investigate the association of bronchodilator response (BDR) and clinical parameters in bronchiectasis, and the utility of BDR to indicate lung function decline and risks of bronchiectasis exacerbations (BEs).

Methods: We recruited 129 patients with clinically stable bronchiectasis. Baseline measurements included assessment of sputum inflammation and matrix metalloproteinase-8 and -9, sputum bacterial culture, spirometry, bronchial dilation test (for baseline FEV_1 less than 80% predicted only) and chest high-resolution computed tomography (HRCT). Bronchiectasis patients were followed-up for 1 year to determine the incidence of BEs and lung function trajectories. Significant BDR was defined as FEV_1 improvement from pre-dose value by at least 200 mL and 12%. Clinical trial registry No.: NCT01761214; URL: www.clinicaltrials.gov.

Results: BDR was negatively correlated with baseline FEV_1 percentage predicted, but not blood or sputum eosinophil count. Significant BDR was not associated with greater proportion of never-smokers, poorer past history, greater HRCT scores, poorer diffusing capacity or increased sputum matrix metalloproteinases (all P>0.05). There was a trend towards higher bronchiectasis severity index (BSI) and greater proportion of patients with *Pseudomonas aeruginosa* isolation or infection. Significant BDR at baseline was linked to poorer spirometry, but not more rapid lung function decline, throughout follow-up. Patients with significant BDR demonstrated non-significantly lower risks of experiencing the first BEs than those without (P=0.09 for log-rank test).

Conclusions: Significant BDR is associated with poorer lung function compared with non-significant BDR. Whether BDR predicts future risks of BEs needs to be tested in a larger cohort.

Keywords: Bronchiectasis; bronchodilator response (BDR); clinical parameter; bronchiectasis exacerbation (BE)

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Bacterial β-Ketoacyl-Acyl Carrier Protein Synthase III (FabH) as a Target for Novel Antibacterial Agents Design

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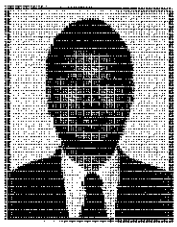

Abstract: In bacterial type II fatty acid biosynthesis (FAS-II), β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH) initiates the first condensation of acyl-CoA and malonyl-ACP to form acetoacetyl-ACP. Its key role for organism survival and specificity to bacteria make it as an essential target for the discovery of novel antibacterial agents. Over the last decade, several structures of FabH from diverse microorganisms have been solved, giving detailed information about the three-dimensional features of the catalytic pocket. This has facilitated the rational design of FabH inhibitors, which provides a framework for future development of antibiotics against multi-drug resistant strains. This review covers recent advances in the biochemical and structural research of FabH and updates the main families of related inhibitors.

Keywords: Antibacterial, active site, β-Ketoacyl-acyl carrier protein synthase III (FabH), inhibitors, type II fatty acid biosynthesis (FAS-II).

1. INTRODUCTION

Bacterial resistance to antibiotics remains a serious medical problem in clinical practice, where antibiotics are widely used with the emergence of multi-drug resistant (MDR) strains [1, 2]. In the case of tuberculosis (TB), the World Health Organization (WHO) estimated in 2012 that over 0.6 million people worldwide are infected with MDR-TB and extensively drug-resistant TB (XDR-TB) [3, 4]. Novel antibiotics are urgently required to overcome these resistances. The enzymes of FAS II stand out among the many potential targets for the development of novel antibiotics [5-8].

There are two basic types of FAS architectures existing in nature, designated FAS I and FAS II [7]. In the type I FAS system, each reaction is catalyzed by distinct domains of large multifunctional proteins, while in the type II FAS pathway, a series of monofunctional enzymes is involved in individual reaction step [9]. β-Ketoacyl acyl carrier protein synthase (FabH or KAS III), one of the pivotal enzyme in bacterial type II FAS, initiates the biosynthetic process by catalyzing the condensation reaction between acyl-CoA and malonyl-ACP, and the released long-chain acyl-ACPs act as feedback regulation of the fatty acid biosynthesis [10-12]. The essentiality of FabH for bacterial viability [10, 13], together with no resistant gene found in FabH, suggests the ideal that FabH can serve as a particular promising target for the development of novel antibiotics against MDR strains [14, 15].

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So far, several three-dimensional (3D) structures of FabH from different microorganisms have been solved [11, 16-19]. Discovering and designing FabH inhibitors would therefore be of prime interest. In 2012, the biological features and inhibitors of FabH have been reviewed [20, 21]. In this paper, we summarize recent advances in the biochemical and structural research of FabH in terms of mode of action and crystal structural features, and provide an update of the main families of the inhibitors designed based on this knowledge.

2. FABH: ROLE IN TYPE II FAS SYSTEM

Fatty acid biosynthesis is catalyzed by the fatty acid synthase (FAS) system, which includes two related but distinct forms. In the FAS I system, mainly identified in eukaryotic organisms, all of the elongation of fatty acid chain is catalyzed by a single multifunctional polypeptide [9, 22]. FAS II, a dissociated system, has been identified among most bacterial strains and plants, and each reaction of chain initiation and elongation in this pathway is catalyzed by a unique protein [5, 7]. A typical FAS II pathway, with the detailed enzymatic reactions for chain initiation and elongation, has been studied extensively in *E. coli* [23, 24].

In the whole type II FAS pathway, FabH (KAS III) initiates the process through the Claisen condensation of acyl-CoA with malonyl-ACP [25], and participates in the feedback regulation of the entire pathway by product inhibition [26]. The other two bacterial condensing enzymes, FabB (KAS I) and FabF (KAS II), carry out the elongation reactions of fatty acid chain, but they are distinguished from FabH in terms of prim selctivity, sequence and structure. FabB and FabF are selective for acyl-ACP over acyl-CoA, the prim of FabH [12, 27, 28]. The sequence homology between FabB and FabF is about 38%, while FabH has less

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OPEN

Button Battery Intake as Foreign Body in Chinese Children

Review of Case Reports and the Literature

Wenjing Liao, Guangyi Wen,* and Xiaowen Zhang, MD†*

Objectives: Button batteries have been recognized as one of the dangerous foreign bodies to children for more than 30 years, but few related studies have been published to give more concern in China.

Methods: We reported 6 cases of button battery intake as foreign body in children. The Chinese literature on button battery as foreign body in children was reviewed.

Results: The interval between the accidental ingestion and battery removal ranged from 6 hours to 3 days. Two patients had no sequela, 3 patients had tracheoesophageal fistulas, and 1 patient had nasal septal perforation. Twenty-eight articles about button battery as foreign body in children were obtained by Chinese-language literature searches including 25 case reports, 2 health education articles, and 1 imaging article. In total, 172 cases of button battery intake as foreign body in children were identified, 23 and 10 of the 159 cases involving nasal button battery lodgment developed nasal septal perforation and nasal adhesion, respectively. Tracheoesophageal fistula was identified in 4 of the 12 ingestion cases. One case of button battery intake was in external auditory canal.

Conclusions: A small number of children with button battery as foreign body were reported in China, which is 1 of the biggest countries with large population of children.

Key Words: button battery, foreign body, China, review

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Button batteries were recognized as hazardous to kids as early as 3 decades ago.[1] Over the recent years, increasing miniaturization of electronic devices has expedited the widespread use of button batteries in household appliances and children's toys. As a result, button batteries with smooth and shiny appearance are more appealing and accessible to young children.[2] In parallel, the annual incidence of button battery ingestion has been reckoned to be 6.3 to 15.1 per million.[3]

Between 1997 and 2010, an estimated 40,400 children aged younger than 13 years in the United States visited hospital emergency departments for treatment of battery-related injuries (BRI), including confirmed or possible battery intake. Nearly 75% of the BRI cases involved children aged 4 years or younger and 10% required hospitalization.[4] Although these data have posed a health concern over accidental BRI in family caregiving in the United States, less attention to these injuries was aroused in China, another largest toy consumer and manufacturer worldwide. So far, in this country, epidemiological data regarding both the incidence of BRI and a treatment observation protocol remain limited. Here, we presented 6 cases of button battery intake as foreign body, with review of related literatures about BRI in Chinese children.

METHODS

Between July 2009 and February 2013, there were 6 consecutive pediatric cases of button battery intake treated in the Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital of Guangzhou Medical University. The diagnosis of button battery intake in these children was based on history, clinical manifestations, and imaging studies. Data on the patient age, time to first treatment, route of button battery intake (ingestion or inhalation), length of hospital stay, imaging findings, and medical outcomes were reviewed (Table 1).

Furthermore, we conducted a thorough search for case series of injuries related to button battery intake as a foreign body among Chinese children. The search was limited to English- or Chinese-language articles by authors from the mainland China. Four databases (PubMed, Web of Knowledge, Scopus, and ProQuest) were used for searching of English-language articles. For Chinese-language articles, we used China National Knowledge Infrastructure, Wanfang Database, and VIP Journal Integration Platform, the first 3 largest global databases of academic full-text articles in Chinese language online. The date of target publications was from January 1979 up to December 2012. The terms used for the literature search were "button battery" and "foreign body" and "Chinese" and "children," or where applicable, "Niukou Dianchi" ("button battery" in Chinese) and "Yiwu" ("foreign body" in Chinese) and "Ertong" ("children" in Chinese). The full text of resultant articles was read to exclude any irrelevant studies. To obtain additional literature that was not indexed, a secondary manual search was performed by checking all the reference lists from within the retrieved articles.

RESULTS

Of the 6 children (4 boys and 2 girls) in this study, the patient age ranged from 11 months to 6 years. The mean time from button battery intake to treatment was 18.33 hours (range, 6 hours-3 days). The mean length of hospital stay was 18 days.

BRIEF PRESENTATION OF 3 TYPICAL CASES

Case 1

A 2-year-old boy was admitted to the Department of Otolaryngology-Head and Neck Surgery within 2 hours of foreign body ingestion, presenting with sore throat and dysphagia. Esophagography showed a round opacity in the upper esophagus that seemed to be a button battery (Figs. 1A, B).

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Review Article

Ca^{2+} and ion channels in hypoxia-mediated pulmonary hypertension

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Abstract: Alveolar hypoxia, a consequence of many lung diseases, can have adverse effects on the pulmonary vasculature. The changes that occur in the pulmonary circulation with exposure to chronic hypoxia include reductions in the diameter of the pulmonary arteries due to structural remodeling of the vasculature. Although the structural and functional changes that occur in the development of pulmonary hypertension have been well investigated, less is known about the cellular and molecular mechanisms of this process. This review will discuss the role of several potassium and calcium channels in hypoxic pulmonary vasoconstriction, both in elevating calcium influx into pulmonary artery smooth muscle cells (PASMCs). In addition to other signal transduction pathways, Ca^{2+} signaling in PASMCs plays an important role in the development and progression of pulmonary hypertension due to its central roles in vasoconstriction and vascular remodeling. This review will focus on the effect of chronic hypoxia on ion channels and the potential pathogenic role of Ca^{2+} signaling and regulation in the progression of pulmonary hypertension.

Keywords: Intracellular calcium, chronic hypoxia, pulmonary vascular smooth muscle, calcium regulation, hypoxic pulmonary hypertension

Introduction

Sustained pulmonary hypertension is a common complication of chronic lung diseases and alveolar hypoxia is thought to be a key stimulus to the development of this complication. If this disease will not be treated properly, pulmonary hypertension can lead to right-sided heart failure and attendant increases in morbidity and mortality. Exposure to chronic hypoxia (CH) leads to pulmonary hypertension in several animal models: hypoxia leads to structural changes in the walls of distal PA, known as pulmonary vascular remodeling, and a sustained elevation of pulmonary vascular resistance [1, 2]. The characteristic pathological findings in the hypoxic hypertensive pulmonary circulation are increased wall thickness of small muscular arteries and muscularization of normally nonmuscular arteries at the level of the alveolar ducts.

Chronic hypoxic pulmonary hypertension (CHPH) results from the complicated yet poorly understood direct effects of hypoxia and indirect effects of endogenous factors such as endothelin-1 [3-6], angiotensin II [7-10], serotonin [11-13], prostacyclin [14-16], nitric oxide [17-19], platelet derived growth factor [20-22], and metalloproteinases on the cellular and matrix elements of the pulmonary arterial wall. Histologically, progressive hyperplasia and hypertrophy of PASMCs, extension of smooth muscle into previously nonmuscular arteries and other structural changes reduce vascular cross-sectional area, leading to increases in resistances that are not completely reversed by acute administration of vasodilators. The relative contributions of structural remodeling and increased vasomotor tone to CHPH may vary with time, age, species and other factors. The vascular remodeling that occurs in the lung is due, in part, to proliferation and migration of PASMCs [23]. Despite extensive study, the exact mechanisms underlying pulmonary vascular remodeling, growth and migration of PASMCs in pulmonary hypertension remain incompletely understood.

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Carbocisteine attenuates hydrogen peroxide-induced inflammatory injury in A549 cells *via* NF-κB and ERK1/2 MAPK pathways

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ABSTRACT

Carbocisteine is a mucolytic drug with anti-oxidative effect. We had previously proved that carbocisteine remarkably reduced the rate of acute exacerbations and improved the quality of life in patients with chronic obstructive pulmonary disease (COPD), however, very little is known about its mechanisms. In this study, we aimed to investigate the anti-inflammatory effects of carbocisteine against hydrogen peroxide (H_2O_2). A549 cells were cultured *in vitro* and treated with H_2O_2 as damaged cell models, carbocisteine was administered 24 h prior to or after H_2O_2 exposure, and the protective effects of carbocisteine were determined by MTT, qRT-PCR, ELISA, western blot and immunofluorescence assays. The results showed that carbocisteine could increase cell viability and decrease LDH, IL-6 and IL-8 levels in the supernatant. Additionally, carbocisteine decreased IL-6, IL-8, TNF-α, IP-10 and MIP-1β mRNA in a dose-dependent manner. Moreover, carbocisteine could attenuate phosphorylation of NF-κB p65 and ERK1/2 and inhibit the nuclear translocation of pNF-κB p65 induced by H_2O_2. In conclusion, carbocisteine inhibited H_2O_2-induced inflammatory injury in A549 cells, NF-κB and ERK1/2 MAPK were the target pathways.
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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide and is characterized by progressive airflow limitation associated with high levels of inflammatory mediators and marked oxidative stress, which can further promote the inflammatory process in COPD *via* enhancing NF-κB and/or MAPK-driven inflammatory gene transcription [1–3]. Oxidative stress and inflammation are inseparably intertwined in the pathogenesis of COPD.

NF-κB is a critical signaling molecule in H_2O_2-induced inflammation and in responses produced by a variety of stimuli including oxidant stress [4,5]. Mitogen activated protein kinases (MAPKs) are evolutionarily conserved mediators in signal transduction pathways, which modulate embryogenesis, gene expression and cell functions [6]. The target genes of NF-κB and MAPK signal pathways include cytokines and chemokines, such as IL-1β, IL-6, IL-8, TNF-α, MCP-1, IP-10 and MIP.

Though inhaled bronchodilators and inhaled corticosteroids are recommended as a first-line therapy for the management of COPD, it is necessary to develop other effective, safe, non-expensive and easy-to-use medications [7]. Carbocisteine, known as *S*-carboxymethylcysteine, has been prescribed as a mucoregulatory drug which has the ability of decreasing mucus viscosity and improving the mucociliary transport function in the airway. We have previously proved that carbocisteine markedly reduced the rate of acute exacerbations and improved the quality of life in patients with COPD [8], other publications had shown similar results [9,10], but the mechanism remains unclear.

In contrast to N-acetylcysteine, carbocisteine does not carry a free sulfhydryl (thiol) group, but its thioether group can be oxidized by reactive oxygen species (ROS). Carbocisteine could act as a direct scavenger of ROS and an indirect antioxidant, possessing potential anti-oxidant effects [11–13], and could reduce the production of pro-inflammation cytokines after rhinovirus or respiratory syncytial virus infection [14,15]. The reports about anti-inflammatory abilities of carbocisteine are still scarce.

Hydrogen peroxide (H_2O_2), a small molecule and functions as oxidative stress and a second messenger which contributes to cell damage or death [16,17], could directly activate NF-κB and MAPK, and induce inflammation in several cell lines [5,18]. However, whether carbocisteine has anti-inflammatory effect against H_2O_2 and the mechanisms is underdetermined. Airway epithelial cells and macrophages are the first defense cells against environmental stimuli and are important sources of pro-inflammatory cytokines, consequently we chose human lung alveolar type II epithelial cells (A549 cells). We hypothesized that carbocisteine attenuated H_2O_2-induced inflammation by inactivation of NF-κB and MAPK, leading to less release of cytokines

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C-Aryl glucoside SGLT2 inhibitors containing a biphenyl motif as potential anti-diabetic agents

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ABSTRACT

A series of highly active *C*-aryl glucoside SGLT2 inhibitors containing a biphenyl motif were designed and synthesized for biological evaluation. Among the compounds tested, compound **16l** demonstrated high inhibitory activity against SGLT2 (IC_{50} = 1.9 nM) with an excellent pharmacokinetic profile. Further study indicated that the in vivo efficacy of compound **16l** was comparable to that of dapagliflozin, suggesting that further development would be worthwhile.

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国家重点实验室 糖尿病

Inhibition of renal sodium-dependent glucose co-transporter (SGLT) proteins is an attractive strategy for the mitigation of hyperglycemia in type 2 diabetes.[1] SGLT1 and SGLT2 are two major SGLT isoforms, SGLT1 is distributed mainly in the small intestine and also present in the S3 segment of the proximal tuble. Inhibition of SGLT1 is likely to cause gastrointestinal side effects.[2] Unlike SGLT1, SGLT2 is a glucose transport protein expressed primarily on the S1 and S2 segment of proximal tubules in the kidney, and it took charge of 90% renal glucose reabsorption.[2,3] selective SGLT2 inhibitors would be desirable, since gastrointestinal side effects associated with SGLT1 inhibition would be minimized.[4] By promoting urinary glucose excretion (UGE), inhibitors of SGLT2 show promise for the treatment of diabetes by attenuation of postprandial plasma glucose levels.[5,6]

The *O*-arylglucoside natural product phlorizin **1** is a well-known potent SGLTs inhibitor (**1**, Fig. 1).[7] Phlorizin **1** was not developed as a drug for the non-selective against SGLT1 and the poor oral bioavailability.[8] The *C*-aryl glycoside SGLT2 inhibitors, such as dapagliflozin (**2**, Fig. 1),[4,9,10] reported as metabolically more stable SGLT2 inhibitor, it's glycoside carbon linker is more stable than the glycoside oxygen linker.[10] Dapagliflozin developed by Bristol-Myers Squibb Company was the first SGLT2 inhibitor to be approved by the EMA. Currently, another potent C-glucoside-derived SGLT2 inhibitor canagliflozin (**3**, Fig. 1),[11] was developed by Mitsubishi Tanabe Pharma and Johnson & Johnson. On March 29, the US Food and Drug Administration (FDA) granted approval of Invokana (canagliflozin) for the treatment of adult type 2 diabetes. In addition, Boehringer Ingelheim's empagliflozin (**4**, Fig. 1),[12] Lexicon's LX4211 (**5**, Fig. 1),[13] Astellas's ipragliflozin (**6**, Fig. 1)[14] and Pfizer's ertugliflozin (**7**, Fig. 1)[15] are reported to be in various phases of clinical trials.

The biphenyl moiety is considered to be a privileged structure in the drug design process,[16,17] and the use of biphenyl motifs in the field of medicinal chemistry is very common. A survey of the literature revealed that certain biphenyl derivatives possess significant pharmacological and therapeutic activity. Among drug molecules, 4.3% have the biphenyl moiety in their framework. Biphenyl derivatives are known to have antiamebic, antifungal, and antiarrhythmic activities.[16,17] We hypothesized that introduction of the biphenyl motif into *C*-aryl glucosides might offer a new strategy for the design of novel SGLT2 inhibitors. Our preliminary investigation involving replacement of the distal ring of dapagliflozin with a biphenyl group provided structure **16e** (Fig. 2), a compound with good SGLT2 inhibitory activity (IC_{50} = 4.0 nM) and high selectivity versus SGLT1 (525-fold). A series of *C*-aryl glucosides bearing the

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Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial

Nan Shan Zhong, Tieying Sun*, Chao Zhuo*, George D'Souza, Sang Haak Lee, Nguyen Huu Lan, Chi-Huei Chiang, David Wilson, Fang Sun, Joseph Iaconis, David Melnick*

Summary

Background Ceftriaxone with or without a macrolide antibiotic is a recommended treatment for patients with community-acquired pneumonia requiring hospital admission and intravenous antibiotic treatment. We aimed to assess the efficacy and safety of ceftaroline fosamil compared with ceftriaxone in the treatment of Asian patients admitted to hospital with community-acquired pneumonia.

Methods In this international, randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial, adult Asian patients with Pneumonia Outcomes Research Team (PORT) risk class III–IV acute community-acquired pneumonia were randomly assigned (1:1) to receive intravenous ceftaroline fosamil (600 mg every 12 h) or ceftriaxone (2 g every 24 h) for 5–7 days. Patients were randomly assigned via centralised telephone and web-based system; patients and treating clinicians were masked to treatment allocation. Investigators who did study assessments remained masked to treatment allocation until completion of the study. The primary endpoint was clinical cure at the test-of-cure visit (8–15 days after last dose of study drug) in the clinically evaluable population. Non-inferiority of ceftaroline fosamil was defined as a lower limit of the two-sided 95% CI for the difference in the proportion of patients clinically cured of –10% or higher; if non-inferiority was achieved, superiority was to be concluded if the lower limit of the 95% CI was greater than 0%. This trial is registered with ClinicalTrials.gov, number NCT01371838.

Findings Between Dec 13, 2011, and April 26, 2013, 847 patients were enrolled at 64 centres in China, India, South Korea, Taiwan, and Vietnam, of whom 771 were randomly assigned and 764 received study treatment. In the clinically evaluable population (n=498) 217 (84%) of 258 patients in the ceftaroline fosamil group and 178 (74%) of 240 patients in the ceftriaxone group were clinically cured at the test-of-cure visit (difference 9·9%, 95% CI 2·8–17·1). The superiority of ceftaroline fosamil was consistent across all preplanned patient subgroup analyses (split by age 65 years, age 75 years, sex, PORT risk class, and previous antibiotic use) apart from patients younger than 65 years. The frequency of adverse events was similar between treatment groups and the safety results for ceftaroline fosamil were consistent with the cephalosporin class and previous clinical trial data.

Interpretation Ceftaroline fosamil 600 mg given every 12 h was superior to ceftriaxone 2 g given every 24 h for the treatment of Asian patients with PORT III–IV community-acquired pneumonia. These data suggest that ceftaroline fosamil should be regarded as an alternative to ceftriaxone in empirical treatment regimens for this patient population.

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See Comment page 132

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Introduction

The morbidity and mortality associated with community-acquired pneumonia of sufficient severity to require hospital admission remain high despite existing management strategies.[1,2] Clinical treatment guidelines in the USA,[3] Europe,[4] and Asian countries[5–8] recommend intravenous broad-spectrum cephalosporins such as ceftriaxone, often in combination with a macrolide antibiotic, as a treatment option for such patients.

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin with in-vitro activity against pathogens that often cause community-acquired pneumonia, including Gram-positive species such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, and non-extended-spectrum β-lactamase (non-ESBL) phenotype Gram-negative species including *Klebsiella pneumoniae* and *Haemophilus influenzae*. Compared with other β-lactams, ceftaroline has enhanced in-vitro activity against meticillin-resistant *S aureus* (MRSA) and penicillin-non-susceptible *S pneumoniae*, although ceftaroline fosamil is not currently approved for the treatment of community-acquired pneumonia caused by these pathogens. Ceftaroline fosamil is licensed in Europe for the treatment of adult patients admitted to hospital with community-acquired pneumonia or complicated skin and soft-tissue infection at a dose of 600 mg every 12 h, adjusted for renal function, and for similar indications in several other countries, including the USA.[9,10]

内部资料 国家临床重点实验室

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Cell-death-inducing DFFA-like Effector B Contributes to the Assembly of Hepatitis C Virus (HCV) Particles and Interacts with HCV NS5A

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Hepatitis C virus (HCV) uses components of the very-low-density lipoprotein (VLDL) pathway for assembly/release. We previously reported that hepatocyte nuclear factor 4α (HNF4α) participates in HCV assembly/release through downstream factors those participate in VLDL assembly/secretion. Cell-death-inducing DFFA-like effector B (CIDEB) is an important regulator of the VLDL pathway. CIDEB is required for entry of HCV particles from cell culture (HCVcc), but the effects of CIDEB on the post-entry steps of the HCV lifecycle are unclear. In the present study, we determined that CIDEB is required for HCV assembly in addition to HCVcc entry. Furthermore, CIDEB interacts with the HCV NS5A protein, and the N terminus of CIDEB and the domain I of NS5A are involved in this interaction. Moreover, CIDEB silencing impairs the association of apolipoprotein E (ApoE) with HCV particles. Interestingly, CIDEB is also required for the post-entry stages of the dengue virus (DENV) life cycle. Collectively, these results indicate that CIDEB is a new host factor that is involved in HCV assembly, presumably by interacting with viral protein, providing new insight into the exploitation of the VLDL regulator CIDEB by HCV.

As a positive-strand RNA virus belonging to *Hepacivirus* of *Flaviviridae*, hepatitis C virus (HCV) hijacks host lipid metabolism during its life cycle[1], including viral particle assembly/release. HCV assembly begins on the ER-lipid droplet (LD) surface, where the viral core protein, surface glycoproteins (E1 and E2), and viral RNA are assembled and packaged in a temporally and spatially regulated manner[2–4]. Nascent HCV particles then form by budding into the ER and fuse with pre-very-low-density lipoprotein (VLDL) particles to form lipo-viro particles (LVPs)[2,5], or nascent HCV particles then form by budding of viral capsids into the ER lumen, incorporate cholesterol and triglycerides (TGs), and further bind ApoB and exchangeable apolipoproteins in a manner similar to lipoproteins to form LVPs[6]. The LVPs fi ally bud from the ER and transit via the secretory pathway[2,5].

It has been widely discussed that HCV hijacks the VLDL secretory pathway to facilitate its assembly and secretion[7–9]. LDs, which are sources of VLDL lipidation, play a crucial role in HCV assembly[10]. Several VLDL key components, such as apolipoprotein E (ApoE), ApoC-I, ApoC-III, and ApoA-I, are involved in HCV assembly/release[8,11–17]. We previously reported that PLA_2GXIIB, another VLDL component, also participates in HCV release[18]. One of the mechanisms by which HCV exploits the VLDL components is via protein-protein interactions between HCV proteins and VLDL components, as illustrated by the participation of ApoE in HCV assembly[12,19,20]. ApoE is an exchangeable apolipoprotein in VLDL assembly and participates in the formation of infectious HCV particles by interacting with HCV NS5A and E2 proteins[12,19,20].

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parallel with similar efforts in Europe, strategies need to be developed to protect commercial and pet rabbits.

Tracking the spread of RHDV2 in Australia, in competition with existing field strains, highlights the value of Australia's rabbits and their diseases as a model system for emerging infectious diseases. The point releases of both myxoma virus and RHDV into large naive host populations represent a grand experiment in disease emergence and evolution (*10*), which provides a unique opportunity to study the virulence evolution of emerging pathogens as well as their complex interactions with each other. It is notable that since the release of RHDV in Australia in 1995, strains of 1 viral lineage dominate the viral population nationwide despite hundreds of deliberate re-releases of the original virus strain for local rabbit control, which strongly suggests it has a major selective advantage (*7*). That RHDV2 appeared in a wild rabbit is therefore remarkable, particularly because Australian field strains were spreading simultaneously in the same area. Comparing the epidemiology of this strain in Australia to the epidemiology of its well-documented spread in Europe will provide valuable insights into RHDV epidemiology relevant to both continents.

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Characteristics of Traveler with Middle East Respiratory Syndrome, China, 2015

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To the Editor: A traveler returning from the Middle East initiated an outbreak of Middle East respiratory syndrome (MERS) in South Korea in 2015, which resulted in 186 cases and 36 deaths (*1–3*). We report a case of

[1]These authors contributed equally to this article.

中国疾病预防控制中心重庆实验室

Original Article

Characterization of a new subtype of allergen in dermatophagoides farinae—Der f 28

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Contributions: (I) Conception and design: J Lin, X Liu; (II) Administrative support: Z Liu, P Yang, J Li; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: J Lin, Y Wang, X Xiao; (V) Data analysis and interpretation: J Lin, Y Wu, B Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: House dust mites (HDMs) are the major sources of indoor allergens which induce asthma, dermatitis, rhinitis, and some other allergic diseases. Close to 30 sub-allergens have been identified.

Methods: Through analyzing the full genome sequence of dust mite, a new allergen whose primary structure belongs to the heat shock protein family was identified. The sequence of this allergen was determined by cDNA cloning. The allergenicity was assayed by skin prick test, Western-blot and enzyme-linked immunosorbent assay (ELISA).

Results: r-Der f 28 bound to serum IgE from mite allergic patients. Positive responses to r-Der f 28 were shown in 11.5% by skin prick testing from 26 DM-allergic patients. Airway hyperresponsiveness, serum specific IgE and IL-4 were significantly increased in allergic asthma mouse model sensitized to r-Der f 28.

Conclusions: Der f 28 is a new subtype of allergen in dermatophagoides farinae.

Keywords: Dermatophagoides farinae; Der f 28; western-blotting; enzyme-linked immunosorbent assay (ELISA); skin prick test; allergic asthma; mouse model

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肿胶类病国家重点实验室

Introduction

A significant increase in the prevalence of allergic diseases has been an important public health problem in the world (1,2). House dust mites (HDMs) are globally important sources of indoor allergens (3), responsible for the sensitization of more than 50% of allergic patients (4,5). At present, *antigen SIT* (specific immunotherapy) with HDM extracts is the most efficient treatment for *dust mite* allergic diseases. However, the crude extracts of HDM not only contain inflammatory molecules, such as ceramides, kallikreins and the ever popular endotoxin, but also include allergens, which have been proved having side effects in the clinical treatment (6). Specific immunotherapy with HDM extracts is an efficient treatment but severe side-effects may occur in the course of treatment. Therefore, recombinant allergens have been regarded as a substitute for crude mite extracts used in clinical immunotherapy which may effectively improve the efficacy and safety of house dust-mites-specific immunotherapy.

A large number of studies have been conducted to understand the structural properties, chemical and biological of dust mite allergens. Two groups of mite allergens (group 1 and 2) have been proven to be the major

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CORRIGENDUM

Chronic Hypoxia Increases Intracellular Ca^{2+} Concentration via Enhanced Ca^{2+} Entry Through Receptor-Operated Ca^{2+} Channels in Pulmonary Venous Smooth Muscle Cells

Gongyong Peng, MD; Shaoxing Li, BSc; Wei Hong, MD; Jinxing Hu, MD; Yongliang Jiang, MD; Guoping Hu, MD; Yimin Zou, MD; Yumin Zhou, MD; Juan Xu, BSc; Pixin Ran, MD

(*Circ J* 2015; **79**: 2058–2068)

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Page 2067, right column, lines 43–48:

Incorrect:

This work was supported by the National Natural Science Foundation of China (81000020), the Natural Science Foundation of Guangdong Province (2014A030313486), the Scientific Research Grant of Guangzhou City (201510010226), Guangzhou Department of Education Yangcheng Scholarship (10A025G) and the Science Foundation of State Key Laboratory (2011011).

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呼吸疾病国家重点实验室

PLOS ONE

RESEARCH ARTICLE

Clinical, Virological and Immunological Features from Patients Infected with Re-Emergent Avian-Origin Human H7N9 Influenza Disease of Varying Severity in Guangdong Province

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Abstract

Background

The second wave of avian influenza H7N9 virus outbreak in humans spread to the Guangdong province of China by August of 2013 and this virus is now endemic in poultry in this region.

Methods

Five patients with H7N9 virus infection admitted to our hospital during August 2013 to February 2014 were intensively investigated. Viral load in the respiratory tract was determined by quantitative polymerase chain reaction (Q-PCR) and cytokine levels were measured by bead-based flow cytometery.

Results

Four patients survived and one died. Viral load in different clinical specimens was correlated with cytokine levels in plasma and broncho-alveolar fluid (BALF), therapeutic modalities used and clinical outcome. Intravenous zanamivir appeared to be better than peramivir as salvage therapy in patients who failed to respond to oseltamivir. Higher and more prolonged

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c-MYB regulates cell growth and DNA damage repair through modulating MiR-143

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ABSTRACT

Radiotherapy is the most successful nonsurgical treatment for nasopharyngeal carcinoma (NCP). Although NPCs initially respond well to a full course of radiation, recurrence and metastasis are frequent. In this study, we found that down-regulated c-MYB expression was associated with increased radiation resistance and DNA damage repair ability. Interestingly, c-MYB was over-expressed in cancer tissues but not in the adjacent tissues. Down-regulation of c-MYB expression inhibited cell proliferation, and led to cell cycle arrest at the M phase in NPC cells. Luciferase and chromatin immunoprecipitation assays demonstrated that c-MYB transactivated miR-143 through direct binding to its promoter. Based on these results, c-MYB might target miR-143 in order to regulate stem cell properties, cell growth, apoptosis, and DNA damage repair.
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1. Introduction

The c-MYB protein is a transcription factor [1] that plays a key role in the cell cycle regulation, proliferation, and differentiation of hematopoietic cells. High expression levels of c-MYB were first found in immature bone marrow hematopoietic cells and thymocytes, and subsequently in the neuroectodermal gastrointestinal epithelium and vascular smooth muscle cells. Recent studies have also shown that abnormal expression of c-MYB can lead to colon, breast, and gastro-esophageal cancer [2]. c-MYB can activate crucial target genes related to cancer progression and metastasis, including Sox-2, Bcl-2, Bax, and c-MYC [3]. Studies have indicated that the transcription factor MYB governs intestinal stem cell gene expression through the Wnt signaling pathway and thereby affects tumor cell self-renewal [4]. MicroRNAs (miRNAs) are an extensive class of 18–24-nucleotide long non-coding RNAs that regulate gene expression at the post-transcriptional level [5]. They have been reported to play an important role in the development, proliferation, and differentiation of various types of cells [6–8]. MiRNAs have also been linked to radio- and chemoresistance [9]. Recent studies have indicated that the expression of miRNA-143 was significantly down-regulated in several human neoplasms including colon, ovarian, esophageal, and bladder cancer [10,11]. Noguchi et al. reported that miR-143 inhibits cell growth through down-regulation of the translational expression level of ERK5 and AKT [12]. In addition, Lin et al. showed that miR-143 targeted the *RAS* oncogene, contributing to inhibition of tumor invasion and metastasis [13]. Radiation therapy is the main treatment for nasopharyngeal carcinoma (NPC). However, patients with an early diagnosis who receive radiation therapy nonetheless experience frequent recurrence. During the past in the last decades, evidence has been provided that the cancer stem cell (CSC) content and intrinsic radiosensitivity can affect their radiocurability potential. In this study, we detected the level of expression of c-MYB and miR-143 in normal nasopharyngeal and NPC tissues. Furthermore, we analyzed the relationships between the expression levels of c-MYB and the clinicopathological parameters of NPC patients. We also studied the effects of c-MYB on cell growth and its radiation-resistant mechanism in NPC cells, with the aim of determining a novel potential therapeutic approach for the treatment of NPC.

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ORIGINAL ARTICLE

Component-Resolved Diagnostic Study of *Dermatophagoides Pteronyssinus* Major Allergen Molecules in a Southern Chinese Cohort

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Abstract

Background and Objective: Little is known about component-resolved diagnosis (CRD) for *Dermatophagoides pteronyssinus* (Der p) sensitization in the Chinese population. We aimed to evaluate sensitization to Der p components in southern China.
Methods: Two-hundred immunotherapy-naïve patients with asthma and/or rhinitis positive to specific IgE (sIgE) against Der p extract, along with 20 Der p-negative nonallergic healthy controls, were tested for sIgE against Der p 1, Der p 2, and Der p 10 using ImmunoCAP 100. Seventy-five were further examined with the ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC). Der p 10-positive patients were also tested for sIgE against crude extracts of cockroach, moth, and shrimp.
Results: In total, 183 (91.5%) of the 200 patients were sensitized to Der p 1 and/or Der p 2. The proportion of positive results and the median level of sIgE against Der p 1 were higher in children than in adults. Der p 1 and Der p 2 correlated with Der p in sIgE levels. ImmunoCAP ISAC demonstrated 100% specificity and 84% sensitivity in detecting Der p 1, Der p 2, and Der p10 compared with ImmunoCAP 100. Sensitization to Der p 10 correlated well with sIgE to shrimp, moths, cockroaches, Pen m 1, Bla g 7, and Ani s 3.
Conclusions: The detection of Der p 1 and Der p 2 provided a good reflection of atopy to Der p in a Chinese cohort. Sensitization to Der p 10 may result from cross-reactivity with seafood and cockroaches in coastal southern China. ImmunoCAP ISAC may be a useful tool for CRD, with comparable performance to ImmunoCAP 100.

Key words: Component-resolved diagnosis. Asthma. Allergic rhinitis. Der p 1. Der p 2. Der p 10. Tropomyosin. Microarray-based specific IgE detection assay.

Resumen

Introducción y Objetivo: El diagnóstico por componentes en pacientes sensibilizados a *Dermatophagoides pteronyssinus* (Der p) en la población china es un tema poco estudiado.
El objetivo de este estudio fue evaluar la sensibilización a componentes de Der p en el sur de China.
Método: Para ello se estudiaron 200 pacientes con asma y /o rinitis con IgE específica positiva frente a extracto completo de Der p (d 1) no sometidos a inmunoterapia y 20 controles sanos no alérgicos (Der p-negativos) con IgEesp negativa frente a Der p 1, Der p 2, y Der p 10 mediante ImmunoCAP 100. Setenta y cinco fueron analizados mediante ISAC (ImmunoCAP Immuno Solid-Phase Allergen Chip). Los sujetos positivos a Der p 10 fueron, además, analizados mediante IgEesp frente a extracto de cucaracha, polilla y gamba.
Resultados: En cuanto a los resultados obtenidos, 183/200 (91.5%) pacientes estaban sensibilizados a Der p 1 y /o Der p 2. La proporción positiva y la mediana de IgEesp frente a Der p 1 fue mayor en niños que en adultos. La IgEesp frente a Der p 1 y Der p 2 se correlacionaba con los niveles de IgEesp frente a extracto completo. El ISAC mostró una especificidad del 100% y una sensibilidad del 84% para Der p 1, Der p 2 y Der p 10. La sensibilización a Der p 10 se correlacionó bien con la IgEesp frente a gamba, polilla y cucaracha, Pen m 1, Bla g 7, Ani s 3.
Conclusiones: La detección de Der p 1 y Der p 2 refleja adecuadamente la sensibilización a *Dermatophagoides pteronyssinus* en la población

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SCIENTIFIC REPORTS

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Comprehensive analysis of the T-cell receptor beta chain gene in rhesus monkey by high throughput sequencing

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Profiling immune repertoires by high throughput sequencing enhances our understanding of immune system complexity and immune-related diseases in humans. Previously, cloning and Sanger sequencing identified limited numbers of T cell receptor (TCR) nucleotide sequences in rhesus monkeys, thus their full immune repertoire is unknown. We applied multiplex PCR and Illumina high throughput sequencing to study the TCRβ of rhesus monkeys. We identified 1.26 million TCRβ sequences corresponding to 643,570 unique TCRβ sequences and 270,557 unique complementarity-determining region 3 (CDR3) gene sequences. Precise measurements of CDR3 length distribution, CDR3 amino acid distribution, length distribution of N nucleotide of junctional region, and TCRV and TCRJ gene usage preferences were performed. A comprehensive profile of rhesus monkey immune repertoire might aid human infectious disease studies using rhesus monkeys.

T cell receptors (TCR) are protein complexes on the cell surface of T lymphocytes that play key roles in adaptive immune responses. They are heterodimeric molecules, and greater than 95% of TCRs in the circulation belongs to the αβ type. In humans, there are more than 2×10^7 unique TCRα and TCRβ pairs in the peripheral blood of an individual[1,2]. The complexity of the immune repertoire is generated by genomic rearrangement of Variable (V), Diversity (D), Joining (J) gene segments during the maturation of lymphocytes. The joining region of the VDJ gene segments is the major antigen recognition site, also called complementarity-determining region 3 (CDR3), which represents the most diverse and complex region of the variable region.

Th rhesus monkey (*Macaca mulatta*) is employed in animal model systems for a number of important human diseases in which T lymphocytes play a central role in pathogenesis. Therefore, characterization of the TCR sequences of this nonhuman primate is very important. Early in 1992, Gene Levinson *et al.* sequenced 23 rearranged TCRβ cDNA clones derived from peripheral blood of a rhesus monkey[3]. Later, Emma E. M. Jaeger further expanded the TCRβ pool in this species[4]. Sequencing alignment of rhesus monkey, chimpanzee and human showed that the diversity, structure and evolution of TCRβ gene repertoire in primates are closely linked with each other[4–8]. These works and others totally identifi d more than 23 V beta genes in rhesus monkey and established a public sequence library of TCRβ sequences, which is critically important for further studies[9]. However, due to the low throughput nature

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COP9 Signalosome Controls the Degradation of Cytosolic Misfolded Proteins and Protects Against Cardiac Proteotoxicity

Huabo Su, Jie Li, Hanming Zhang, Wenxia Ma, Ning Wei, Jinbao Liu, Xuejun Wang

Rationale: **Impaired degradation of misfolded proteins is associated with a large subset of heart diseases. Misfolded proteins are degraded primarily by the ubiquitin-proteasome system, but the ubiquitin ligases responsible for the degradation remain largely unidentified. The cullin deneddylation activity of the COP9 signalosome (CSN) requires all 8 CSN subunits (CSN1 through CSN8) and regulates cullin-RING ligases, thereby controlling ubiquitination of a large number of proteins; however, neither CSN nor cullin-RING ligases is known to regulate the degradation of cytosolic misfolded proteins.**

Objective: **We sought to investigate the role of CSN8/CSN in misfolded protein degradation and cardiac proteinopathy.**

Methods and Results: **Cardiac CSN8 knockout causes mouse premature death; hence, CSN8 hypomorphism ($CSN8^{hypo}$) mice were used. Myocardial neddylated forms of cullins were markedly increased, and myocardial capacity of degrading a surrogate misfolded protein was significantly reduced by CSN8 hypomorphism. When introduced into proteinopathic mice in which a bona fide misfolded protein R120G missense mutation of αβ-crystallin ($CryAB^{R120G}$) is overexpressed in the heart, CSN8 hypomorphism aggravated $CryAB^{R120G}$-induced restrictive cardiomyopathy and shortened the lifespan of $CryAB^{R120G}$ mice, which was associated with augmented accumulation of protein aggregates, increased neddylated proteins, and reduced levels of total ubiquitinated proteins and LC3-II in the heart. In cultured cardiomyocytes, both CSN8 knockdown and cullin-RING ligase inactivation suppressed the ubiquitination and degradation of $CryAB^{R120G}$ but not native CryAB, resulting in accumulation of protein aggregates and exacerbation of $CryAB^{R120G}$ cytotoxicity.**

Conclusions: **(1) CSN8/CSN promotes the ubiquitination and degradation of misfolded proteins and protects against cardiac proteotoxicity, and (2) cullin-RING ligases participate in degradation of cytosolic misfolded proteins. (*Circ Res*. 2015;117:956-966. DOI: 10.1161/CIRCRESAHA.115.306783.)**

Key Words: autophagy ■ COP9 signalosome ■ Cops8 ■ desmin-related cardiomyopathy ■ proteasome ■ ubiquitin

Protein quality control (PQC) functions to minimize the level and toxicity of misfolded proteins in the cell, pivotal to intracellular proteostasis and cell survival.[1,2] PQC is accomplished by intricate collaboration between molecular chaperones and targeted proteolysis. The latter is done primarily by the ubiquitin (Ub)-proteasome system (UPS) and, sometimes, the autophagic-lysosomal pathway (ALP). PQC inadequacy allows misfolded proteins to undergo aberrant aggregation which can further impair PQC via mechanisms, including suppressing UPS function;[3–5] hence aberrant protein aggregation is both a consequence and a further cause of PQC inadequacy. Striking aberrant protein aggregation in cardiomyocytes, as evidenced by the presence of intracellular pre-amyloid oligomers and congophilic fibrils,[6,7] occurs in a large subset of human heart failure (HF) resulting from idiopathic cardiomyopathies. This links PQC inadequacy to the pathogenesis of common forms of heart diseases. PQC suppression via either ablating a chaperone gene or inhibiting targeted proteolysis is sufficient to cause cardiomyopathy and HF or to facilitate maladaptive cardiac remodeling;[8–11] conversely, PQC improvement via chaperone overexpression or enhancement of target proteolysis confers cardiac protection against proteotoxicity in experimental animals.[12–15] These experimental demonstrations are corroborated by clinical observations that a significant portion of cancer patients receiving proteasome

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Editorial, see p 914

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Correlation between EGFR mutations and expression of female hormone receptors in NSCLC: A meta-analysis.

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Abstract Disclosures

Abstract

e22228

Background: Compared with males, female NSCLC patients represented more frequent EGFR mutations. Despite the difference in smoking history, an association between female hormones and EGFR mutation might be an underlying reason. Some evidence support this hypothesis, however, the existed results were inconclusive. We sought to examine the link between the expression of female hormone receptors and EGFR mutations in NSCLC. **Methods:** Electronic databases were searched for the relevant articles. The primary endpoints were the presence of EGFR mutations between different expression levels of estrogen receptor (ER) and progesterone receptor (PR). **Results:** After applying inclusion and exclusion criteria, five studies were included. The involved hormone receptors included ER (both α and β subtypes) and PR. Based on random-effects model, patients with high ER-β had significantly greater EGFR mutation rate than low ER-β patients (44.2% vs. 23.7%; OR 3.44, 95% CI 2.40 to 4.93, P < 0.001) without heterogeneity (Chi^2 = 0.62, P = 0.73, I^2 = 0%). There was no difference in EGFR mutations between high and low expression of ER-α (OR 1.18, 95% CI 0.62 to 2.33, P = 0.58; heterogeneity: P < 0.01, I^2 = 73%), as well as PR (OR 1.29, 95%CI 0.40 to 4.10, p = 0.67; heterogeneity: P = 0.08, I^2 = 68%). **Conclusions:** High ER-β expression is correlated with EGFR mutations in NSCLC, but not ER-α and PR. Although some trends were observed, the correlation between female hormone receptors and EGFR mutations was still not valid. Next, we are going to clarify this issue based on a large database from our center.

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Original Article

Correlation between epidermal growth factor receptor mutations and nuclear expression of female hormone receptors in non-small cell lung cancer: a meta-analysis

Qihua He[1,2], Mingzhe Zhang[3], Jianrong Zhang[1,2], Ying Chen[1,2], Jiaxi He[1,2], Jianfei Shen[1,2], Yang Liu[1,2], Shengyi Zhong[1,2], Long Jiang[1,2], Chenglin Yang[1,2], Yuan Zeng[1,2], Minzhang Guo[1,2], Xuewei Chen[1,2], Jianxing He[1,2], Wenhua Liang[1,2]

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Background: Compared with male, female non-small cell lung cancer (NSCLC) patients have better response when treated with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), suggesting a potential association between female hormones and EGFR mutation. However, the results provided by previous studies were inconclusive and controversial. We sought to examine the link between the expression of nuclear female hormone receptors and EGFR mutations in NSCLC.

Methods: Electronic databases were used to search the relevant articles. The involved hormone receptors included estrogen receptor (ER) and progesterone receptor (PR). The primary endpoint was the occurrence of ER/PR expression and EGFR mutation in NSCLC patients.

Results: Five studies fulfilled the criteria and were included in our analysis. Patients with high ER-β expression had higher positive EGFR mutation than low ER-β patients (44.2% *vs.* 23.7%), and there was a significant difference between the two groups [odds radio (OR) 3.44, 95% confidence interval (CI): 2.40-4.93, Z=6.72, P<0.001]. However, there is no significant correlation between EGFR mutations and ER-α (when included ER-α3, OR 1.20, 95% CI: 0.62-2.33, Z=0.55, P=0.58; and when included ER-α4, OR 1.18, 95% CI: 0.62-2.25, Z=0.51, P=0.61) or PR (OR 1.29, 95% CI: 0.40-4.10, Z=0.43, P=0.67). No significant publication bias was observed.

Conclusions: High nuclear expression of ER-β, but not ER-α or PR is correlated with EGFR mutations in NSCLC. The underlying mechanism and potential translational relevance warrant further investigation.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR) mutation; estrogen receptor (ER); progesterone receptor (PR); meta-analysis

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Cough and environmental air pollution in China

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ABSTRACT

With fast-paced urbanization and increased energy consumption in rapidly industrialized modern China, the level of outdoor and indoor air pollution resulting from industrial and motor vehicle emissions has been increasing at an accelerated rate. Thus, there is a significant increase in the prevalence of respiratory symptoms such as coughing, wheezing, and decreased pulmonary function. Experimental exposure research and epidemiological studies have indicated that exposure to particulate matter, ozone, nitrogen dioxide, and environmental tobacco smoke have a harmful influence on development of respiratory diseases and are significantly associated with cough and wheeze. This review mainly discusses the effect of air pollutants on respiratory health, particularly with respect to cough, the links between air pollutants and microorganisms, and air pollutant sources. Particular attention is paid to studies in urban areas of China where the levels of ambient and indoor air pollution are significantly higher than World Health Organization recommendations.

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1. Introduction

With fast-paced urbanization and increased energy consumption in rapidly industrialized China, the level of outdoor and indoor air pollution resulting from industrial and motor vehicle emissions has quickly increased. According to People's Daily Online news, 25 provinces representing nearly half of the country were covered by heavy smog during 2013. There were 104 cities with high levels of pollution that resulted in smog that required military intervention. A recent study suggested that only 24 of 350 districts in China had an average annual concentration of particulate matter $PM_{2.5}$ less than 10 m g/m^3 whereas 166 districts had average annual $PM_{2.5}$ concentrations greater than 35 m g/m^3 (the World Health Organization (WHO) Interim Target 1) [1]. Air pollutants from factories and motor vehicle emissions have drawn special attention with respect to enhancing the prevalence of respiratory diseases and symptoms such as cough. As China's Ministry of Health has shown, there has been significantly increased morbidity and mortality among urban citizens over about the past 20 years [2]. In an animal study, exposure to the same $PM_{2.5}$ concentrations often present in urban areasled to several adverse airway effects [3]. There are various airway inflammatory and immune responses that are dependent on the airway's response to the particulate chemical matter present in air pollution in urban areas. Evidence suggests that respiratory symptoms among children in northern China are positively associated with high concentrations of ambient air pollution and associations with environmental tobacco smoke (ETS) are greater than those with sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) [4]. The aim of this review is to discuss the effect of air pollutants on respiratory health, especially cough, the association between air pollutants and microorganisms, and the sources of pollutants, with particular attention paid to studies in urban areas of China.

2. Cough and the effects of particulate matter

Particulate matter (PM) differs in magnitude, form particle size, and chemical composition. PM comprises a mix of tiny solid fragments or liquid matter. PM of diameter less than 2.5 μm ($PM_{2.5}$) makes up an important group of air pollutants that result in smog [5]. PM are divided according to their size, into PM_{10} (2.5–10 μm), $PM_{2.5}$ (0.1–2.5 μm), and $PM_{0.1}$ (<0.1 μm). The largest source of airborne PM is diesel-powered motor vehicle engines [6]. Other sources of PM include factories, power stations, wood and biomass fuel combustion, construction sites, and mining operations. Diesel powered car ownership has recently increased in China. Combustion of diesel fuel produces up to 100 times more particles than gasoline, indicating that diesel smoke may be a chief culprit in the increased morbidity owing to respiratory diseases [7]. In particular, $PM_{2.5}$ and $PM_{0.1}$ interact with alveolar epithelial cells and pulmonary alveolar macrophages and can directly reach the small airways and pulmonary alveoli. Additionally, nano-sized, ultrafine particles can directly infiltrate pulmonary alveoli and enter the bloodstream, which may produce a harmful effect on different body organs [8].

Controlled indoor exposure of normal subjects to diesel exhaust particles at levels of 200 μg/m^3 led to neutrophilic inflammation and neutrophil release [9]. In a study of patients with asthma walking

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Design, Synthesis, and Biological Evaluation of Pyrazolo[1,5-*a*]pyridine-3-carboxamides as Novel Antitubercular Agents

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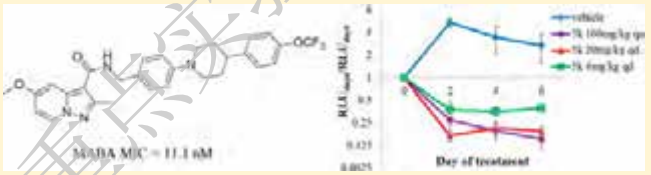
Supporting Information

ABSTRACT: A series of pyrazolo[1,5-*a*]pyridine-3-carboxamide derivatives were designed and synthesized as new anti-*Mycobacterium tuberculosis* (Mtb) agents. The compounds exhibit promising *in vitro* potency with nanomolar MIC values against the drug susceptive H37Rv strain and a panel of clinically isolated multidrug-resistant Mtb (MDR-TB) strains. One of the representative compounds (**5k**) significantly reduces the bacterial burden in an autoluminescent H37Ra infected mouse model, suggesting its promising potential to be a lead compound for future antitubercular drug discovery.



KEYWORDS: *Antitubercular agent, H37Rv, pyrazolo[1,5-a]pyridine, structure−activity relationship, tuberculosis*

Tuberculosis (TB) remains one of the world's deadliest pandemic diseases with over 9.0 million new cases and 1.5 million deaths estimated by the World Health Organization (WHO) in 2013.[1] Despite the forty-year success of the inexpensive quadruple-drug therapy [a combination of isoniazid (INH), rifampicin (RIF), pyrazinamide, and ethambutol], development and dissemination of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Mycobacterium tuberculosis* (Mtb) strains, together with coinfection with Human Immunodeficiency Virus (HIV), have intensified an urgent need for new anti-TB drug discovery.[2,3] Encouragingly, for the first time since 1970s, an ATP synthase inhibitor bedaquiline[4] (**1**, also known as TMC207) was approved by the US FDA as a novel active ingredient of combinational therapies for clinical management of adult patients with MDR pulmonary TB in 2012.[5] However, the drug possesses serious adverse effects such as cardiac arrhythmias[5] and displayed higher death rates than that of the placebo group in a clinical investigation,[6] which may limit its wide application in clinical practice. Several other anti-TB molecules were also identified with different modes of action.[2] For instance, a bicyclic nitroimidazofuran pro-drug PA-824 (**2**) was reported to kill both replicating and hypoxic nonreplicating Mtb through a Ddn-mediated activation and has been advanced to phase II clinical trial.[7,8] Imidazo[1,2-*a*]pyridine amide (IPA)[9−13] analogues [e.g., Q203 (**3**)[9,10] and compound **4**[11]] were also discovered to demonstrate strong inhibitory potencies against a panel of drug-susceptible and drug-resistant Mtb strains by targeting the QcrB subunit of the menaquinol cytochrome c oxidoreductase (bc1 complex), which is a critical component of mycobacterial energy metabolism.[14] Clinical outcomes of the compounds, particularly their capability against MDR and XDR Mtb strains in patients, are eagerly awaited. However, given the fact of only one singular FDA approval in 40 years and the high attrition rate of drug development, it is still highly valuable to identify new molecules with alternative scaffolds as effective anti-TB drug candidates.

Pyrazolo[1,5-*a*]pyridine moiety is a drug-like scaffold that is frequently observed in FDA approved or clinically investigating drugs including antiallergic agent Ibudilast,[15] platelet aggregation inhibitor KC-764,[16] dopamine D4 antagonist FAUC213,[17] etc. (Supporting Information). It shares highly similar 3-dimensional conformation and electronic property to that of imidazo[1,2-*a*]pyridine, which is the pharmaceutical core of Q203 (**3**) and compound **4**. Therefore, a series of pyrazolo[1,5-*a*]pyridine-3-carboxamide derivatives (**5a−5v**) were designed as new anti-TB agents by using a scaffold hopping strategy in which 2,5-dimethyl groups were introduced at first because of

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Developing influenza treatments using traditional Chinese medicine

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Humans have been faced the threat of epidemics such as influenza throughout their existence. Traditional Chinese medicine (TCM) practitioners began documenting their diagnostic and treatment principles related to epidemic diseases in the classic Chinese medical book, "Emperor Internal Medical Classic" (*1*). The unique treatments and herbal formulas used to combat influenza may serve as a source of information and inspiration for the development of new drugs (*2*).

Chinese herbal medicines and influenza

A major difference between Western and Chinese influenza treatments is the mode and targets of their actions. The first antiviral chemical drugs appeared in the West in the mid-1960s. Since then, many single-target therapeutics have been designed, but drug resistance is common. To circumvent this, Western medicine has incorporated multiple molecular targets into a single treatment using combination therapies, a practice now well accepted in the West.

Chinese herbal formulas (CHFs), on the other hand, often act via multiple modes that target not only the virus, but also various components of the host's immune response (Table 1), creating a synergistic effect. For example, *jinchai* capsules blunt viral replication by blocking adsorption of virions and preventing virus hyperalgesia-induced membrane fusion (*3*), while evodiamine blocks viral action by interfering with the AMPK/TSC2/mTOR signaling pathway, which is associated with virus-induced autophagy (*4*). Figure 1 summarizes the points of action of CHFs when treating influenza.

Isatis indigotica roots and influenza

Isatis indigotica roots (IIR) (*Banlangen*) have long been used to treat seasonal influenza in China. Currently, more than 100 chemical constituents of IIR have been identified. Among them, the compounds of epigoitrin; 2,4(1H,3H)-quinazolinedione; 4(3H)-quinazolinone; and clemastanin B have been demonstrated to kill or significantly inhibit the influenza virus. Studies from our laboratory have shown that polysaccharides extracted from IIR can prevent the influenza virus from attaching to host cell surfaces through a process involving hemagglutinins (*5*). Moreover, an indole alkaloid has been found to play a major role in preventing viral infection of host cells (*6*), while compounds derived from IIR can block translocation of the nucleocapsid protein at the early stage of replication, primarily through modulation of NF-κB signaling, thus inhibiting viral replication (*7*). In addition, IIR has been shown to exert immune modulatory effects in vitro and in vivo. In lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages, the methanolic extracts of IIR inhibited degradation of IκBα and production of nitric oxide, prostaglandin E_2, and interleukin (IL) 6 (*8*). The polysaccharides from IIR could promote proliferation of lymphocytes and macrophages, as well as production of IL-2 and interferon (IFN) γ in mouse models (*9*). Indirubin and its derivatives can suppress a number of pro-inflammatory cytokines/chemokines in infected human bronchial epithelial cells, human peripheral blood-derived macrophages, and alveolar epithelial cells (Table 1) (*10*, *11*). Taken together, these data imply that IIRs play a variety of roles protecting against viral infection by targeting both the virus and the host—a markedly different effect than that of marketed chemically synthesized drugs.

Drug development strategies using TCM

High-quality consistency, treatment effectiveness, safety assurance, and patient affordability are the key factors for drug development. TCM can inform research into these areas in the following ways.

Firstly, the strategies and principles underpinning the translational research used in TCM-based influenza treatments could be applied more broadly. Two possible approaches can be taken: the standard, bottom up bench-to-bedside strategy, or a more innovative approach that transitions empirical medical knowledge from TCM into an evidence-based research strategy. We proffer that the latter better reflects the real-world interaction between basic science and the TCM clinical experience.

Secondly, basic research and clinical studies on CHFs could be conducted in parallel. For example, the effects of extracts and/or combinations of the active compounds from commonly prescribed CHFs could be investigated concurrently with standardized clinical trials based on documented clinical experience.

Thirdly, well-defined methodologies for standardized assessment of the quality, efficacy, and safety of CHFs are still lacking. It is important to standardize the composition and level of active components of herbs in CHFs before including them in a basic research project or clinical trial so as to maintain the data integrity.

Finally, TCM research is complex. It therefore behooves all researchers to develop interdisciplinary, innovative, and collaborative research projects, through which the scientific foundation of TCMs can be elucidated and a new framework that incorporates modern medical science can be built.

We have been pioneers in an attempt to implement the abovementioned strategies using IIR, launching the first randomized control trial in China in 2010. Various 'omics

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ORIGINAL REPORT

Development and Validation of a Nomogram for Predicting Survival in Patients With Resected Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
A nomogram is a useful and convenient tool for individualized cancer prognoses. We sought to develop a clinical nomogram for predicting survival of patients with resected non–small-cell lung cancer (NSCLC).

Patients and Methods
On the basis of data from a multi-institutional registry of 6,111 patients with resected NSCLC in China, we identified and integrated significant prognostic factors for survival to build a nomogram. The model was subjected to bootstrap internal validation and to external validation with a separate cohort of 2,148 patients from the International Association for the Study of Lung Cancer (IASLC) database. The predictive accuracy and discriminative ability were measured by concordance index (C-index) and risk group stratification.

Results
A total of 5,261 patients were included for analysis. Six independent prognostic factors were identified and entered into the nomogram. The calibration curves for probability of 1-, 3-, and 5-year overall survival (OS) showed optimal agreement between nomogram prediction and actual observation. The C-index of the nomogram was higher than that of the seventh edition American Joint Committee on Cancer TNM staging system for predicting OS (primary cohort, 0.71 *v* 0.68, respectively; $P < .01$; IASLC cohort, 0.67 *v* 0.64, respectively; $P = .06$). The stratification into different risk groups allowed significant distinction between survival curves within respective TNM categories.

Conclusion
We established and validated a novel nomogram that can provide individual prediction of OS for patients with resected NSCLC. This practical prognostic model may help clinicians in decision making and design of clinical studies.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths worldwide, with non–small-cell lung cancer (NSCLC) accounting for approximately 85% of all diagnosed patients.[1] For early-stage NSCLC, including stage I and II and a subset of stage III disease, the standard and potentially curative treatment is radical resection.[2] The seventh edition of the American Joint Committee on Cancer TNM classification represents the most widely used staging system, in which patients with nonmetastatic NSCLC are stratified based on tumor size and invasion, as well as extent of lymph node involvement.[3] However, survival of patients with the same stage varies widely.[4-6] It is believed that other independent prognostic factors such as sex, age, histology, and treatment-related factors could significantly contribute to individualized prediction of survival.[4-6]

Nomograms have been accepted as reliable tools to quantify risk by incorporating and illustrating important factors for oncologic prognoses.[7-9] By creating an intuitive graph of a statistical predictive model, a nomogram gives rise to a numerical probability of a clinical event, such as overall survival (OS). In several types of cancers, nomograms have been proved to generate more precise prediction when compared with the traditional TNM staging systems.[10,11] However, nomograms for predicting long-term survival outcome after surgery in NSCLC

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Diagnostic yield and postoperative mortality associated with surgical lung biopsy for evaluation of interstitial lung diseases: A systematic review and meta-analysis

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Abstract Full Text Images References Supplemental Materials

Objectives

Surgical lung biopsy plays an important role in providing pathologic results, thus complementing the diagnostic rationale for suspected interstitial lung diseases. We performed a systematic review and meta-analysis regarding the diagnostic yield and postoperative mortality rate of surgical lung biopsy in patients with suspected interstitial lung diseases because of the wide variation in previously reported effectiveness and safety concerns.

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Mini-review

Dichotomous role of protein kinase A type I (PKAI) in the tumor microenvironment: A potential target for 'two-in-one' cancer chemoimmunotherapeutics

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ABSTRACT

An emerging trend in cancer chemoimmunotherapeutics is to develop 'two-in-one' therapies, which directly inhibit tumor growth and progression, as well as enhance anti-tumor immune surveillance. Protein kinase A (PKA) is a cAMP-dependent protein kinase that mediates signal transduction of G-protein coupled receptors (GPCRs). The regulatory subunit of PKA exists in two isoforms, RI and RII, which distinguish the PKA isozymes, PKA type I (PKAI) and PKA type II (PKAII). The differential expression of both PKA isozymes has long been linked to growth regulation and differentiation. RI/PKAI is particularly implicated in cellular proliferation and neoplastic transformation. Emerging experimental and pre-clinical data also indicate that RI/PKAI plays a key role in tumor-induced immune suppression. More briefly, RI/PKAI possesses a dichotomous role in the tumor microenvironment: not only contributes to tumor growth and progression, but also takes part in tumor-induced suppression of the innate and adaptive arms of anti-tumor immunosurveillance. This review specifically discusses this dichotomous role of RI/PKAI with respect to 'two-in-one' chemoimmunotherapeutic manipulation. The reviewed experimental and pre-clinical data provide the proof of concept validation that RI/PKAI may be regarded as an attractive target for a new, single-targeted, 'two hit' chemoimmunotherapeutic approach against cancer.

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Introduction

Cancer chemoimmunotherapeutics strategically integrate chemotherapy and immunotherapy in order to optimize the chance for cure. The holy grail of chemoimmunotherapeutic treatment regimens is to execute a 'double-edge sword' impact, able on the one hand to mount a robust anti-tumor immune response, and on the other hand, selectively eradicate tumor growth and progression. Tremendous progress is being, and has been, made in this sense by evaluating a variety of drug combinations, including pharmacological and biological agents, with complimentary mechanisms of action [1–4]. A novel concept in cancer chemoimmunotherapeutics is focused on developing single-targeted 'two hit' therapies by manipulating the molecular events having dichotomous role – promote tumor growth and aid tumor immunoescape – in the tumor microenvironment [5]. In this regard, the multilevel pharmacological manipulation of tumor-derived, adenosine- and prostaglandin E2 (PGE2)-induced, cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling in the tumor microenvironment seems to be an attractive approach [6].

PKA is a multi-unit serine-threonine protein kinase comprising regulatory (R) subunits; including RIα, RIβ, RIIα, and RIIβ isoforms, and the catalytic (C) subunits; including Cα, Cβ, and Cγ isoforms [7]. Structurally, PKA exists as two distinct isozymes; PKA type I (PKAI) and PKA type II (PKAII). Both PKA isozymes differ in R subunits, termed RI in PKAI and RII in PKAII, while the C subunit remains the same. RI and RII have two cooperative cAMP-binding sites, called A and B (Fig. 1). Functionally, both PKA isozymes are inactive heterotetrameric holoenzymes of two R and two C subunits [7]. The dissociation of PKA holoenzyme complex, via G-protein coupled receptors (GPCRs)-induced cAMP signaling, releases the free and activated forms of two C and two R subunits, which ultimately perform certain kind of functional activities (Fig. 1). More briefly,

Abbreviations: 3LL, Lewis lung carcinoma; AC, adenylyl cyclase; AS-PKAI, antisense oligonucleotide targeted against RI/PKAI; ATP, adenosine-5'-triphosphate; bFGF, basic fibroblast growth factor; C, catalytic subunit; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte macrophage colony stimulating factor; GPCRs, G-protein coupled receptors; IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; LPA, lysophosphatidic acid; MBOs, mixed backbone oligonucleotides; MDR, multidrug resistance; NK, natural killer; PG, prostaglandin; PKA, protein kinase A; RI, regulatory subunit I; RII, regulatory subunit II; S1P, sphingosine-1-phosphate; TGF, transforming growth factor; TNF, tumor necrosis factor; Tr1, adaptive Treg; Treg, T regulatory cells; VEGF, vascular endothelial growth factor.

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Disseminated penicilliosis marneffei in immunocompetent patients: A report of two cases

Feng Ye, Qun Luo, Ying Zhou, Jiaxing Xie, Qingsi Zeng, Guoqin Chen, Danhong Su, Rongchang Chen*

Abstract

Disseminated penicilliosis marneffei is rarely seen in immunocompetent persons. We report here two cases of disseminated penicilliosis marneffei in immunocompetent hosts. *Penicillium marneffei* disseminated to the brain in one patient and to the bone marrow in the other patient. Both patients received amphotericin B liposome. The cases illustrate the importance of considering penicilliosis marneffei as causes of systemic infections in immunocompetent patients.

Key words: *Disseminated, immunocompetent hosts, penicilliosis marneffei*

Introduction

Penicilliosis marneffei is a lethal form of systemic fungiosis due to *Penicillium marneffei*. With its recent upright trend in incidence, the disease has emerged as a serious public health concern in Southeast Asia[1] and its incidence has reached 12.3% in some regions in China.[2] Penicilliosis marneffei is more common in immunocompromised hosts; in Thailand, it ranks third in opportunistic infections behind tuberculosis and cryptococcosis in patients with acquired immunodeficiency syndrome (AIDS).[3-5] In Hong Kong, penicilliosis marneffei lags only behind *Pneumocystis* pneumonia and tuberculosis in immunocompromised hosts.[6] However, it is extremely rare to find systemic *Penicillium marneffei* infections in immunocompetent persons. Here, we report disseminated penicilliosis marneffei in two immunocompetent hosts.

Case Reports

Case 1

A 37-year-old male patient was admitted because of recurrent episodes of coughing and fever for 1 month. The cough, which started 1 month ago, was irritating and nonproductive. The body temperature reached as high as 40°C. The patient developed night sweats, chest pain, chest tightness, dizziness, headache and pain in both shoulders. He had received antibiotics including ceftriaxone, azithromycin and vancomycin and anti-tuberculosis medications including isoniazid, rifampin, ethambutol and pyrazinamide at two other hospitals, but showed no apparent improvement. His body weight decreased more than 9 kg in the interim. The patient was otherwise healthy with no underlying disease. He denied drug use and contact with pets or rats. He also denied any history of homosexual contact.

Physical examination upon admission showed a body temperature of 38.9°C, a pulse of 88/min, a respiration rate of 20/min, and a blood pressure of 129/74 mmHg. The patient appeared normally developed and was mentally alert. An enlarged left supraclavicular lymph node, 1 × 1.5 cm^2 in size, and an enlarged left inguinal lymph node, 1 × 1 cm^2 in size, were palpated and both were non-tender, movable and non-adherent. Migrant papules were palpable in many parts of the body [Figure 1]. The bilateral chest was symmetrical. The chest was tender, especially on the left 2nd-4 intercostal space. His respiration was smooth. The bilateral lung field was clear with no rales. The heart and liver were normal. Chest roentography revealed occupying lesion in the left upper lobe [Figure 2a]. Chest computed tomography (CT) scan showed left upper lobe consolidation, atelectasis and enlargement of multiple mediastinal lymph nodes [Figure 2b and c]. In addition, a moderate amount of pericardial effusions was noted and there were chronic inflammatory changes in the lower basal segment of the left lung. The admission diagnoses were occupying disease on the upper left pulmonary lobe and obstructive pneumonia.

Laboratory studies revealed a white blood cell (WBC) count of 23.49 × 10^9/L (neutrophils 78.2%), a red blood cell (RBC) count of 3.7 × 10^9/L, and a haemoglobin content of 92 g/L. The erythrocyte sedimentation rate (ESR) was 23 mm/h, the C-reactive protein (CRP) content was 12.92 mg/dL, and the rheumatic factor content was 21 IU/mL. The renal and liver function was normal. Arterial blood gas analysis results were as follows: pH, 7.506, P_{CO2}, 30.98 mmHg, P_{O2}, 67.59 mmHg, and HCO_3^-, 24.3 mmol/L on O_2 at 2 L/min. The patient was negative for Widal test, Weil-Felix test, serum cryptococcal antigen latex agglutination

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Drug exposure in a metastatic human lung adenocarcinoma cell line gives rise to cells with differing adhesion, proliferation, and gene expression: Implications for cancer chemotherapy

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Abstract. The Am1010 cell line was previously established from a metastatic deposit in an arm muscle from a patient with lung adenocarcinoma who had undergone four cycles of chemotherapy with cisplatin and taxol. Am1010 cells were labeled with red fluorescent protein or green fluorescent protein. A total of eight sublines were isolated following *in vitro* exposure to cisplatin or taxol. The sublines differed with regard to their adhesion and proliferation properties, with certain sublines exhibiting an increased proliferation rate and/or decreased surface adhesion. Gene expression assays demonstrated that tenascin C; cyclin D1; collagen, type 1, α2; integrin α1; related RAS viral (r-ras) oncogene homolog 2; platelet-derived growth factor C; and Src homolog 2 domain containing in the focal adhesion pathway, and intercellular adhesion molecule 1, F11 receptor, claudin 7 and cadherin 1 in the cell adhesion pathway, varied in expression among the sublines. The results of the present study suggested that drug exposure may alter the aggressiveness and metastatic potential of cancer cells, which has important implications for cancer chemotherapy.

Introduction

Lung cancer is the leading cause of mortality among all types of malignancy (1). Regardless of the treatment provided, the 5-year survival rate in lung cancer is <15%. The poor prognosis is predominantly attributed to the development of drug resistance (2). It is therefore important to identify the mechanisms underlying drug resistance in lung cancer.

Cancer stem cells (CSCs) exhibit increased drug resistance and tumorigenicity (3,4). Levina *et al* (1) suggested that CSCs may be enriched and subsequently isolated from cancer cell populations following drug treatment. The authors isolated what they termed drug-surviving cells (DSCs) from human cancer cell lines treated with cisplatin, doxorubicin or etoposide. The isolated DSCs were clonogenic, expressed CSC cell surface and embryonic stem cell markers, exhibited self-renewal and differentiation, and were tumorigenic and metastatic in severe combined immunodeficiency mice. It was concluded that the DSCs were CSCs and that enrichment of CSCs following drug treatment *in vitro* may result in a similar selection of drug-resistant CSCs in patients during chemotherapy (1).

Our group previously established the cell line Am1010 (5) directly from a lung cancer patient who was treated with chemotherapy but developed multidrug resistance. In the present study, the establishment of eight sublines of DSCs from Am1010, labeled with red fluorescent protein (RFP) or green fluorescent protein (GFP), by long-term exposure to cisplatin or taxol is described. Cell proliferation and gene expression were then determined, in order to define the differences between the sublines.

Materials and methods

Ethics statement. All experimentation presented in the current study has been approved by the local institutional review board. The tumor sample was obtained from the Department of Thoracic Surgery at the 1st Affiliated Hospital of Guangzhou Medical College with the approval of the local ethical committee. Written informed consent was obtained from the patient.

RFP or GFP expression in Am1010 cells. The RFP (DsRed-2) gene (Clontech Laboratories, Mountain View, CA, USA) was

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Abbreviations: DSC, drug surviving cell; CSC, cancer stem cell

Key words: lung adenocarcinoma cell line, drug resistance, cell adhesion, cell proliferation, green fluorescent protein, red fluorescent protein

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ARTICLE

Duplicated copy of *CHRNA7* increases risk and worsens prognosis of COPD and lung cancer

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Recent genome-wide association studies implicated that the nicotinic acetylcholine receptors (*nAChRs*) are common susceptible genes of two contextual diseases: chronic obstructive pulmonary disease (COPD) and lung cancer. We aimed to test whether the copy number variations (CNVs) in *nAChRs* have hereditary contributions to development of the two diseases. In two, two-stage, case–control studies of southern and eastern Chinese, a common CNV-3956 that duplicates the *cholinergic receptor, nicotinic, α7* (*CHRNA7*) gene was genotyped in a total of 7880 subjects and its biological phenotype was assessed. The ≥4-copy of CNV-3956 increased COPD risk (≥4-copy *vs* 2/3-copy: OR = 1.44, 95% CI = 1.23–1.68) and caused poor lung function, and it similarly augmented risk (OR = 1.49, 95% CI = 1.29–1.73) and worsened prognosis (hazard ratio (HR) = 1.25, 95% CI = 1.07–1.45) of lung cancer. The ≥4-copy was estimated to account for 1.56% of COPD heritability and 1.87% of lung cancer heritability, respectively. Phenotypic analysis further showed that the ≥4-copy of CNV-3956 improved CHRNA7 expression *in vivo* and increased the carriers' smoking amount. The CNV-3956 of *CHRNA7* contributed to increased risks and poor prognoses of both COPD and lung cancer, and this may be a genetic biomarker of the two diseases.
European Journal of Human Genetics (2014) **00,** 1–6. doi:10.1038/ejhg.2014.229

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and lung cancer are two major striking lung diseases that are contextual.[1,2] It has been reported that 40–70% of lung cancer patients complicate with COPD,[3] whereas COPD patients have an extremely high incidence of lung cancer, up to 16.7 cases per 1000 person-years.[4] In addition, a meta-analysis revealed that COPD patients suffer 2.76-fold risk of lung cancer compared with the common population.[5] COPD is now assumed to be a potentially intermediate phenotype ahead of lung malignant transformation, on account of the mediation effect that COPD has on lung cancer development as earlier reported.[6] Early screening of COPD is reported to be very important during lung cancer surveillance.[7]

Epidemiological evidences indicated that COPD and lung cancer have similar pathogenesis with regard to shared etiological factors, including environmental exposures and genetic susceptibility.[8–10] The most predominant commonality of COPD and lung cancer in hereditary is the overlap of susceptible loci residing on the *nicotinic acetylcholine receptors* (*nAChRs*). Several single-nucleotide polymorphisms (SNPs) in the gene cluster *CHRNA3*/*CHRNB4*/*CHRNA5* were reported to be associated with the risk of both diseases.[11–13] These variants are also associated with prognosis of lung cancer.[11,14,15] However, these SNPs can only explain a small proportion of disease heritability as shown by the relatively small increments in risk they have, reflecting 'Missing heritability' exists. Copy number variations (CNVs) are suggested to account for a large proportion of this 'Missing heritability'. As a prevalent genetic aberration covering >1 kb duplication or deletion, CNVs encompass genes leading to dosage imbalances and aberrant expression of genes,[16] and thus influence development of human diseases. The CNVs located in these *nAChRs* genes may affect their function. We therefore hypothesized that the CNVs in *nAChRs* may alter the carriers' susceptibility and prognosis to COPD and lung cancer.

To the above object, we screened all common CNVs (altered copy number frequency, ACNF >5%) in the 11 neuronal *nAChRs* genes and genotyped the common CNVs in two, two-stage, case–control studies of southern and eastern Chinese with a total of 1791 COPD patients and 1940 normal lung function controls, as well as 2072 lung cancer cases and 2077 cancer-free controls. Functional assays were further performed to assess the biological effect of the CNVs.

MATERIALS AND METHODS

Study subjects

Two, two-stage, case–control studies were conducted respectively for COPD and lung cancer in southern and eastern Han Chinese. The southern population was used as a discovery set, whereas the eastern population was the validation set. In brief, 1025 COPD patients and 1061 normal lung function controls from Guangzhou city, as well as 766 COPD patients and 879 normal controls from Suzhou city, were enrolled as described in previous studies.[11,17] In addition, 1056 lung cancer cases and 1056 cancer-free controls from Guangzhou city, as well as 1016 lung cancer cases and 1021 cancer-free controls from Suzhou city, were used as described previously.[18,19] All controls were age (±5 years) and sex frequency matched with the cases. Having signed a written informed consent, each subject provided data regarding the demographic characters and potential risk factors and donated one-time 5 ml blood sample. Among these subjects, there were 427 individuals having at least 4-year follow-up of lung function between 2002 and 2010 with annual spirometric

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Editorial

Early screening of lung cancers: an effort arduous but worthwhile

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国家重点实验室

Cancers are a concerning health catastrophe worldwide that may become the end of lifetime for many of us—they overwhelmingly exhaust medical resources, lead to huge economic burdens, and separate people from their beloved ones. Fewer and fewer insurance agencies are willing to include primary cancers on their general health insurance plan, just because cancers have been so flummoxingly usual in our daily life that many primary cancer claims would give rise to much less profits.

Globally, lung cancer is the leading cause of all cancer deaths. It was estimated that 1.4 million deaths in 2008 were caused by lung cancer (1). Although the epidemiology varies due to socio-economic factors in various countries and regions (2-4), lung cancers are fatal in all nations: the 5-year survival of lung cancer is below 20% everywhere in Europe, among 15–19% in North America, and as low as 7–9% in Mongolia and Thailand (5).

Given the high incidence and poor survival rate, the only solution to increase the efficiency of lung cancer control should be the earliness in detection, diagnosis and treatment, because many patients were at the advanced stage of lung cancer when first diagnosed, and were thus ineligible for radical resection or impossible for surgery. And to this end, early detection achievable by lung cancer screening may greatly result in clinical benefits for patients.

Until recently, the controversy over low-dose CT scan for lung cancer screening was hectic, but now has finally been ended as the release of the outcome of the National Lung Screening Trial (NLST), which observed that low-dose CT screening reduces the mortality from lung cancer at 20.0% (6).

Lung cancer is not diagnosed by symptoms alone; on the contrary, a large majority of early-stage lesions may appear clinically silent, and therefore escape detection (7). As the tumor progresses, multiple symptoms often co-occur: a lingering cough with occasional bloody sputum, weight loss, fatigue, dyspnoea, anxiety and depression. Then, the tumor involves surrounding tissues, with notable various clinical signs (8). In most of the cases, the sight of clinical signs may mean middle to late phase of the disease. A survey showed that the median total wait time is approximately 4.5 months for patients suspected with lung cancers to visit doctors, receive examinations and undergo treatments (9). This interval might be much longer in developing and under-developed countries. On the other hand, the time to first proper diagnosis is crucially important for patients with lung cancer; for instance, small cell lung cancer would become fatal shortly within two to four months if undetected and untreated (10).

The Centers for Medicare & Medicaid Services (CMS) in the US determined earlier this year to use low-dose computed tomography (LDCT) for lung cancer annual screening as a preventive service benefit for those under the Medicare program. The CMS also gave detailed criteria for institution entry, eligibility of radiologists, and radiological imaging facilities (11). The CMS program is the first one to pay for early screening fee in the elderly and the disabled by the government in a hope to save more life.

The NLST finding does bring us hope to better control lung cancer and the US is in action. However, a trial by Infante *et al*. has pointed out the uncertainty on the efficacy of LDCT screening in a community setting (12). The

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Original Article

Effect of airway *Pseudomonas aeruginosa* isolation and infection on steady-state bronchiectasis in Guangzhou, China

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Background: Current status of *Pseudomonas aeruginosa* (PA) infection in clinically stable bronchiectasis in mainland China remains unclear.

Objective: To compare the inflammation and lung function impairment in bronchiectasis patients isolated or infected with PA, potentially pathogenic microorganisms (PPMs) and commensals, and to identify factors associated with PA isolation and infection.

Methods: Patients with steady-state bronchiectasis and healthy subjects were recruited. Peripheral blood and sputum were sampled to determine inflammatory markers and bacterial loads in steady-state bronchiectasis and health. Spirometry and diffusing capacity were also measured.

Results: We enrolled 144 bronchiectasis patients and 23 healthy subjects. PA isolation and infection accounted for 44 and 39 patients, who demonstrated significant inflammatory responses and markedly impaired spirometry, but not diffusing capacity, compared with healthy subjects and patients isolated with other PPMs and commensals (all $P<0.05$). Except for heightened sputum inflammatory responses, there were no notable differences in serum inflammation and lung function as with the increased density of PA. Female gender [odds ratio (OR): 3.10 for PA isolation; OR: 3.74 for PA infection], 4 or more exacerbations within 2 years (OR: 3.74 for PA isolation, OR: 2.95 for PA infection) and cystic bronchiectasis (OR: 3.63 for PA isolation, OR: 4.47 for PA infection) were the factors consistently associated with PA isolation and infection.

Conclusions: PA elicits intense inflammation and lung function impairment in steady-state bronchiectasis. The density of PA does not correlate with most clinical indices. PA infection is associated with females, frequent exacerbations and cystic bronchiectasis.

Keywords: Bronchiectasis; *Pseudomonas aeruginosa* (PA); bacterial density; airway inflammation; systemic inflammation; infection

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Effect of tiotropium on neural respiratory drive during exercise in severe COPD

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ABSTRACT

Background: Studies have shown that tiotropium once daily reduces lung hyperinflation and dyspnea during exercise and improves exercise tolerance in patients with COPD. Mechanisms underlying the effects of the muscarinic receptor antagonist tiotropium on COPD have not been fully understood.
Objective: In this study, we investigated whether improvement in neural respiratory drive is responsible for reducing dyspnea during exercise and improving exercise tolerance in COPD.
Methods: Twenty subjects with severe COPD were randomized into two groups: no treatment (Control, $n = 10$, 63.6 ± 4.6 years, FEV_1 29.6 ± 13.3%pred) or inhaled tiotropium 18 μg once daily for 1 month ($n = 10$, 66.5 ± 5.4 years, FEV_1 33.0 ± 11.1%pred). All subjects were allowed to continue their daily medications other than anti-cholinergics during the study. Constant cycle exercise with 75% of maximal workload and spirometry were performed before and 1 month after treatment. Diaphragmatic EMG (EMGdi) and respiratory pressures were recorded with multifunctional esophageal catheter. Efficiency of neural respiratory drive, defined as the ratio of minute ventilation (VE) and diaphragmatic EMG (VE/EMGdi%max), was calculated. Modified British Medical Research Council Dyspnea Scale (mMRC) was used for the evaluation of dyspnea before and after treatment.
Results: There was no significant difference in spirometry before and after treatment in both groups. Diaphragmatic EMG decreased significantly at rest (28.1 ± 10.9% vs. 22.6 ± 10.7%, $P < 0.05$) and mean efficiency of neural respiratory drive at the later stage of exercise increased (39.8 ± 2.9 vs. 45.2 ± 3.9, $P < 0.01$) after 1-month treatment with tiotropium. There were no remarkable changes in resting EMGdi and mean efficiency of neural respiratory drive post-treatment in control group. The score of mMRC decreased significantly (2.5 ± 0.5 vs. 1.9 ± 0.7, $P < 0.05$) after 1-month treatment with tiotropium, but without significantly difference in control group.
Conclusion: Tiotropium significantly reduces neural respiratory drive at rest and improves the efficiency of neural respiratory drive during exercise, which might account for the improvement in exercise tolerance in COPD.

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呼吸疾病临床重点实验室

Abbreviations: IC, inspiratory capacity; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity; VE, minute ventilation; RMS, root mean square; BMI, body mass index; mMRC, Modified British Medical Research Council Dyspnea Scale; EMG, electromyogram; EMGdi, diaphragm electromyogram; NRD, neural respiratory drive; Pes, esophageal pressure; Pga, gastric pressure; Pdi, transdiaphragmatic pressure; P0.1, occlusion pressure.

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Effectiveness of digital infrared thermal imaging in detecting lower extremity deep venous thrombosis

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Purpose: The authors aimed to determine the effectiveness of infrared thermal imaging (IRTI) as a novel, noninvasive technique in adjunctive diagnostic screening for lower limb deep venous thrombosis (DVT).

Methods: The authors used an infrared thermal imaging sensor to examine the lower limbs of 64 DVT patients and 64 healthy volunteers. The DVT patients had been definitively diagnosed with either Doppler vascular compression ultrasonography or angiography. The mean area temperature (T_area) and mean linear temperature (T_line) in the region of interest were determined with infrared thermal imaging. Images were evaluated with qualitative pseudocolor analysis to verify specific color-temperature responses and with quantitative temperature analysis. Differences in T_area and T_line between the DVT limb and the nonaffected limb in each DVT patient and temperature differences (TDs) in T_area (TD_{area}) and T_line (TD_{line}) between DVT patients and non-DVT volunteers were compared.

Results: Qualitative pseudocolor analysis revealed visible asymmetry between the DVT side and non-DVT side in the presentation and distribution characteristics (PDCs) of infrared thermal images. The DVT limbs had areas of abnormally high temperature, indicating the presence of DVT. Of the 64 confirmed DVT patients, 62 (96.88%) were positive by IRTI detection. Among these 62 IRTI-positive cases, 53 (82.81%) showed PDCs that agreed with the DVT regions detected by Doppler vascular compression ultrasonography or angiography. In nine patients (14.06%), IRTI PDCs did not definitively agree with the DVT regions established with other testing methods, but still correctly indicated the DVT-affected limb. There was a highly significant difference between DVT and non-DVT sides in DVT patients ($P < 0.01$). The TD_{area} and TD_{line} in non-DVT volunteers ranged from 0.19 ± 0.15 °C to 0.21 °C ± 0.17 °C; those in DVT patients ranged from 0.86 °C ± 0.71 °C to 1.03 °C ± 0.79 °C ($P < 0.01$).

Conclusions: Infrared thermal imaging can be effectively used in DVT detection and adjunctive diagnostic screening because of its specific infrared PDCs and TDs values. © *2015 American Association of Physicists in Medicine.* [http://dx.doi.org/10.1118/1.4907969]

Key words: infrared thermal imaging (IRTI), deep venous thrombosis (DVT), presentation and distribution characteristics (PDCs), adjunctive diagnostic screening

1. INTRODUCTION

Venous thromboembolism includes pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT). DVT alone is not life-threatening, but undiagnosed DVT may lead to potentially fatal complications, including PTE, which carries significant morbidity and mortality.[1–3] Approximately 300 000 people die from acute PTE in the United States each year; regrettably, many cases are diagnosed only at autopsy.[4] Ninety percent of PTE cases originate from lower limb DVT.[5] The incidence of lower extremity DVT is approximately 50 per 100 000 people per year.[1] Surprisingly, most cases are asymptomatic. Therefore, screening older individuals for DVT is worthwhile to avoid sudden onset of PTE.

Diagnosis of symptomatic DVT using Doppler vascular compression ultrasonography (CPUS) is well established.[6] The sensitivity and specificity of CPUS in diagnosing proximal DVT are 100% and 98%, respectively. Distal venous thrombosis is diagnosed with 94% sensitivity and 75% specificity

TABLE V. Reasons for discordant findings in nine patients.

Location	Number	Reasons
Myenteric vein	2	PDCs were expressed on foot where the located venous was smaller than the distal venous.
	2	PDCs were expressed on popliteal where the PDCs of located venous were enlarger.
Tibial or fibular vein	2	Nonstanding patients, with position could affect the IRTI result.
	1	After joint replacement surgery, the expressed PDCs was fold with the surgical wound area, where could be identified as highly doubtful DVT.
Femoral vein	2	Patients had very severe varicose veins. IRTI can clearly distinguish mild and moderate varicose veins, but very severe varicose veins could be identified as highly doubtful DVT.

on the normal side and than those in non-DVT volunteers (Table III).

Our findings indicate that abnormal body surface temperature in a lower limb suggests abnormal blood flow in that area. Slow blood flow probably indicates obstructed blood supply or thrombosis in the embolic region. Given the similar temperature of the skin and the limb vessels, assessment of skin temperature is useful for indirect diagnosis of vascular diseases in the limbs. Peripheral arterial diseases are typically associated with ischemia, while peripheral venous diseases are generally congestive. In view of the close relationship between infrared radiation and blood flow volume, it is not surprising that abnormal hypothermia is commonly detected by IRTI in peripheral arterial diseases,[15,24] while local hyperthermia is seen with IRTI in DVT patients, as found in our study.

Ambient temperature is important when conducting IRTI testing, because it affects body temperature measurement, interfering with the background of the thermal imaging. Therefore, the ambient temperature in this study was standardized at 23°C ± 2°C. Participants are also more comfortable in standardized room temperature. To reduce possible errors, a single room was used for testing, with steady ambient temperature and humidity. This standardization minimized the impact of these variables on body temperature measurements.

However, this study has several limitations. Many factors can interfere with the discrimination and analysis of IRTI, including skin wounds, patient positioning, activity, ambient temperature, and clothing and those factors leaded to certain heterogeneities in the patients included. This study also had several deficiencies in study design that limits its clinical importance such as noncontrolled, nondouble-blinded, and with no comparison to CPUS or angiography. Nevertheless, the present study was a preliminary and early attempt to explore the possible diagnostic role of IRTI in lower limb DVT patients. Future studies should address these limitations and preferably include a larger sample size of subjects which enable stratifying the subjects by normal controls, patients with or without skin wounds in different positionings. Hopefully, this will adequately validate our findings.

In summary, we found that IRTI PDCs and IRTI TDs values could effectively detect lower limb DVT. As a simple, noncontact, economical, and rapid test, IRTI can be used as an adjunct to CPUS in diagnostic screening of clinically suspected DVT cases.

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Research Paper

Effects of *Schisandra chinensis* extracts on cough and pulmonary inflammation in a cough hypersensitivity guinea pig model induced by cigarette smoke exposure

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ABSTRACT

Schisandra chinensis (*S. chinensis*) is a traditional Chinese medicine commonly used in prescription medications for the treatment of chronic cough. However, the material basis of *S. chinensis* in relieving cough has not been completely elucidated yet. This study established a guinea pig model of cough hypersensitivity induced by 14 days of cigarette smoke (CS) exposure, to evaluate the antitussive, antioxidant, and anti-inflammatory effects of three *S. chinensis* extracts. And then the function of four lignans in reducing expression of TRPV1 and TRPA1 was examined using A549 cells induced by cigarette smoke extract (CSE). The results demonstrated that both ethanol extract (EE) and ethanol–water extract (EWE) of *S. chinensis*, but not water extract (WE), significantly reduced the cough frequency enhanced by 0.4 M citric acid solution in these cough hypersensitivity guinea pigs. Meanwhile, pretreatment with EE and EWE both significantly attenuated the CS-induced increase in infiltration of pulmonary neutrophils and total inflammatory cells, as well as pulmonary MDA, TNF-α, and IL-8, while remarkably increased activities of pulmonary SOD and GSH. According to H&E and immunofluorescence staining assays, airway epithelium hyperplasia, smooth muscle thickening, inflammatory cells infiltration, as well as expression of TRPV1 and TRPA1, were significantly attenuated in animals pretreatment with 1 g/kg EE. Moreover, four lignans of EE, including schizandrin, schisantherin A, deoxyschizandrin and γ-schisandrin, significantly inhibited CSE-induced expression of TRPV1, TRPA1 and NOS3, as well as NO release in A549 cells. In conclusion, *S. chinensis* reduces cough frequency and pulmonary inflammation in the CS-induced cough hypersensitivity guinea pigs. Lignans may be the active components.

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1. Introduction

Cough hypersensitivity syndrome (CHS) is a new clinical phenotype of chronic cough, for which there is still no clinically effective drugs in the current treatment strategies (Chung, 2011). The pathogenesis of CHS has not yet been completely elucidated. Groneberg et al. (2004) showed that there was an increase in transient receptor potential vanillic-1 (TRPV1) containing subepithelial sensory nerves within the bronchial wall of chronic cough patients. Moreover, the existing results showed that cigarette smoke (CS) is an important cause of CHS, which may mediate expression and activation of transient receptor potential ankyrin-1 (TRPA1) (Benich and Carek, 2011; Shapiro et al., 2013). Previous study has described an exacerbated cough model mimicing to CHS by exposing the guinea pigs to CS for 10 days. It was demonstrated that the cough enhanced by citric acid was significantly increased after 10 days of CS exposure, which was significantly inhibited by codeine, DNK333 (a selective NK1/NK2 antagonist), terbutaline, or atropine (Lewis et al., 2007). Moreover, the CS

Abbreviations: BALF, Bronchoalveolar lavage fluid; CHS, Cough hypersensitivity syndrome; CS, Cigarette smoke; DMEM, Dulbecco's modified eagle medium; EE, Ethanol extract; Eos, Eosinophil; EWE, Ethanol–water extract; GSH-Px, Glutathione peroxidase; H&E, Hematoxylin–eosin; HPLC, High performance liquid chromatography; IL-8, Interleukin 8; IgG, Immunoglobulin G; Lym, Lymphocyte; Mac, Macrophage; MDA, Malondialdehyde; Neu, Neutrophil; NK1, Neurokinin-1 receptor; NK2, Neurokinin-2 receptor; NO, Nitric oxide; PBS, Phosphate buffered saline; PCR, Polymerase chain reaction; PEG, Polyethylene glycol; Penh, Enhanced pause; RIPA, Radio Immunoprecipitation Assay; RNA, Ribonucleic Acid; SOD, Superoxide Orgotein Dismutase; TNF-α, Tumor necrosis factor α; TRPV1, Transient receptor potential vanillic-1; TRPA1, Transient receptor potential ankyrin-1; WE, Water extract

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RESEARCH PAPER

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Effects of the fusion design and immunization route on the immunogenicity of Ag85A-Mtb32 in adenoviral vectored tuberculosis vaccine

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Keywords: immunization routes, immunogenicity, fusion strategies, multiple antigens, mycobacterium tuberculosis

Abbreviations: Mtb, Mycobacterium tuberculosis; TB, tuberculosis; BCG, Mycobacterium bovis bacille Calmette-Guérin; rAd5, recombinant adenovirus type 5; CMI, cell-mediated immune responses; IM, intramuscular; IN, intranasal; SC, subcutaneous; IFN-γ, interferon gamma; ELISPOT, Enzyme-linked immune-sorbent spot; SFC, spot-forming cells; tPA, tissue plasminogen activator; HA tag, hemagglutinin tag; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; IL-2, Interleukin 2; TNF-α, tumor necrosis factor α; ICS, Intracellular cytokine staining; PCR, polymerase chain reaction; HEK, human embryo kidney; PBS, Phosphate Buffered Saline; NBT/BCIP, Nitro blue tetrazolium/ 5-Bromo-4-chloro-3-indolyl phosphate; DMSO, Dimethyl sulfoxide; BSA, bovine serum album; FITC, fluorescein isothiocyanate; PE, Phycoerythrin; DAPI, 4′,6-diamidino-2-phenylindole; RPMI, Roswell Park Memorial Institute; APC, Allophycocyanin; PerCP, Peridinin-ChlorophylL-Protein Complex; FACS, Fluorescence Activated Cell Sorter; FBS, fetal bovine serum; vp, viral particles

Vaccines containing multiple antigens may induce broader immune responses and provide better protection against *Mycobacterium tuberculosis* (Mtb) infection as compared to a single antigen. However, strategies for incorporating multiple antigens into a single vector and the immunization routes may affect their immunogenicity. In this study, we utilized recombinant adenovirus type 5 (rAd5) as a model vaccine vector, and Ag85A (Rv3804c) and Mtb32 (Rv0125) as model antigens, to comparatively evaluate the influence of codon usage optimization, signal sequence, fusion linkers, and immunization routes on the immunogenicity of tuberculosis (TB) vaccine containing multiple antigens in C57BL/6 mice. We showed that codon-optimized Ag85A and Mtb32 fused with a GSG linker induced the strongest systemic and pulmonary cell-mediated immune (CMI) responses. Strong CMI responses were characterized by the generation of a robust IFN-γ ELISPOT response as well as antigen-specific $CD4^+$ T and $CD8^+$ T cells, which secreted mono-, dual-, or multiple cytokines. We also found that subcutaneous (SC) and intranasal (IN)/oral immunization with this candidate vaccine exhibited the strongest boosting effects for *Mycobacterium bovis* bacille Calmette-Guérin (BCG)-primed systemic and pulmonary CMI responses, respectively. Our results supported that codon optimized Ag85A and Mtb32 fused with a proper linker and immunized through SC and IN/oral routes can generate the strongest systemic and pulmonary CMI responses in BCG-primed mice, which may be particularly important for the design of TB vaccines containing multiple antigens.

Introduction

Tuberculosis (TB) remains one of the most threatening infectious diseases in the world. Approximately 8.6 million newly-infected cases and 1.3 million deaths were recorded in 2012.[1] Although Mycobacterium bovis bacille Calmette-Guérin (BCG), the only available vaccine against Mycobacterium tuberculosis (Mtb) infection, provides effective protection against the most severe form of childhood TB, its protection efficacy against adult pulmonary TB is variable.[2,3] With the emergence and increased prevalence of drug-resistant TB strains, the development of new vaccines that can either replace BCG or boost and prolong protection efficacy are urgently needed.

Several TB vaccine candidates are currently undergoing clinical trials. Among these, the recombinant viral vector-based vaccines AdAg85a, MV85A, and Aeras-402 (Crucell Ad35), showed some promising potentials in inducing cell-mediated immune (CMI) responses.[4-6] Although Ag85A, a component of Mtb

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Original Article

Efficacies and adverse reactions of modified vitamin supplement programs before pemetrexed chemotherapy as a second-line treatment against epidermal growth factor receptor (EGFR) mutant wild-type lung adenocarcinoma

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Abstract: Objective: This study aims to observe the efficacies and adverse reactions of modified vitamin programs before pemetrexed chemotherapy (second-line treatment) against epidermal growth factor receptor (EGFR) mutant wild-type lung adenocarcinoma. Methods: 477 patients with IIIB, phase IV glomerular filtration rate (GFR) mutant-negative lung adenocarcinomas and performed pemetrexed chemotherapy were collected and divided into group A (167 cases, with modified program) and group B (310 cases, with traditional program). The modified program was: orally administrated 400 μg folic acid once per day and 1 day before the first-round pemetrexed chemotherapy, until the 21st day of the final administration of pemetrexed, and intramuscularly injected 500 μg vitamin B12 1 day before the first-round pemetrexed chemotherapy, and injected once 1 day before every round pemetrexed treatment. Results: Comparison between group A and group B: mean chemotherapy cycles (4.08 vs 3.98); effectiveness rate (22.16% vs 22.90%); disease control rate (56.51% vs 55.00%); without significant difference (P > 0.05). Two groups currently all reached the median overall survival (OS). The median progression-free survival (PFS): 4.2 vs 4.1 months; OS: 12.9 vs 13.2 months, without statistical difference (P > 0.05). Such side effects between the two groups as leukopenia, neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, fatigue, creatinine increasing, alanine transaminase (ALT) increasing, stomatitis, peripheral neuropathy, alopecia and rash had no significant difference (P > 0.05). Conclusions: The modified vitamin supportive treatment could ensure the efficacy, significantly simplify, facilitate the clinical application, and increase the associated toxicities, indicating that the pemetrexed-based chemotherapy did not need to be delayed because applying the vitamin supportive treatment.

Keywords: Lung adenocarcinoma, pemetrexed, folic acid, vitamin B12

Introduction

Lung cancer was one of the most common malignancies in world nowadays [1], non-small cell lung cancer (NSCLC), especially adenocarcinoma, was the main type of lung cancer [2]. Nowadays, chemotherapy was the first treatment choice for NSCLC, while pemetrexed was mainly used as the second-line drug [3-5], and also could be chosen as maintenance or first-line therapy as monotherapy or combined with cisplatin for advanced NSCLC [6-8], even better efficacies and safeties than gemcitabine against non-squamous non-small cell lung cancer [9, 10].

Pemetrexed was a new generation based on the classic anti-metabolic drug, which increased therapeutic effect on multiple enzymes in the folate-dependent metabolic pathways, including inhibit the activities of thymidylate synthase, dihydrofolate reductase and glycinamide nucleoside formyl transferase, reducing the biosynthesis of purine and thymidine, thus specifically

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TRIALS

STUDY PROTOCOL Open Access

Efficacy and safety of Ban-Lan-Gen granules in the treatment of seasonal influenza: study protocol for a randomized controlled trial

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Abstract

Background: Ban-Lan-Gen (BLG) is a traditional Chinese herbal medicine. It has been used for the prevention and treatment of virus-related respiratory diseases such as influenza virus infection. BLG contains some antiviral compounds, but few evidence-based clinical studies have been conducted to assess its efficacy against influenza. We assessed the effects of BLG (including efficacy and safety) on the treatment of seasonal influenza in an evidence-based clinical trial.

Methods/Design: We conducted a randomized, double-blinded, oseltamivir- and placebo-controlled, parallel-design clinical trial. A total of 177 subjects are going to be recruited after satisfying the criteria: (i) 18 to 65 years of age; (ii) illness onset within 36 h; (3) axillary temperature ≥38.0°C; and (iv) positive influenza (type A/B) virus test. Subjects will be assigned randomly into three groups in equal proportions: oseltamivir treatment, BLG granule treatment, and placebo treatment. Each group receives 5-day treatment and is followed up 1, 3, 5, 7 and 21 days later. Symptoms and patient compliance are recorded, and virus/serum viral antibodies tested. We will use the primary outcome, secondary outcome, and safety indicators to evaluate the efficacy and safety of BLG granules in the treatment of seasonal influenza.

Discussion: We have described the first clinical trial for treatment using a single herb against influenza A and B viruses in China. We will hold a large-scale clinical trial to comprehensively evaluate the effectiveness and safety of BLG against influenza infection based on the results of this pilot study. And this clinical trial will serve as an example for the study of other traditional herbal medicines in evidence-based clinical trials.

Trial registration: This study has been registered at ClinicalTrials.gov: NCT02232945 (3 September 2014).

Keywords: Ban-Lan-Gen granule, Seasonal influenza, Oseltamivir, Evidence-based clinical trial

Background

The influenza epidemic

Influenza is an acute respiratory disease caused by highly infectious influenza viruses such as H1N1, H3N2, H5N1, H7N9, and influenza B. It has a strong capability of spreading globally, leading to adverse health effects [1]. Such respiratory diseases are usually caused by type A or type B influenza, and the symptoms include headache, muscle aches, cough, and sudden fever [2]. Infection by the pandemic (H1N1) 2009 virus emerged initially in Mexico in early 2009 and has become a global pandemic [3-5]. Now, influenza A (H1N1, H3N2 and pandemic (H1N1) 2009) and influenza B have induced co-infection worldwide, thereby causing considerable panic among general populations.

Drug resistance in Western medicine

M2 ion channel blockers (for example, amantadine and rimantadine) and neuraminidase (NA) inhibitors (for example, oseltamivir, zanamivir, and peramivir) are commonly used for the prevention and treatment of influenza [6]. Amantadine and rimantadine, however, have been associated with neurologic toxicities and gastrointestinal

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International Journal of COPD

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ORIGINAL RESEARCH

Efficacy and safety of once-daily inhaled umeclidinium/vilanterol in Asian patients with COPD: results from a randomized, placebo-controlled study

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Background: Combination of the inhaled long-acting muscarinic antagonist umeclidinium (UMEC; GSK573719) with the long-acting β_2-agonist vilanterol (VI) is an approved maintenance treatment for COPD in the US and EU. We compared the efficacy and safety of UMEC/VI with placebo in patients with COPD of Asian ancestry.

Patients and methods: In this 24-week, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients were randomized 1:1:1 to UMEC/VI 125/25 µg, UMEC/VI 62.5/25 µg, or placebo. The primary efficacy end point was trough forced expiratory volume in 1 second (FEV_1) on day 169; secondary end points were Transition Dyspnea Index (TDI) focal score at week 24 and weighted mean (WM) FEV_1 over 0–6 hours postdose on day 1. Additional end points and safety were also assessed.

Results: Both UMEC/VI 125/25 µg and UMEC/VI 62.5/25 µg statistically significantly improved trough FEV_1 at day 169 versus placebo (UMEC/VI 125/25 µg, 0.216 L, [95% confidence interval [CI] 0.175–0.257]; UMEC/VI 62.5/25 µg, 0.151 L, 95% CI 0.110–0.191; both $P<0.001$). Statistically significant improvements in TDI score were observed for both UMEC/VI groups versus placebo (UMEC/VI 125/25 µg, 0.9, 95% CI 0.3–1.4, $P=0.002$; UMEC/VI 62.5/25 µg, 0.7, 95% CI 0.1–1.2, $P=0.016$). On day 1, both UMEC/VI groups improved 0–6-hour WM FEV_1 versus placebo (UMEC/VI 125/25 µg, 0.182 L 95% CI 0.161–0.203; UMEC/VI 62.5/25 µg, 0.160 L, 95% CI 0.139–0.181; both $P<0.001$). Statistically significant improvements for UMEC/VI groups versus placebo were observed for rescue albuterol use at weeks 1–24 (puffs/day, both $P<0.001$). The incidence of adverse events was similar across groups.

Conclusion: In Asian patients with COPD, once-daily UMEC/VI 125/25 µg and UMEC 62.5/25 µg resulted in clinically meaningful and statistically significant improvements in lung-function end points versus placebo. Symptomatic and quality of life measures also improved. The safety profile of UMEC/VI was consistent with previous studies.

Keywords: chronic obstructive pulmonary disease, umeclidinium, vilanterol, Asian

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Introduction

What is known?

Previous studies have shown that combination treatment with umeclidinium (UMEC)/vilanterol (VI) improves lung function compared with monotherapies, and the tolerability and safety of UMEC/VI has also been studied. However, few patients in these studies were Asian, and specific subanalyses of these populations were not carried out.

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Endoplasmic Reticulum Stress Links Hepatitis C Virus RNA Replication to Wild-Type PGC-1α/Liver-Specific PGC-1α Upregulation

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ABSTRACT

Hepatitis C virus (HCV) causes not only severe liver problems but also extrahepatic manifestations, such as insulin resistance (IR). Wild-type peroxisome proliferator-activated receptor gamma coactivator 1 alpha (WT-PGC-1α) is essential in hepatic gluconeogenesis and has recently been demonstrated to link HCV infection to hepatic insulin resistance (IR). A recent study has characterized a novel human liver-specific PGC-1α (L-PGC-1α) transcript, which is proposed to reflect human adaption to more complex pathways. However, the effect of HCV infection on L-PGC-1α expression and the mechanism by which HCV modulates WT-PGC-1α/L-PGC-1α remain unclear. In this study, we showed that HCV infection upregulated both WT-PGC-1α and L-PGC-1α, which further promoted HCV production. The upregulation of both PGC-1α isoforms depended on HCV RNA replication. By using promoter-luciferase reporters, kinase inhibitors, and dominant negative mutants, we further observed that the HCV-induced upregulation of WT-PGC-1α was mediated by the phosphorylation of cyclic AMP (cAMP)-responsive element-binding protein (CREB), whereas that of L-PGC-1α was mediated by CREB phosphorylation and forkhead box O1 dephosphorylation. Moreover, HCV infection induced endoplasmic reticulum (ER) stress, and pharmacological induction of ER stress upregulated WT-PGC-1α/L-PGC-1α and phosphorylated CREB. In contrast, pharmacological inhibition of HCV-induced ER stress impaired WT-PGC-1α/L-PGC-1α upregulation along with decreased phosphorylated CREB. The correlation of hepatic mPGC-1α with ER stress was further confirmed in mice. Overall, HCV infection upregulates both WT-PGC-1α and L-PGC-1α through an ER stress-mediated, phosphorylated CREB-dependent pathway, and both PGC-1α isoforms promote HCV production in turn.

IMPORTANCE

HCV causes not only severe liver problems but also extrahepatic manifestations, such as insulin resistance (IR). As a key regulator in energy metabolism, wild-type PGC-1α (WT-PGC-1α), has recently been demonstrated to link HCV infection to hepatic IR. A recent study has characterized a novel human liver-specific PGC-1α (L-PGC-1α), which reflects human adaption to more complex pathways. However, the effect of HCV infection on L-PGC-1α expression and the mechanism by which HCV regulates WT-PGC-1α/L-PGC-1α remain unclear. In this study, we showed that HCV infection upregulated both WT-PGC-1α and L-PGC-1α, which further promoted HCV production. WT-PGC-1α upregulation was mediated by CREB phosphorylation, whereas L-PGC-1α upregulation was mediated by CREB phosphorylation and FoxO1 dephosphorylation. HCV-induced ER stress mediated WT-PGC-1α/L-PGC-1α upregulation and CREB phosphorylation. Overall, this study provides new insights into the mechanism by which HCV upregulates WT-PGC-1α/L-PGC-1α and highlights the novel intervention of HCV-ER stress-PGC-1α signaling for HCV therapy and HCV-induced IR therapy.

Hepatitis C virus (HCV) infection has become a serious health issue associated with substantial morbidity and mortality (1). The World Health Organization estimates that approximately 185 million people are or have been infected with HCV worldwide (2). HCV causes not only severe liver problems but also extrahepatic manifestations, such as insulin resistance (IR) and type 2 diabetes mellitus (T2DM). In patients with chronic HCV, the achievement of sustained virological response with drugs prevents the development of *de novo* IR (3). HCV-infected patients also have increased risk of T2DM compared with noninfected controls and hepatitis B virus-infected controls (4). These studies suggest that HCV directly contributes to the development of IR and T2DM.

Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) is an inducible transcription factor coactivator that controls cellular energy metabolism (5). Cumulative studies link altered PGC-1α signaling to IR and T2DM. PGC-1α induced in liver during fasting promotes hormone-stimulated gluconeogenesis (6). PGC-1α is robustly upregulated in diabetic liver (7), increasing hepatic glucose production. PGC-1α serves as a metabolic sensor; hence, PGC-1α expression is finely regulated to meet energy demands. Several levels of regulation have been implicated, including transcriptional regulation and posttranslational modifications (8). The transcriptional regulation of PGC-1α by the cyclic AMP (cAMP)-responsive element-binding protein (CREB) is a common pattern in the metabolic adaptions of the liver to gluconeogenic status in response to glucagon and glucocorticoids (7, 9) or in response to free fatty acids (10). Alternative splicing or transcription initiation represents another mode of regu-

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PLOS ONE

RESEARCH ARTICLE

Engineering More Stable, Selectable Marker-Free Autoluminescent Mycobacteria by One Step

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呼吸疾病国家重点实验室

Abstract

In our previous study, we demonstrated that the use of the autoluminescent *Mycobacterium tuberculosis* as a reporter strain had the potential to drastically reduce the time, effort, animals and costs consumed in evaluation of the activities of drugs and vaccines in live mice. However, the strains were relatively unstable and lost reporter with time without selection. The kanamycin selection marker used wasn't the best choice as it provides resistance to amino glycosides which are an important class of second line drugs used in tuberculosis treatment. In addition, the marker could limit utility of the strains for screening of new potential drugs or evaluating drug combinations for tuberculosis treatment. Limited selection marker genes for mycobacterial genetic manipulation is a major drawback for such a marker-containing strain in many research fields. Therefore, selectable marker-free, more stable autoluminescent mycobacteria are highly needed. After trying several strategies, we created such mycobacterial strains successfully by using an integrative vector and removing both the resistance maker and integrase genes by Xer site-specific recombination in one step. The corresponding plasmid vectors developed in this study could be very convenient in constructing other selectable marker-free, more stable reporter mycobacteria with diverse applications.

OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files

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Competing Interests: The important plasmids including pOPHI and engineered strains were applied

Introduction

Many severe bacterial diseases, such as tuberculosis (TB), leprosy and Buruli ulcers are caused by mycobacteria. For example, TB, an infectious disease caused by *Mycobacterium tuberculosis* (MTB), is one of the greatest single infectious diseases causing morbidity and death in the world. The only TB vaccine in use for over 90 years, *Mycobacterium bovis* BCG (BCG), has very limited protection efficacy in older children and adults. The 9.0 million incident cases of

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DAY-TO-DAY PRACTICE

Erlotinib in combination with pemetrexed/cisplatin for leptomeningeal metastases and cerebrospinal fluid drug concentrations in lung adenocarcinoma patients after gefitinib faliure

Haihong Yang · Xinyun Yang · Yalei Zhang · Xin Liu · Qiuhua Deng · Meiling Zhao · Xin Xu · Jianxing He

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Abstract Limited treatment options are available for lung cancer with brain metastases. Recent reports indicated that erlotinib and pemetrexed had synergistic effects in lung adenocarcinoma. Thus, we speculated that erlotinib plus pemetrexed/cisplatin may be more effective for the treatment of refractory central nervous system metastases in patients after gefitinib failure. Six lung adenocarcinoma patients with leptomeningeal metastasis (LM) who showed initial good response to gefitinib and subsequent gefitinib resistance were enrolled in this retrospective study. Five of the six patients had an epidermal growth factor receptor (*EGFR*) mutation in the primary tumor tissues or plasma. One patient showed complete remission, two patients showed a partial response, and two patients had stable disease. Performance and symptoms improved in the six patients. The survival time after the combination therapy was from 8 to 15 months (median, 9 months). There was no significant difference in cerebrospinal fluid (CSF) penetration rates of erlotinib between the erlotinib-only and the combination groups (P=0.44). Erlotinib combined with pemetrexed/cisplatin may be effective in the treatment of LM in *EGFR* mutation patients after gefitinib failure. Small but measurable penetration of erlotinib and pemetrexed into the CSF was observed.

Keywords Erlotinib · Pemetrexed · Adenocarcinoma · Brain metastases · Cerebrospinal fluid

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. Brain metastases are a frequent complication of NSCLC, especially in lung adenocarcinoma. Thirty to fifty percent or more patients will develop brain metastases before or during the treatment [1]. Limited treatment options, such as whole-brain radiotherapy (WBRT) combined with or without stereotactic radiosurgery (SRS) as the primary treatment approach, are available for brain metastases patients, with poor disease progression-free survival (PFS) generally occurring about 6 months [2]. Thus, the availability of effective therapies is of great importance.

Currently, two agents (erlotinib and pemetrexed) are reported to be more effective in lung adenocarcinoma patients with brain metastases. Erlotinib, an epidermal growth factor receptor (*EGFR*) tyrosine-kinase inhibitor (TKI), is a small molecular agent that might more easily penetrate into the brain. Erlotinib significantly improved the response rate of metastatic brain tumors and survival in lung adenocarcinoma patients with asymptomatic synchronous brain metastasis, especially in patients with *EGFR*-activating mutations in exons 19 or 21 [3, 4]. Recently, it was reported that pemetrexed plus platinum appears to be particularly effective in terms of intracranial radiological response and overall survival in NSCLC patients with newly diagnosed brain metastases [5].

Haihong Yang and Xinyun Yang contributed equally.

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Adis

Original Article

Establishment of a mathematic model for predicting malignancy in solitary pulmonary nodules

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Background: The aim of this study was to establish a model for predicting the probability of malignancy in solitary pulmonary nodules (SPNs) and provide guidance for the diagnosis and follow-up intervention of SPNs.

Methods: We retrospectively analyzed the clinical data and computed tomography (CT) images of 294 patients with a clear pathological diagnosis of SPN. Multivariate logistic regression analysis was used to screen independent predictors of the probability of malignancy in the SPN and to establish a model for predicting malignancy in SPNs. Then, another 120 SPN patients who did not participate in the model establishment were chosen as group B and used to verify the accuracy of the prediction model.

Results: Multivariate logistic regression analysis showed that there were significant differences in age, smoking history, maximum diameter of nodules, spiculation, clear borders, and Cyfra21-1 levels between subgroups with benign and malignant SPNs (P<0.05). These factors were identified as independent predictors of malignancy in SPNs. The area under the curve (AUC) was 0.910 [95% confidence interval (CI), 0.857-0.963] in model with Cyfra21-1 significantly better than 0.812 (95% CI, 0.763-0.861) in model without Cyfra21-1 (P=0.008). The area under receiver operating characteristic (ROC) curve of our model is significantly higher than the Mayo model, VA model and Peking University People's (PKUPH) model. Our model (AUC =0.910) compared with Brock model (AUC =0.878, P=0.350), the difference was not statistically significant.

Conclusions: The model added Cyfra21-1 could improve prediction. The prediction model established in this study can be used to assess the probability of malignancy in SPNs, thereby providing help for the diagnosis of SPNs and the selection of follow-up interventions.

Keywords: Solitary pulmonary nodule (SPN); malignant tumor; logistic model; prediction; diagnosis

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Evaluation of spiropiperidine hydantoins as a novel class of antimalarial agents

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呼吸疾病国家重点实验室

Abstract

Given the rise of parasite resistance to all currently used antimalarial drugs, the identification of novel chemotypes with unique mechanisms of action is of paramount importance. Since *Plasmodium* expresses a number of aspartic proteases necessary for its survival, we have mined antimalarial datasets for drug-like aspartic protease inhibitors. This effort led to the identification of spiropiperidine hydantoins, bearing similarity to known inhibitors of the human aspartic protease β-secretase (BACE), as new leads for antimalarial drug discovery. Spiropiperidine hydantoins have a dynamic structure-activity relationship profile with positions identified as being tolerant of a variety of substitution patterns as well as a key piperidine N-benzyl phenol pharmacophore. Lead compounds **4e** (CWHM-123) and **12k** (CWHM-505) are potent antimalarials with IC_{50} values against *Plasmodium falciparum* 3D7 of 0.310 μM and 0.099 μM, respectively, and the former features equivalent potency on the chloroquine-resistant Dd2 strain.

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Author Contributions

All authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

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Original Article

Evaluation of the efficacy and safety of anti-PD-1 and anti-PD-L1 antibody in the treatment of non-small cell lung cancer (NSCLC): a meta-analysis

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Background: Currently, blockade of the programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) signaling pathway has been proved one of the most promising immunotherapeutic strategies against cancer. Several antibodies have been developed to either block the PD-1 or its ligand PD-L1 are under development. So far, a series of phase I trials on PD-1/PD-L1 antibodies for non-small cell lung cancer (NSCLC) have been completed, without reports of results from phase II studies. Thus, we sought to perform a meta-analysis incorporating all available evidences to evaluate the efficacy and safety of PD-1 or PD-L1 inhibition therapy.

Methods: Electronic databases were searched for eligible literatures. Data of objective respond rate (ORR) and rate of adverse effects (AEs) with 95% confidence interval (CI) evaluated by immunohistochemistry (IHC) was extracted. The outcomes were synthesized based on random-effect model. Subgroup analyses were proposed.

Results: In overall, ORR in the whole population with PD-1 blockage treatment is 22.5% (95% CI: 17.6% to 28.2%). Additionally, the rate of Grade 3-4 AEs is 16.7% (95% CI: 6.5% to 36.8%) and drug-related death rate is 2.5% (95% CI: 1.3% to 4.6%). As for patients with PD-L1 inhibition therapy, an overall ORR is 19.5% (95% CI: 13.2% to 27.7%). A higher rate of Grade 3-4 AEs (31.7%, 95% CI: 14.2% to 56.5%) is observed with a lower drug-related death rate (1.8%, 95% CI: 0.4% to 8.3%). In exploratory analyses of anti-PD-1 agents, we observed that greater ORR was presented in the median-dose cohort (3 mg/kg) than that of both low-dose (1 mg/kg) and high-dose (10 mg/kg) cohort (low-dose *vs.* median-dose: OR =0.12, P=0.0002; median-dose *vs.* high-dose: OR =1.47, P=0.18).

Conclusions: Anti-PD-1 and anti PD-L1 antibodies showed objective responses in approximately one fourth NSCLC patients with a tolerable adverse-effect profile. In addition, median-dose (3 mg/kg) might be a preferential dosage of anti-PD-1 agents.

Keywords: Anti-programmed cell death-1 (anti-PD-1); anti-programmed cell death-ligand 1 (anti-PD-L1); non-small cell lung cancer (NSCLC)

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ORIGINAL ARTICLE

Exon sequencing identifies a novel *CHRNA3-CHRNA5-CHRNB4* variant that increases the risk for chronic obstructive pulmonary disease

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ABSTRACT

Background and objective: **Recent genome-wide association studies have established that single nucleotide polymorphisms in the *CHRNA3-CHRNA5-CHRNB4* genes are susceptibility loci for chronic obstructive pulmonary disease COPD. However, further effort is still required to reveal their genetic contribution to COPD, considering the existence of 'missing heritability', which may be mediated by variants that are of a low frequency or rare. Here we aimed to identify genetic variants in the coding regions of the *CHRNA3-CHRNA5-CHRNB4* genes and determine their associations with COPD risk in Chinese.**

Methods: **We directly sequenced the coding regions of the *CHRNA3-CHRNA5-CHRNB4* genes in 160 Chinese subjects, and then genotyped the missense or synonymous variants that have previously been reported to be associated with COPD risk in a two-stage case–control study involving 1013 COPD cases and 1030 controls of southern Chinese.**

Results: **We found nine variants, three of which were missense variations (Ser140Gly, His462Gln and Asp398Asn), while two were synonymous variants (Tyr215Tyr and Val53Val). The variants Ser140Gly, Tyr215Tyr and Asp398Asn were significantly associated with COPD risk. By combining these variants, the number of risk genotypes significantly increased the risk for COPD in a dose-dependent manner ($P_{trend} = 5.00 \times 10^{-4}$). The risk genotype number was also significantly correlated with several lung function parameters, including forced expiratory volume in 1 s (FEV_1), FEV_1% predicted, FEV_1/forced vital capacity ratio and peak expiratory flow.**

Conclusions: **The present study identified a novel exon variant Ser140Gly, and two previously reported variants Tyr215Tyr and Asp398Asn are significantly associated with COPD risk in Chinese. These variants may be genetic biomarkers for predicting COPD risk in Chinese. Validation in other ethnicities is warranted.**

SUMMARY AT A GLANCE

We identified a novel exon variant Ser140Gly of *CHRNB4*, and validated two previously reported variants, Tyr215Tyr and Asp398Asn, which are associated with increasing risk for developing COPD. These variants also influence pulmonary function. They are potentially useful genetic biomarkers for predicting COPD risk in Chinese.

Key words: chronic obstructive pulmonary disease, exon variant, nicotinic cholinergic receptor.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GWAS, genome-wide association studies; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; PEF, peak expiratory flow.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) will be the third cause of mortality and the fifth cause of chronic disability by the year 2020.[1] In China, the prevalence of COPD is 8.2% in people aged 40 and above.[2] Although cigarette smoking is the major risk factor for COPD incidence, only 15.1% of smokers develop COPD,[3] suggesting that other factors also influence the development of COPD, such as genetic susceptibility.[4] Although the relatives of COPD patients may share a risk environment and thus have

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Expression and refolding of mite allergen pro-Der f1 from inclusion bodies in *Escherichia coli*

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ABSTRACT

House dust mite (*Dermatophagoides farinae*) allergen Der f1 is one of the most important indoor allergens associated with asthma, eczema and allergic rhinitis in humans. Therefore, sufficient quantities of Der f1 cysteine protease to be used for both experimental and therapeutic purposes are very much needed. Using recombinant DNA technology, high expression rates of cysteine proteases were obtained. The cDNA sequence encoding pro-Der f1 was cloned and expressed in *Escherichia coli* using the T7 based expression vector pET-44a and induced by isopropyl-β-D-thiogalactoside at a final concentration of 0.2 mM. Recombinant pro-Der f1 (pro-rDer f1) was expressed as an inclusion body and the isolated protease was solubilized, refolded and purified. The protease activities and IgE reactivities of pro-rDer f1 that were refolded by size-exclusion chromatography (SEC) were higher than those obtained by dilution. The pair of pro-rDer f1 polypeptides produced by this method could be used for more effective and safer allergen-specific immunotherapy or to produce enzymatically and immunologically active Der f1 for diagnostic testing and deciphering of immunotherapy mechanisms.

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呼吸疾病国家重点实验室

Introduction

The house dust mites *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* are the most important causative factors linked to various allergic diseases [1]. Some of the approaches for the treatment of allergic diseases are allergen avoidance, non-specific pharmacotherapy and allergen-specific immunotherapy (SIT)[1] [2]. SIT is attractive as it targets the underlying disease process and is potentially curative. Conventional SIT is administered by subcutaneous injection of allergen extract that has easily led to side effects in allergic patients. In addition, it is difficult to control the quality and consistency of native allergen extracts making them inefficient for drug development, diagnostic testing and SIT. A solution to this problem was found when recombinant DNA technology was developed that allowed for the large-scale production of recombinant allergens that were equivalent to their native counterparts and genetically engineered variants with reduced IgE reactivities [3–5]. These recombinant allergens now provide approaches for making a detailed diagnosis of a patient's sensitization profile and for clinical trials of subcutaneous immunotherapy [5].

Der f1 and Der p1 allergens derived from *D. farinae* and *D. pteronyssinus* are important group 1 allergens and mainly found in the feces of mites [6,7]. They belong to the papain-like cysteine protease family and have been characterized as pre-pro-enzyme, which consists of a signal peptide, a pro-domain at the N-terminus and a mature region [8]. IgE-binding to group 1 allergens is highly dependent on the natural conformation of allergens [9]. In addition, the cysteine protease Der p1 is involved in the pathogenesis of allergic disease [10–13]. Large quantities of recombinant allergens have been expressed in insect cells, yeast and bacteria expression systems. Shoji et al. produced recombinant Der f1 in insect Sf9 cells by using a baculovirus expression system, but the recombinant Der f1 (rDer f1) had IgE-binding activity that was only 20% of the activity of native Der f1 (nDer f1) [14]. A more efficient expression system is yeast *Pichia pastoris*, where the IgE binding activities of the mature rDer f1 protein were the same as those of nDer f1, however the rDer f1 was shown to be more glycosylated than native Der f1 [1,15]. The mutated N-glycosylation site enabled

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[1] *Abbreviations used:* SEC, size-exclusion chromatography; SIT, specific immunotherapy; nDer f1, native Der f1; IPTG, isopropyl-β-D-thiogalactopyranoside; UV, ultraviolet.

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Original Paper

Extracellular Adenosine Diphosphate Ribose Mobilizes Intracellular Ca^{2+} via Purinergic-Dependent Ca^{2+} Pathways in Rat Pulmonary Artery Smooth Muscle Cells

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Key Words
Adenosine diphosphate ribose • Purinergic receptors • Pulmonary arterial smooth muscle cells • Ca^{2+} mobilization

Abstract
Background/Aims: Adenosine diphosphate ribose (ADPR), a product of β-NAD^+ metabolism generated by the multifunctional enzyme CD38, is recognized as a novel signaling molecule. The catalytic site of CD38 orients extracellularly or intracellularly, capable of generating ADPR outside and inside the cells. CD38-dependent pathways have been characterized in pulmonary artery smooth muscle cells (PASMCs); however the physiological function of extracellular ADPR is unclear. ***Methods:*** Ca^{2+} mobilizing and proliferative effects of extracellular ADPR were characterized and compared with the ATP-induced responses in rat PASMCs; and the expression of purinergic receptor (P2X and P2Y) subtypes were examined in pulmonary arteries. ***Results:*** ADPR elicited concentration-dependent increase in $[Ca^{2+}]_i$ with a fast transient and a sustained phase in PASMCs. The sustained phase was abolished by Ca^{2+} removal and inhibited by the non-selective cation channel blocker SKF-96365, but was unaffected by TRPM2 antagonists or nifedipine. The purinergic receptor (P2X) antagonist pyridoxal-phosphate-6-azophenyl-2', 4'-disulfonate inhibited partially the transient and the sustained Ca^{2+} response, while the P2(XY) inhibitor suramin and the phospholipase C inhibitor U73122 abolished the sustained Ca^{2+} influx. The P2Y1 antagonist MRS2179 had no effect on the response. By contrast, ATP and ADP activated Ca^{2+} response exhibited a high and a low affinity component, and the pharmacological profile of ATP-induced Ca^{2+} response was distinctive from that of ADPR. BrdU incorporation assay showed that ADPR caused significant inhibition whereas ATP caused

C. Huang and J. Hu have equal contribution to this publication.

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FLUOROFENIDONE ATTENUATES TGF-β_1–INDUCED LUNG FIBROBLAST ACTIVATION VIA RESTORING THE EXPRESSION OF CAVEOLIN-1

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ABSTRACT—Caveolin-1 plays an important role in the pathogenesis of idiopathic pulmonary fibrosis. We previously showed that fluorofenidone (FD), a novel pyridine agent, can attenuate bleomycin-induced experimental pulmonary fibrosis and restore the production of caveolin-1. In this study, we explore mainly whether caveolin-1 plays a critical role in the anti–pulmonary fibrosis effects of FD *in vitro*. The normal human lung fibroblasts (NHLFs) were cultured with transforming growth factor-β_1 (TGF-β_1) and then were treated with FD. Subsequently, NHLFs transfected with cav-1-siRNA were treated with TGF-β_1 and/or FD. The expressions of α-smooth muscle actin (α-SMA), fibronectin, collagen I, caveolin-1, phosphorylated extracellular signal–regulated kinase (p-ERK), phosphorylated *c*-Jun *N*-terminal kinase (p-JNK), and phosphorylated P38 were measured by Western blot and/or real-time polymerase chain reaction. Fluorofenidone attenuated TGF-β_1–induced expressions of α-SMA , fibronectin, and collagen I; inhibited phosphorylation of ERK, JNK, and P38; and restored caveolin-1 protein expression but cannot increase caveolin-1 mRNA level *in vitro*. After caveolin-1 was silenced, FD could not downregulate TGF-β_1–induced expressions of α-SMA, fibronectin, and collagen I or phosphorylation of ERK, JNK, and P38. These studies demonstrate that FD, a potential antifibrotic agent, may attenuate TGF-β_1–induced activation of NHLFs by restoring the expression of caveolin-1.

KEYWORDS—Idiopathic pulmonary fibrosis, extracellular matrix, transforming growth factor-β, α-smooth muscle actin, fibronectin, pyridine agent

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is defined as "a specific form of chronic progressive fibrosing interstitial pneumonia of unknown cause" (1). It is characterized by massive activated fibroblasts transdifferentiation into myofibroblasts and excess deposition of extracellular matrix (ECM) (2). In the initial injury phase, activated alveolar epithelial cells and recruited inflammatory cells release potent fibrogenic growth factors, particularly transforming growth factor-β (TGF-β), that perpetuate the cycle of injury, failed repair, and fibrosis (3). With treatment with TGF-β, lung fibroblasts can be activated to myofibroblasts through the activation of mitogen-activated protein kinase (MAPK), Smad, and other signaling pathways, which promotes synthesis of ECM and then increases the expressions of α-smooth muscle actin (α-SMA), collagen I, and fibronectin (4,5). Caveolin-1, a principal component of caveolae, plays an important role in the pathogenesis of IPF. Caveolin-1 conveys a homeostatic function in the process of fibrosis by regulating TGF-β_1 and its downstream signaling and by regulating critical cellular processes involved in tissue repair, such as migration, adhesion, and cellular response to mechanical stress, and antagonizing profibrotic processes, such as proliferation (6). It is well documented that caveolin-1 is abnormally expressed in fibrotic lung tissue from patients with IPF and in bleomycin (BLM)-induced lung fibrosis tissue (7,8). Systemic administration of the caveolin-1 scaffolding domain peptide to BLM-treated mice blocks epithelial cell apoptosis, inflammatory cell infiltration, and changes in tissue morphology, as well as signaling molecule activation and collagen, tenascin-C, and expression of α-SMA associated with lung fibrosis (9).

Fluorofenidone [1-(3-fluorophenyl)-5-methyl-2-(1H)-pyridone] (FD), a novel low-molecular-weight pyridine agent, was developed and patented by the Pharmaceutical School of Central South University (10). Our previously reported data showed that FD exerts a strong antifibrotic effect on renal fibrosis and liver fibrosis (11–14). Meanwhile, FD could attenuate BLM-induced experimental pulmonary fibrosis, inhibit the increase in TGF-β levels in bronchoalveolar lavage fluids, accelerate the production of caveolin-1, and inhibit phosphorylated MAPK signaling pathway (15).

Hence, in this study, we explore mainly whether caveolin-1 plays a critical role in the anti–pulmonary fibrosis effects of FD *in vitro*.

MATERIALS AND METHODS

Ethics statement

Primary fibroblast lines were obtained from unused, anonymous, existing pathological human tissue samples, and we didn't participate in the specimens collection. Therefore we were unable to obtain informed consent of participants.

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Food allergy and related risk factors in 2540 preschool children: an epidemiological survey in Guangdong Province, southern China

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Background: **Although the number of studies on allergic diseases in the general population of southern China is increasing, only a few have addressed food allergy (FA) in children in this region. The present study aimed to investigate the prevalence, clinical manifestations, spectrum of allergens, and related risk factors of FA in preschool children in Guangdong Province, southern China.**

Methods: **A random cluster-sampling method was used to select 24 kindergartens from 12 cities in Guangdong Province. The parents or guardians of the children were requested to complete a questionnaire on general information and data regarding FA diagnosis and symptoms in the children and their first-degree relatives. Thereafter, the Chi-square test, multivariate regression analysis, and Spearman's rank-order correlation coefficient analysis were performed to identify statistically significant differences.**

Results: **Analysis of 2540 valid questionnaires revealed an FA prevalence rate of 4%. Adverse food reactions were due to the consumption of shrimp (4.4%), crab (3.2%), mango (2.3%), cow's milk and dairy products (1.9%), and eggs (1.4%). Logistic regression analysis indicated that a history of FA and a history of allergic rhinitis in the first-degree relatives were the major factors leading to FA in children.**

Conclusions: **The incidence of FA in children in Guangdong Province is higher than that commonly believed. An individual's genetic background is an important risk factor for FA. Hence, mitigation of the impact of lifestyle and environmental factors should be carefully considered to reduce the incidence of childhood FA.**

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Key words: **allergic rhinitis;**
eczema;
epidemiology;
food allergy;
questionnaire

Original article

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Introduction

The incidence of allergies has been increasing worldwide in recent decades.[1] In these allergies, food allergy (FA) in children has become a global health concern in a context of the ever-evolving modern lifestyles and diet.[2] In the United States, about 5.9 million children have a history of FA, representing an increase of 18%[3-6] over the past decade. Of these children, nearly 40% have experienced FA-related events ranging from transient hypotension to life-threatening anaphylaxis.[7,8] Allergic reactions to food are among the common conditions that necessitate immediate medical care in the emergency room visits.[8,9] Given the diversity of foods and scarce options in diagnostics, however, the current understanding of FA remains inadequate.[10] Studies[11,12] have shown that inconsistency between parents' beliefs and expert opinions frequently leads to under-evaluation of childhood FA. Variations in the prevalence of FA across countries may further complicate the scenario. Therefore, a clear epidemiological picture of FA within a geographic region should be important to support evidence-based, local prevention and management of this condition, especially in a large country such as China.

Despite the increasing research into allergic

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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

Frequency of food group consumption and risk of allergic disease and sensitization in schoolchildren in urban and rural China

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Summary

Background Diet is a potential determinant of allergic diseases.

Objective To examine in schoolchildren the association between food intake and allergic diseases and determine whether there is effect of environment – rural vs. urban.

Methods A questionnaire survey was performed in 11 473 children aged 7–12 years in 20 schools from urban Guangzhou and rural Shaoguan, China. A nested case–control group, 402 from Guangzhou and 349 from Shaoguan, was recruited. Food ingestion frequency data were collected. Serum-specific IgE to 34 food and airborne allergens was determined. Associations between food ingestion frequency and clinical outcomes were sought by logistic analyses.

Results The prevalence of self-reported asthma (6.6% vs. 2.5%), rhinitis (23.2% vs. 5.3%) and eczema (34.1% vs. 25.9%) was significantly higher in Guangzhou subjects compared to Shaoguan, whereas prevalence of food hypersensitivity (9.7% vs. 9.2%) and food allergy (4.0% vs. 3.5%) was not significantly different. In this case–control study, seafood and fruits were two major food groups causing food hypersensitivity. Urban children consumed more milk, egg, chocolate, fruits, vegetable and cereals compared to rural children. Significantly higher percentage of Guangzhou children was sensitized to egg and milk, whereas more Shaoguan children were sensitized to seafood, nuts and seeds, fruit, vegetables, legumes and cereals. High consumption of milk (OR 2.604, 95CI% 1.569–4.322, $P < 0.001$) and vegetables (OR 0.382, 95% CI 0.180–0.809, $P = 0.012$) were positively and reversely associated with asthma, respectively.

Conclusion Difference in prevalence of asthma but not food allergy was observed. Diets of schoolchildren are affected by disease-related modification and country's urbanization. High vegetable intake and low milk intake might protect against asthma.

Keywords asthma, food frequency questionnaire, food hypersensitivity, milk, vegetables
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Introduction

A dramatic rise in the prevalence of allergic diseases has been reported in developed countries and more recently in developing countries such as China [1]. The rising trend is often attributed to environmental or lifestyle changes [2]. Diet, especially maternal and early infant diet, is a potential determinant of allergic diseases [3–5]. Population-based studies have examined associations between dietary components and allergic diseases. Intake of dietary components including fruits, vegetables, fish, cereals and starches, various fatty acids, vitamin A/C/E and minerals has been found to be protective against allergic diseases [6]. Other studies observed a protective effect for a higher adherence to Mediterranean diet, characterized by high intakes of fruits and vegetables, nuts, whole grains, unsaturated fatty acids and fish, combined with low meat consumption and moderate dairy intake [7, 8]. Two recent prospective studies confirmed high intake of fruits, vegetables, and increased food diversity within the first year of life was inversely associated with allergic diseases [9, 10]. However, the relationship of diet and allergies diseases in China remains particularly limited.

Food consumption habits in China have changed dramatically over last several decades in association with

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Frequent alterations in cytoskeleton remodelling genes in primary and metastatic lung adenocarcinomas

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The landscape of genetic alterations in lung adenocarcinoma derived from Asian patients is largely uncharacterized. Here we present an integrated genomic and transcriptomic analysis of 335 primary lung adenocarcinomas and 35 corresponding lymph node metastases from Chinese patients. Altogether 13 significantly mutated genes are identified, including the most commonly mutated gene *TP53* and novel mutation targets such as *RHPN2*, *GLI3* and *MRC2*. *TP53* mutations are furthermore significantly enriched in tumours from patients harbouring metastases. Genes regulating cytoskeleton remodelling processes are also frequently altered, especially in metastatic samples, of which the high expression level of *IQGAP3* is identified as a marker for poor prognosis. Our study represents the first large-scale sequencing effort on lung adenocarcinoma in Asian patients and provides a comprehensive mutational landscape for both primary and metastatic tumours. This may thus form a basis for personalized medical care and shed light on the molecular pathogenesis of metastatic lung adenocarcinoma.

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呼吸疾病国家重点实验室

Original Article

Functional residual capacity in beagle dogs with and without acute respiratory distress syndrome

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Contributions: (I) Conception and design: Q Liu, R Chen; (II) Performed the experiments: Q Liu, Y Gao, D Hua, W Li, H Zheng; (III) Data analysis: Q Liu, W Li, H Zheng; (IV) Manuscript writing: Q Liu; (V) Supervised this study, discussed and edited the paper: C Zheng, R Chen; (VI) Final approval of manuscript: All authors.

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Background: Traditionally, the choice of tidal volume for mechanical ventilation was based on body weight (BW) and usually, predicted BW was used to correct actual BW inter-individual variations in obesity and muscle weight. The method of selecting tidal volume depended on the fact that normal lung volumes, especially functional residual capacity (FRC), were mainly determined by height (indirectly by predicted BW), sex and age in healthy persons. However, FRCs in patients with acute respiratory distress syndrome (ARDS) might not abide by the same rule and be significantly different from each other in patients with the same height and sex. We hypothesized that FRC was determined by body length (surrogate for predicted BW) and age in healthy male beagle dogs but not in lung injured ones.

Methods: A total of 24 dogs were recruited and ARDS model was induced by intravenous injection of oleic acid. FRC was measured by chest computer tomography. Blood gas analysis, extra vascular lung water and respiratory system mechanics were tested at baseline and post-lung injury. Age, body length and actual BW were also recorded before experiments.

Results: After lung injury, FRC decreased sharply from baseline (414±84) to (214±70) mL. For healthy lungs, FRC could be estimated by the following formula: FRC =21.86 × age (months) + 20.55 × body length (cm) – 1,337.98 ($P<0.05$), while for injured lungs, the formula of multiple linear regression was invalid ($P=0.305$).

Conclusions: FRC was linearly related to body length in healthy dogs but not in lung injured ones. The traditional view of setting tidal volume based on predicted BW should be challenged cautiously.

Keywords: Functional residual capacity (FRC); predicted body weight (BW); tidal volume; lung protective ventilation

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Introduction

Mechanical ventilation was an important supportive strategy for patients receiving surgery or suffering from respiratory failure. Traditionally, the choice of tidal volume, the most important parameter of ventilator settings, was based on the body weight (BW), which was a certain milliliter for per kilogram of BW. Usually, predicted BW was used to correct actual BW inter-individual variations in obesity and muscle weight (1). For patients with acute respiratory

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Functional Role and Mechanism of LncRNA LOC728228 in Malignant 16HBE Cells Transformed by Anti-Benzopyrene-Trans-7,8-Dihydrodiol-9,10-Epoxide

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Lung cancer is a major health problem, and is considered one of the deadliest cancers in humans. It is refractory to current treatments, and the mechanisms of lung cancer are unknown. Long noncoding RNAs (lncRNAs) are involved in various biological processes and human diseases. However, the exact functional roles and mechanisms of lncRNAs are largely unclear. In this study, we attempted to identify lung-cancer-related lncRNAs. We found changes in lncRNA expression in the anti-benzo(a) pyrene-7,8-diol-9,10-epoxide (anti-BPDE)-transformed human bronchial epithelial cell line (16HBE-T cells) using microarrays and qRT–PCR. Of these lncRNAs, LOC728228 was upregulated relative to its expression in control untransformed16HBE (16HBE-N) cells. LOC728228 knockdown inhibited cell proliferation, caused G0/G1-phase cell-cycle arrest, reduced cellular migration, suppressed colony formation in vitro, and inhibited tumor growth in a nude mouse xenograft model. LOC728228 knockdown also suppressed cyclin D1 expression, and the depletion of cyclin D1 induced G0/G1-phase cell-cycle arrest and inhibited cell proliferation, thus influencing the malignant potential of cancer cells. In summary, our results suggest that lncRNA LOC728228 has an oncogene-like function and plays a vital role in human lung cancer. © 2015 Wiley Periodicals, Inc.

Key words: lung cancer; long noncoding RNA; LOC728228; 16HBE-T cells

INTRODUCTION

Researchers have shown that a large number of noncoding RNAs (ncRNAs) are transcribed from the human genome [1,2]. Long noncoding RNAs (lncRNAs) have more than 200 nucleotides, with no protein-coding potential, and have recently received considerable attention due to their significant roles in diverse biological processes and human diseases [3–7]. The analysis of their roles in cancer development is focus of current research. Accumulating evidence shows that many lncRNAs have a strong association with cancer development and progression [8–12], and some are considered to be a newly emerging class of oncogenic and tumor-suppressor transcripts [13].

Lung cancer is one of the most common cancers worldwide in terms of its incidence and associated mortality. However, the molecular mechanisms involved in lung cancer are complex and are as yet incompletely understood. Recent studies have shown that some lncRNAs are critical in lung cancer. For example, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is upregulated in certain histological subtypes of non-small-cell lung cancer (NSCLC). MALAT1 promotes cell migration and has been identified as an oncogene [12,14,15]. Several other lncRNAs have been reported to play vital roles in lung cancer, including maternally expressed gene 3 (MEG3) [16], H19 [17], and smoke cancer-associated lncRNA-1 (SCAL1) [18]. However, lncRNAs and their

Abbreviations: lncRNAs, long noncoding RNAs; anti-BPDE, anti benzo(a)pyrene-7,8-diol-9,10-epoxide; MALAT1, metastasis associated lung adenocarcinoma transcript 1; NSCLC, non small-cell lung cancer; MEG3, maternally expressed gene 3; SCAL1, smoke cancer associated lncRNA-1; 16HBE, human bronchial epithelial cell line; 16HBE-T, transformed 16HBE cells; 16HBE-N, control untransformed 16HBE cells; qRT–PCR, quantitative real time reverse transcription–polymerase chain reaction; GFP, green fluorescent protein; GAPDH, glyceraldehyde 3 phosphate dehydrogenase; GAS5, growth arrest-specific transcript 5; ncRAN, noncoding RNA expressed in aggressive neuroblastoma; PCAT-1, prostate cancer-associated transcript 1; PCGEM1, prostate specific gene 1; uc.73a, ultraconserved element 73; HOTAIR, HOX antisense intergenic RNA; lncRNA-LET, lncRNA low expression in tumor.

Conflict of Interest: None.

G. Hu, T. Yang and J. Zheng contributed equally to this work.

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Gambogic acid induces apoptosis in diffuse large B-cell lymphoma cells *via* inducing proteasome inhibition

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Resistance to chemotherapy is a great challenge to improving the survival of patients with diffuse large B-cell lymphoma (DLBCL), especially those with activated B-cell-like DLBCL (ABC-DLBCL). Therefore it is urgent to search for novel agents for the treatment of DLBCL. Gambogic acid (GA), a small molecule derived from Chinese herb gamboges, has been approved for Phase II clinical trial for cancer therapy by Chinese FDA. In the present study, we investigated the effect of GA on cell survival and apoptosis in DLBCL cells including both GCB- and ABC-DLBCL cells. We found that GA induced growth inhibition and apoptosis of both GCB- and ABC-DLBCL cells *in vitro* and *in vivo*, which is associated with proteasome malfunction. These findings provide significant pre-clinical evidence for potential usage of GA in DLBCL therapy particularly in ABC-DLBCL treatment.

Diffuse large B-cell lymphoma (DLBCL), an aggressive form of non-Hodgkin's lymphoma (NHL), accounts for approximately 30%–40% of all NHL[1]. There are three subcategories in DLBCL: activated B-cell-like DLBCL (ABC-DLBCL), germinal center B-cell-like DLBCL (GCB-DLBCL) and primary mediastinal DLBCL (PMBCL)[2,3]. These subtypes are characterized by distinct differences in survival, chemoresponsiveness, as well as dependence on signaling pathways, especially the nuclear factor-κB (NF-κB) pathway. In particular, the ABC-DLBCL subtype, which is NF-κB-dependent, appears to have the worst prognosis among the three subtypes[4–6]. Patients with the ABC-DLBCL tend to have the poorest 5-year survival rate (16%), compared to GCB-DLBCL (76%) and PMBCL (64%)[7]. Treatment for DLBCL has been improved over the last decade, especially with the development of Rituximab, an anti-CD20 monoclonal antibody, in combination with CHOP (Cytoxan, Hydroxyrubicin, Oncovin, and Prednisone) therapy program[8,9]. Unfortunately, adverse events including bronchospasm, hypotension, cardiac arrhythmias and renal failure occur during the therapy. Furthermore, at least 25–30% of patients experience disease recurrence and patients with the ABC-DLBCL subtype is much more resistant to current treatment regimens[10,11]. Resistance to the Rituximab-CHOP (R-CHOP) therapy program develops over time and is becoming an emerging problem for DLBCL treatment. Therefore, the development of innovative therapies and identification of more effective drugs for DLBCL are clearly needed.

Gambogic acid (GA), a small molecule extracted from the traditional Chinese medicine gamboges[12], has been approved by Chinese FDA for phase II clinical trial in solid tumor therapy[13,14]. Unlike other chemotherapeutics, GA has very low toxicity to the hematopoietic system[15,16]. Several molecular targets of GA have been proposed[17,18]. Most recently, we have reported that GA is a novel tissue-specific proteasome inhibitor, with potency comparable to bortezomib but much less toxicity[19]. Although proteasome inhibitors such as carfilzomib have been reported to induce cell death in DLBCL cells combining with HDAC (histone deacetylase) inhibitors[20], the effect of GA on DLBCL remains unknown.

Here, we investigated the effects of GA in DLBCL cell lines and in mouse models. Strikingly, GA displays pronounced antineoplastic activity in both GCB- and ABC-DLBCL cells and in *in vivo* DLBCL xenograft models.

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γ Secretase Inhibitor BMS-708163 Reverses Resistance to EGFR Inhibitor via the PI3K/Akt Pathway in Lung Cancer

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ABSTRACT

Lung adenocarcinoma cells harboring epidermal growth factor receptor (EGFR) mutations are sensitive to EGFR tyrosine kinase inhibitor (TKI). Acquired resistance to EGFR TKI develops after prolonged treatment. The aim of this study was to investigate the effect of the novel γ secretase inhibitor BMS-708163 on acquired resistance to the EGFR TKI gefitinib. We did not observe known mechanisms of acquired resistance to EGFR TKI, including the EGFR T790M mutation and MET gene amplification in the gefitinib-resistant PC9/AB2 cells. BMS-708163 inhibited PI3K/Akt expression and sensitized PC9/AB2 cells to gefitinib-induced cytotoxicity. In contrast, BMS-708163 had no significant effect on gefitinib sensitivity in PC9 parental cells. Combined treatment with BMS-708163 and gefitinib induced high levels of apoptosis. Our in vivo studies showed that combined treatment of gefitinib and BMS-708163 inhibited the growth of PC9/AB2 xenografts. In conclusion, our data show that combined treatment of gefitinib and γ secretase inhibitors may be useful for treating lung adenocarcinomas harboring EGFR mutations with acquired gefitinib resistance. J. Cell. Biochem. 116: 1019–1027, 2015. © 2015 Wiley Periodicals, Inc.

KEY WORDS: γ SECRETASE INHIBITOR; GEFITINIB; DRUG RESISTANCE; LUNG CANCER

Lung cancers with mutations in the epidermal growth factor receptor (EGFR) gene are a well-described molecular subgroup of lung adenocarcinomas. This subgroup is characterized by high prevalence in females, never-smokers, and Asians, and sensitivity to EGFR tyrosine kinase inhibitor (TKI) gefitinib or erlotinib [Jackman et al., 2009]. However, disease progression develops in most lung cancer patients with EGFR mutations after a median of 10–14 months of treatment with EGFR TKI. Potential mechanisms associated with acquired resistance to gefitinib include acquisition of the T790M mutation in exon 20 of the EGFR, MET amplification, and hepatocyte growth factor (HGF) overexpression [Godin-Heymann et al., 2007; Yano et al., 2008; Mcdermott et al., 2010].

The Notch signaling pathway is a conserved ligand–receptor signaling pathway that plays critical mechanistic roles in cell proliferation, survival, apoptosis, and differentiation which affects the development and function of many organs [Miele, 2006]. Recently, Notch is found to be involved in not only chemotherapy drug-resistance [Bao et al., 2011; McAuliffe et al., 2012; Liu et al., 2013] but also EGFR TKI resistance [Xie et al., 2013]. Blockade of an upregulated Notch signaling pathway can be achieved by inhibiting the formation of the main force of Notch activity, the Notch intracellular domain (NICD) [Takebe et al., 2014]. Thus, a pharmacological approach using γ secretase inhibitor to prevent the final cleavage step of the precursor form of Notch to decrease the levels of NICD could be a novel therapeutic approach for the treatment of lung cancer by overcoming drug-resistance of cancer cells.

The aim of this study was to investigate the effect of the novel γ secretase inhibitor BMS-708163 on acquired resistance to EGFR TKI. Our results show that BMS-708163 reverses sensitivity to gefitinib in

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Table. Summary of diagnostic and laboratory findings, animal species, sample materials, and region where samples were collected in the study of Shuni virus infection in ruminants, Israel, 2014–15*

Animal no.	Laboratory no.	Species	Clinical manifestation	Region	PCR-positive sample	Vero isolation	Virus isolation in mice
1	2417/1/14	Sheep	Malformed, aborted fetus	Northern valley	Brain, placenta	Negative	Negative
2	2417/2/14	Sheep	Malformed, aborted fetus	Northern valley	Brain	Negative	Negative
3	267/2/14	Sheep	Malformed, aborted fetus	Northern valley	Brain	Not done	Not done
4	267/3/14	Sheep	Malformed, aborted fetus	Northern valley	Brain	Not done	Not done
5	267/4/14	Sheep	Malformed, aborted fetus	Northern valley	Brain	Not done	Not done
6	2498/1/14	Sheep	Weak lamb syndrome	Northern valley	Brain, EDTA-blood	Negative	Negative
7	2504/1/14	Sheep	Malformed aborted fetus	Northern valley	Brain	Not done	Not done
8	2504/2/14	Sheep	Malformed, aborted fetus	Northern valley	Brain, placenta	Negative	Negative
9	273/14	Sheep†	Malformed, aborted fetus	Negev	Brain	Not done	Not done
10	274/14	Sheep	Aborted fetus	Northern valley	Brain, placenta	Not done	Not done
11	2504/3/14	Sheep†	Malformed, aborted fetus	Northern valley	Brain, placenta	Positive	Positive
12	275/1/14	Sheep	Malformed, aborted fetus	Northern valley	Brain, placenta	Negative	Negative
13	275/2/14	Sheep	Malformed aborted fetus	Northern valley	Brain, placenta	Not done	Not done
14	263/14	Goat	Malformed, aborted fetus	Northern valley	Brain, placenta	Not done	Not done
15	215/14	Cattle	Aborted fetus	Upper Galilee	Brain	Negative	Negative

*Not done, not performed if insufficient brain material was available for cerebral inoculation or if the infected brain failed to propagate in the cell line. For some animals, >1 sample was collected.
†Sequences used to build the phylogenetic trees in online Technical Appendix Figure 2 (http://wwwnc.cdc.gov/EID/21/12/15-0804-Techapp1.pdf).

activity. Thus, isolation of SHUV from malformed brains may indicate strong neurotropism of this putative pathogen. The possibility of its replication in the fetal nervous system should also be considered because an affected fetus that is born alive is likely a reservoir. Indeed, AKAV was identified in the hippocampus (only) of adult lactating cows (data not shown), and similar epidemiologic evidence might result from other Simbu virus infections.

A serologic survey conducted in Israel during the 2001–2003 outbreaks of AHS showed reactivity of AINV to serum samples of ruminants in Israel's southern regions (*3*). Because AINV and SHUV are known to have a strong serologic cross-reaction, SHUV has likely previously infiltrated Israel. However, whether the seroreactivity results from AINV or SHUV remains unresolved.

The emergence and reemergence of arboviruses should interest medical practitioners, particularly epidemiologists. The appearance of exotic viruses in unexpected locations might result in more severe pathology in newly invaded regions than in the original arbovirus-endemic areas. Furthermore, SHUV has been detected in a child with febrile illness (*2*), a finding that suggests a potential zoonotic problem.

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Genetic Characterization of Highly Pathogenic Avian Influenza A(H5N6) Virus, Guangdong, China

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Glycomic Signatures on Serum IgGs for Prediction of Postvaccination Response

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Millions of individuals are vaccinated worldwide each year to stimulate their adaptive immune systems to produce protective antibodies and T-cell response against pathogens. Since glycosylation of the Fc region of immunoglobulin G (IgG) can be influenced by the host's immune status, it was inferred that glycosylation profile of IgG might be altered as a result of the immune response. Therefore, subclass-specific glycosylation profiles of serum IgGs from 26 healthy adults before and after vaccination with a trivalent subunit influenza virus vaccine were comprehensively analyzed to explore glycomic signatures for vaccination. The results showed that no significant changes in the glycosylation of total IgGs took place before and after vaccination, but distinct glycosylation profiles in responders (fourfold or more increase of HI titer after vaccination) and nonresponders (less than fourfold increase of HI titer) were observed. This difference between the responders and nonresponders occurred even in the resting state. On the basis of variable importance parameters, glycosylation markers that distinguish responders from nonresponders were identified. These markers can be used as molecular signatures to predict antibody titers after vaccination. This is the first study of serum IgG glycosylation profiles in healthy adults receiving a trivalent inactivated influenza vaccine.

Influenza viruses are respiratory pathogens that cause high morbidity and mortality worldwide every year. Vaccination is one of the most effective methods to prevent influenza infection. The composition of vaccines is recommended annually by the World Health Organization (WHO) to ensure induced immune response against epidemic strain effectively[1]. However, systematic review and meta-analysis on the efficacy and effectiveness of influenza vaccines have shown that pooled efficacy of trivalent inactivated influenza vaccine (TIV) was only 59% in adults aged 18–65 years, which indicated a moderate protection of influenza vaccines against virologically confirmed influenza[2]. The protective effects of the immune response are influenced not only by the antigenic match between the vaccine strains and epidemic strains[3], but also by the immunocompetence of individuals[4–7]. Hence, the identification of markers that can accurately predict vaccination efficacy is a pressing need, of which the information would not only enhance the efficacy of current vaccines through personalized vaccination approaches, but would also aid in exploring important mechanisms affecting efficacy, which would in turn contribute to the rational development of next-generation vaccines[8].

Immunoglobulin G (IgG) is a major antibody isotype in the blood that can protect the body from infection of pathogens. The Fab region of the IgG molecule is responsible for recognizing and binding to non-self antigens, whereas the Fc region implements elimination of foreign substances by interacting with complement molecules and Fc receptors to activate the complement system and induce antibody-dependent cell-mediated cytotoxicity (ADCC)[9,10]. The N-glycan located in the Fc region has been shown to affect the binding affinity of IgG to Fc receptors and complement components[11–14]. Glycosylation pattern of Fc determined by the ratio of B cells with different types of glycosyltransferases varies between different individual IgG molecules[15]. When B cells are stimulated by "environmental" factors, mediators that stimulate the innate immune system, or factors arising from the adaptive immune system, Fc glycosylation could be modulated as a result of significant changes in the expression of glycosylation genes[16,17]. Since 1985, a series of studies have shown that the glycosylation of the Fc region can be used to identify a certain number of autoimmune and inflammatory diseases (e.g. rheumatoid arthritis). The glycosylation of IgG has also been shown to correlate with disease progression and clinical outcome[12,18–24]. These data implicit a close association between variations in the glycosylation of IgG and changes in the immune status of humans.

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SHORT COMMUNICATION

GP73 was upregulated in PBMC stimulated with ConA but failed to promote lymphocyte proliferation

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Abstract

Golgi protein 73-kD (GP73), a type II Golgi transmembrane glycoprotein, is highly expressed in a variety of human diseases, but its physiology and pathology remain unknown. In examining the function of GP73 in the immune system, treatment of human PBMC with ConA significantly increased the intracellular expression of GP73 and its secretion into the culture medium. Two-way MLR and the ConA stimulation assay showed that treatment with purified GP73 protein barely affected the proliferation of PBMC. These results suggest that lymphocyte-secreted GP73 might partially contribute to higher serum GP73 in patients, and secreted GP73 exerts an extremely weak effect on the proliferation of PBMC ex vivo.

Keywords: GP73; ConA; PBMC proliferation

Introduction

GP73, also known as Golgi phosphoprotein 2 (GOLPH2) or Golgi membrane protein 1 (GOLM1), is a type II Golgi transmembrane glycoprotein (Norton et al., 2008), and preferentially expresses in the epithelial cells of various tissues in human (Kladney et al., 2000). Abnormally increased expression of GP73 correlates with many diseases and viral infections. However, the signal pathways associated with GP73 expression in vivo and the biomedical application of GP73 are not well understood, and the function of GP73 in the immune system has never been elucidated.

In the immune system, GP73 gene is expressed in myeloid, monocytes, dentritic cells, and NK cells (data from BioGPS). It is at low concentration in normal lymphocytes, but is higher in lymphoma cells (data from MOPED). GP73 is associated with immune response, since Iftikhar et al. (2004) found that the hepatocyte GP73 expression was significantly increased in patients with acute and autoimmune hepatitis, and treatment of autoimmune hepatitis is associated with restoring GP73 expression to its normal level. Viral infections [e.g., Adenovirus (Kladney et al., 2002b), Hepatitis B (Wei et al., 2013b) and C virus (Hu et al., 2014)] can upregulate GP73 expression. Serum GP73 concentration and HIV viral load are positively correlated (Wei et al., 2013a), and it is also correlated with cytokines. Kladney et al. (2002a) showed that increased GP73 expression in SK-Hep-1 cells is associated with interferon gamma (IFN-γ) stimulation, which could be inhibited by treating with tumor necrosis factor α. Liang et al. (2012) also found that GP73 is raised in HepG2 cells after treatment with either pro-inflammatory cytokine IL-6 or the IL-6-related cytokine, oncostatin M. Tang et al. found that GOLPH2 and IL-12A expression were negatively correlated in human gastric cancer. Mice with truncated-GP73 protein develop focal segmental glomerulosclerosis (FSGS), which is usually observed in

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Abbreviations: GP73, Golgi protein 73-kD; GOLPH2, Golgi phosphoprotein 2; GOLM1, Golgi membrane protein 1; PBMC, Human peripheral blood mononuclear cells; ConA, Concanavalin A; IFN-γ, interferon gamma; qPCR, quantitative PCR; hsGP73, human secreted GP73; MLR, mixed lymphocyte reaction; HCC, Hepatocellular Carcinoma; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; FSGS, focal segmental glomerulosclerosis; CFSE, 5-(and-6)-carboxyfluorescein diacetate succinimidyl ester; FITC, fluorescein isothiocyanate; NC, Negative control; DAPI, 4,6-diamidino-2-phenylindole

Molecular Medicine

Supplemental Data

H5N1 Virus Hemagglutinin Inhibition of cAMP-Dependent CFTR via TLR4-Mediated Janus Tyrosine Kinase 3 Activation Exacerbates Lung Inflammation

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MATERIALS AND METHODS

Preparation of HA Protein

The recombinant HA protein of H5N1 (A/chicken/Guangdong/191/04; GenBank: AY737289) was generated as previously described (1). An insect-baculovirus expression system was used for the expression of the recombinant HA protein of AIV H5N1 using the method described by Nwe *et al*. with minor modifications (2). The *HA* gene of A/chicken/Guangdong/191/04 (H5N1) (GenBank: AY737289) was subcloned into the pFastbacHT plasmid vector, forming a recombinant pFastBacHT-H5HA. Next, pFastBacHT-H5HA was transposited in combination with a baculovirus shuttle vector (bacmid) into MAX Efficiency DH10Bac competent cells by homologous recombination. Using nickel affinity magnet beads, the recombinant HA of H5N1 was purified from SF9 cells transfected with Bacmid-H5HA and identified by western blotting with an anti-HA (H5N1) antibody.

Animal Models

B6129S4-Jak3^{tm1Lj} (JAK3$^{-/-}$) mice and wild type B6129SF2/J (JAK3$^{+/+}$) mice were purchased from the Jackson Laboratory (Bar Harbor, ME, USA). JAK3$^{+/-}$ mice were generated by crossing JAK3$^{-/-}$ mice with JAK3$^{+/+}$ mice. Then, the genotypes were identified via PCR. All mice housed at a constant temperature (20°C) with a 12-h light/dark photoperiod and allowed food and water *ad libitum*. All procedures were carried out in compliance with the National Institutes of Health–adopted *Guide for Care and Use of Laboratory Animals* (3) and were approved by the Bioethics Committee of State Key Laboratory of Respiratory Disease, Guangzhou Medical University. Mice were randomly divided into 8 groups as indicated in the figure legends (n = 5 in each). After anaesthetised with pentobarbital sodium (50 mg/kg), mice were intratracheally inoculated with HA (1 mg/kg) or HA (0.5 mg/kg) in the presence or absence of pretreatment with JAK3 inhibitor VI (JAK3inh, 0.15mg/kg, Calbiochem, Darmstadt, Germany), forskorlin(FSK,10mg/kg, Sigma-Aldrich, St Louis, MO, USA) and gliebenclamide (Gli,10mg/kg, Sigma-Aldrich) respectively by intraperitoneal injection. The control group received an equal volume of PBS. Lung tissues were harvested at 12 h after HA inoculation.

Measurements of CFTR-Dependent Short-Circuit Current

The tracheas of Jak3$^{+/-}$ and Jak3$^{+/+}$ mice that had or had not received JAK3 inhibitor VI (0.15mg/kg) and TLR4 inhibitor (TLR4inh, candesartan, 100mg/kg, 3B Scientific Corporation, Wuhan, China) respectively by intraperitoneal injection, were removed, fixed on a sample clamp with exposure of apical membranes (exposed surface area of 0.04 cm^2) to HA or saline for ~10–20 min, and then mounted into an Ussing chamber bathed in both sides with Krebs-Henseleit (K-H) at 37°C. The transepithelial PD were clamped at 0 mV, then the short circuit current was recorded with VCC MC6 voltage-current clamp amplifier (VCC MC6, Physiologic Instruments, San Diego, USA), and simultaneously displayed via a signal collection and analysis system (Acquire & Analyze Rev II, San Diego, USA). Forskolin (10 μM apical and basal), an adenylate cyclase activator known to activate CFTR, was used to induce anion secretion via an increase in cAMP. To inhibit electrically conductive Na^+ transport, amiloride (100 μM) was added to the apical solution in all studies.The K-H solution contained (in mM): 117 NaCl, 4.7 KCl, 1.2 KH_2PO_4, 1.2 $MgSO_4$, 24.8 $NaHCO_3$, 2.56 $CaCl_2$ and 11.1 glucose. The solution was bubbled with 95% O_2/5% CO_2 to maintain the pH at 7.4 (4). In the Cl^--free perfusion solution, chloride was substituted by gluconate.

Cell Culture and Treatment

16HBE and calu-3 cells were cultured in Dulbecco's modified Eagle medium supplemented with 10% FCS/FBS (Gibco, NY, USA), 5 mg/ml penicillin and 10 mg/ml streptomycin. Prior to treatment, cells were cultured for 12 h in tissue culture-treated plates, and fresh culture medium was added to the cells

OPEN

High Incidence of EGFR Mutations in Pneumonic-Type Non-Small Cell Lung Cancer

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Abstract: To retrospectively identify computed tomography (CT) features that correlate with epidermal growth factor receptor (EGFR) mutation in surgically resected pneumonic-type lung cancer (P-LC).

A total of 953 consecutive patients with surgically resected lung cancer in the First Affiliated Hospital of Guangzhou Medical University from August 2011 to August 2013 were studied. The CT manifestations were reevaluated independently by 2 radiologists. The presence of pneumonic-type consolidation with pathological confirmed non-small lung cancer (NSCLC) was defined as P-LC. EGFR mutation was determined by direct DNA sequencing or amplification refractory mutation system-PCR. EGFR mutation rates as well as clinical and pathological manifestations between P-LC and control lung cancer patients were compared.

P-LC was diagnosed in 85 patients. Among these patients, 82 were adenocarcinoma (including 78 cases of invasive adenocarcinoma and 4 cases of microinvasive adenocarcinoma), 2 were squamous carcinoma and 1 was other type. P-LC occurred more frequently in female (58.8% vs 37.1%, $P < 0.01$), nonsmoking (76.5% vs 56.5%, $P = 0.001$) and adenocarcinoma (58.8% vs 37.1%, $P < 0.01$) patients. Moreover, EGFR mutations were found in 39 of 52 P-LC patients (75%) and 263 of 542 non-P-LC NSCLC patients (48.5%). However, no difference was found on the mutation sites of EGFR. Histological type, sex, and radiological manifestations (P-LC vs non-P-LC) but not smoking or sequencing method can be served as the independent predictor of EGFR mutations.

P-LC patients showed a significant higher incidence of EGFR mutations, which was independent of sex, histological type, and smoking history. The patients with imaging manifestation of pneumonic-type consolidation are highly suggested to perform EGFR mutation analysis to guide the sequential treatment.

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Abbreviations: AIS = adenocarcinoma in situ, BAC = bronchioloalveolar carcinoma, CI = confidence interval, CT = computed tomography, EGFR = epidermal growth factor receptor, MIA = minimally invasive adenocarcinoma, NSCLC = non-small lung cancer, P-LC = pneumonic-type lung cancer, OR = odds ratio, WHO = World Health Organization.

INTRODUCTION

Lung cancer is the most common fatal malignancy worldwide and approximately 80–90% of cases involve non-small cell lung cancer (NSCLC).[1] NSCLC is divided into several histological subtypes, including squamous cell carcinoma, adenocarcinoma, large cell undifferentiated carcinoma, etc. Smoking is not only associated with the incidence and mortality of lung cancer, but also with the frequency of the different histological types. For example, recently we have seen a decrease in the frequency of squamous cell carcinoma and an increase in the frequency of adenocarcinoma specifically in nonsmoking individuals.[2]

Pneumonic-type lung cancer (P-LC), also known as consolidation-type lung cancer, is defined as nonobstructive diffuse solid infiltrated lung carcinoma on histology and imaging, and is usually misdiagnosed as inflammatory pulmonary consolidation. The pathological manifestation of this specific type of lung cancer, shown by only few studies, was characterized by frequent female occurrence, low correlation with smoking, lepidic growth, and dispersed alveolar consolidation.[3,4] Even still, little is known about the cause and clinical manifestation of P-LC.

Epidermal growth factor receptor (EGFR) is a receptor with tyrosine kinase, and activating mutations in its tyrosine kinase domain promote several oncogene-driven malignancies in NSCLC. Studies have shown that (the) combination (of) chemotherapy with EGFR tyrosine kinase inhibitors could be given to patients as first-line treatment.[5,6] It is, therefore, important to assess the EGFR mutation in the patients with NSCLC. Characteristics of EGFR mutations include frequent female occurrence, nonsmoker inclination, and a higher frequency of mutation in Asians than in Westerners.[7] A recent epidemiology study of EGFR mutations in Asian patients with advanced NSCLC showed that the mutation frequency was 43% in Asian patients, 52% of those being Chinese patients.[8] Most recently, Nakamura et al[9] reported that positive EGFR mutation status may be associated with longer volume doubling time in NSCLC patients. In our study, we found that P-LC patients have significant higher incidence of EGFR mutations, independent of sex, histological type, and smoking history.

PATIENTS AND METHODS

Patients

The clinical data and imaging manifestations obtained from 1214 consecutive patients who underwent lung cancer

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CORRESPONDENCE

HLA class I deficiency as an additional cause of bronchiectasis

To the Editor:

We read with interest the recent paper by Guan *et al.* about the aetiology of bronchiectasis in Guangzhou, southern China.[1] The authors find that idiopathic, post-infectious and immunodeficiency-related causes are the most common origins of this syndrome. The idiopathic form is likewise a predominant aetiology in similar studies performed in other countries, as the authors well present. Bronchiectasis is considered as idiopathic after the exclusion of all known aetiologies.[1] However, although we do not want to criticize this important and considerable work, we nevertheless would like to mention that one possible cause has not been eliminated in this study, namely human leucocyte antigen (HLA) class I deficiency syndrome, which is in most cases the result of a defect either in one of the transporter associated with antigen processing (TAP1 or TAP2) genes or in the β2-microglobulin (β2m) gene.[2,3] In both situations, the expression level of HLA class I molecules at the cell surface is extremely low,[2,3] and at least in TAP deficiency most patients also have, in addition to necrotizing skin ulcers, chronic bacterial infections of the airways, which frequently evolve to bronchiectasis even at a young age.[2] Although predominantly αβ CD8+ T cells are affected in this disease, the patients do not suffer from severe viral infections, which might nevertheless contribute to the overall airway pathology due to a potentially insufficient viral clearance.[2]

Up to now, only 33 cases of TAP deficiency have been confirmed at the molecular level. One could therefore conclude that this disease is extremely rare. However, given the very high number of cases labelled as idiopathic bronchiectasis, it could well be that a substantial fraction of those in fact corresponds to HLA class I deficiencies and would therefore have a clear and precise aetiology.

Therefore, we propose, as already several times before,[4,5] to systematically include the screening for this defect into the biological investigations of bronchiectasis cases. The argument of the authors that cellular immunodeficiencies are complicated and costly[1] would not be so valid in this situation because it is cost-effective and easy to stain whole blood cells from patients with a fluorochrome-conjugated pan anti-HLA class I antibody, and then to analyse the expression level of HLA class I molecules by flow cytometry, in comparison with cells from a healthy control donor. Another alternative is serological HLA typing.

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From the authors:

We thank Zimmer and Ollert for their valuable suggestions of adding a transporter associated with antigen processing (TAP) gene defect test to improve screening procedures of aetiologies of bronchiectasis.

While idiopathic bronchiectasis accounted for the majority of patients in literature reports, TAP or β2-microglobulin (β2m) gene defects have neither been systematically investigated nor mentioned, possibly because of their low prevalence or the small numbers of patients reported thus far (only 33 patients of TAP deficiency have been reported to

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date). Nonetheless, the roles of TAP gene defect have been recognized in children with bronchiectasis.[1] A clearer picture has gradually emerged as to human leucocyte antigen disorders in eliciting recurrent lower respiratory tract infections. However, there remains a significant gap in the understanding of this gene defect in adults with bronchiectasis. This is not surprising because of the following: (i) Children with bronchiectasis have a greater likelihood of immunodeficiency[2] as compared with the aetiological spectra in adult patients. It is likely that adults would have a significantly lower rate of TAP gene defect. (ii) The lack of standardized testing methodology might have rendered the screening of TAP or β2m gene defects less clinically available. For instance, TAP1 alone[1] or in combination with TAP2[3] has been employed in the diagnosis, whereas the definition of TAP defect has not been well defined. (iii) TAP defect has not yet been formally recommended by the British Thoracic Society guidelines.[4] Unlike immunoglobulin deficiency, which could be significantly ameliorated by intravenous immunoglobulin supplementation, the clinical implications for identifying this rare condition remain less clear, presumably due to the absence of effective therapeutic approaches. We acknowledge that the lack of testing for TAP or β2m gene defects might be considered a limitation of our study. However, since we sought to establish a scheme for screening the aetiologies of bronchiectasis in mainland China, we were not in a position to derive a 'once-for-all' protocol for identifying all possible aetiologies associated with bronchiectasis. Screening of gene defects would be challenging at many settings in developing countries such as China. We therefore focused on improving future patient health care by raising physician's awareness of exploring the fundamental aetiologies that might shift the paradigms of management. This is important since post-infectious bronchiectasis might have been more common in vast rural areas. Nonetheless, in future clinical practice, physicians should be vigilant to TAP or β2m gene defects in patients labelled as having 'idiopathic bronchiectasis'. Investigation of these gene defects should be encouraged in medical facilities where experts and instruments (i.e. flow cytometry) are available.

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Hybrid pyrimidine alkynyls inhibit the clinically resistance related Bcr-Abl^{T315I} mutant

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ABSTRACT

A series of pyrimidine alkynyl derivatives were designed and synthesized as new Bcr-Abl inhibitors by hybriding the structural moieties from GNF-7, ponatinib and nilotinib. One of the most potent compounds **4e** strongly suppresses Bcr-Abl^{WT} and Bcr-Abl^{T315I} kinase with IC_{50} values of 5.0 and 9.0 nM, and inhibits the proliferation of K562 and murine Ba/F3 cells ectopically expressing Bcr-Abl^{T315I} cells with IC_{50} values of 2 and 50 nM, respectively. It also displays good pharmacokinetics properties with an oral bioavailability of 35.3% and $T_{1/2}$ value of 48.7 h, and demonstrates significantly suppression on tumor growth in xenografted mice of K562 and Ba/F3 cells expressing Bcr-Abl^{T315I}. These inhibitors may serve as lead compounds for further developing new anticancer drugs overcoming the clinically acquired resistance against current Bcr-Abl inhibitors.

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Chronic myeloid leukemia (CML) is a hematological malignancy representing about 20% of adult leukemia and characterized by the occurrence of the Philadelphia (Ph) chromosome. The first generation Bcr-Abl inhibitor imatinib has shown significant clinical benefit and become the first-line treatment of CML.[1,2] However, many patients eventually develop acquired resistance to imatinib. The 2-year incidence of resistance reaches 80% in the blastic phase, 40–50% in the accelerated phase, and 8–10% in the chronic phase.[3] Point mutation in the kinase domain of Bcr-Abl is the primary mechanism to imatinib resistance, and about 100 point mutations have been identified to date.[4–6] Nilotinib (**1**),[7,8] dasatinib[9,10] and bosutinib[11] have been approved for the treatment of adults in all phases of CML with resistance to the first Bcr-Abl inhibitor drug, whereas bafetinib[12] has also been developed in phase II clinical trials. However, these second-generation inhibitors are not capable of inhibiting all of the resistant mutants, especially the most notable Bcr-Abl^{T315I} gatekeeper mutation accounting for 15–20% in all clinical acquired resistance.[13] Thus, T315I mutation induced resistance remains a serious medical problem.

Structurally, the T315I mutation diminished a key hydrogen bond interaction between the inhibitors and Thr315 residue in the kinase domain of Abl protein. The bulky isoleucine side chain also makes a steric clash to prevent inhibitor binding into the hydrophobic pocket.[14,15] Several third generation inhibitors are capable of inhibiting the Bcr-Abl^{T315I} mutant have been identified.[16,17] Examples include the type I inhibitors PPY-A,[18] SGX-393,[19,20] c-Src/Abl dual inhibitors TG100598 and TG101223,[21,22] and aurora inhibitors MK-0457,[23,24] PHA-739358,[25,26] and AT9283,[27,28] as well as non-ATP competitive or allosteric inhibitors ON012380[29] and DCC2036.[30] However, these molecules have to be formulated for intravenous administration, and clinical development for MK-0457 has been discontinued due to cardiac toxicity.[24,31]

Recently, the 'third-generation' type II Bcr-Abl inhibitors GZD824,[32] GNF-7 (**2**),[33] AP24534 (**3**)[34,35] and 5-(arenethynyl)hetero-monocyclic derivatives[36] were reported to strongly inhibit Bcr-Abl^{T315I} and other mutants. AP24534 (ponatinib, Iclusig®) has been approved for the treatment of resistant or intolerant CML and Ph$^+$ ALL patients against imatinib, especially those harboring Bcr-Abl (T315I) mutation.[35,37] However, US FDA soon temporarily suspended the marketing of this drug due to the increasing numbers of blood clots observed in ponatinib-treated patients.[37] The drug was later reauthorized for sale after a revised indication statement and a boxed warning were made by the manufacture. As acquired resistance increasingly observed in the clinic, the newly

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Hypoxia inducible factor-1-dependent up-regulation of BMP4 mediates hypoxia-induced increase of TRPC expression in PASMCs

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Aims Previously we demonstrated that both hypoxia inducible factor-1 (HIF-1) and bone morphogenetic protein-4 (BMP4) up-regulate transient receptor potential canonical (TRPC) 1 and TRPC6, resulting in increased basal intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in pulmonary arterial smooth muscle cells (PASMCs), driving development of chronic hypoxia (CH)-induced pulmonary hypertension (CHPH). This study aims to determine whether HIF-1 regulates BMP4, and whether BMP4 mediates TRPC and basal $[Ca^{2+}]_i$ increases in hypoxic PASMCs.

Methods and results The level of BMP4 mature protein was increased for ~183% in distal pulmonary arterial smooth muscle (PA) from CH (10% O_2 for 21 days; CH) exposed rats, and 143% in PASMCs cultured under prolonged hypoxia (4% O_2 for 60 h). In rat PASMCs, HIF-1α overexpression up-regulated, whereas HIF-1α knockdown under hypoxia decreased BMP4 expression; site-mutation identified two functional HIF-1-binding sites in *Bmp4* gene promoter; noggin or BMP4 siRNA treatment blocked hypoxia-induced increases of TRPC1 and TRPC6 expression and basal $[Ca^{2+}]_i$. Likewise, in mice, exposure to CH increased BMP4 expression in distal PA for ~80%, which was absent in HIF-1α heterozygous mutant mice. Comparing with wild-type littermates, *BMP4* heterozygous mutant mice exposed to CH displayed lower BMP4 and TRPC levels in PA, decreased basal $[Ca^{2+}]_i$ in PASMCs, and attenuated CHPH. In human PASMCs, HIF-1α knockdown attenuated hypoxia-induced BMP4 expression and knockdown of either HIF-1α or BMP4 abolished hypoxia-induced TRPC expression and basal $[Ca^{2+}]_i$.

Conclusions BMP4 acts downstream of HIF-1 and mediates hypoxia-induced up-regulation of TRPC, leading to increased basal $[Ca^{2+}]_i$ in PASMCs, promoting CHPH pathogenesis.

Keywords HIF-1 • BMP4 • TRPC • Basal $[Ca^{2+}]_i$ • PASMCs

1. Introduction

Pulmonary hypertension (PH) is a group of progressive diseases characterized by increased pulmonary arterial pressure and pulmonary vascular remodelling, leading to right heart failure and death in the absence of suitable therapy. PH is frequently a complication of chronic obstructive pulmonary disease (COPD), in which global alveolar hypoxia is an important trigger for hypoxic pulmonary vasoconstriction, endothelial dysfunction, and medial wall smooth muscle hypertrophy in the pulmonary vasculature, contributing to development of PH.[1–3] Experimental animals with chronic hypoxia (CH)-induced PH (CHPH) manifest pulmonary vascular changes similar to those in PH patients associated with COPD, particularly with chronic bronchitis.[4–6]

Increased intracellular calcium concentration ($[Ca^{2+}]_i$) is a critical signal facilitating both contraction and growth of pulmonary arterial smooth muscle cells (PASMCs).[7,8] Elevation of $[Ca^{2+}]_i$ may occur via

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Article

Identification and Application of Neutralizing Epitopes of Human Adenovirus Type 55 Hexon Protein

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Abstract: Human adenovirus type 55 (HAdV55) is a newly identified re-emergent acute respiratory disease (ARD) pathogen with a proposed recombination of hexon gene between HAdV11 and HAdV14 strains. The identification of the neutralizing epitopes is important for the surveillance and vaccine development against HAdV55 infection. In this study, four type-specific epitope peptides of HAdV55 hexon protein, A55R1 (residues 138 to 152), A55R2 (residues 179 to 187), A55R4 (residues 247 to 259) and A55R7 (residues 429 to 443), were predicted by multiple sequence alignment and homology modeling methods, and then confirmed with synthetic peptides by enzyme-linked immunosorbent assay (ELISA) and neutralization tests (NT). Finally, the A55R2 was incorporated into human adenoviruses 3 (HAdV3) and a chimeric adenovirus rAd3A55R2 was successfully obtained. The chimeric rAd3A55R2 could induce neutralizing antibodies against both HAdV3 and HAdV55. This current study will contribute to the development of novel adenovirus vaccine candidate and adenovirus structural analysis.

Keywords: adenovirus type 55; neutralizing epitope; bivalent vaccine

1. Introduction

Human adenovirus (HAdV) has been recognized as a common cause of acute respiratory disease (ARD) [1–3]. To date, there are at least 69 HAdV genotypes reported [4], which are classified within seven species using a new paradigm based on genomics [5]. Among these, HAdV55 is a newly identified re-emergent acute respiratory disease (ARD) pathogen causing outbreaks in Singapore in 2005 and in Shanxi Province of China in 2006. After this first reported HAdVB55-associated ARD outbreak in China, this pathogen apparently re-emerged among military and civilian populations in many provinces of China [6–10]. HAdV55 infection causes both mild and severe diseases, presenting clinical signs and symptoms including high fever, cough, myalgia, sore throat, bronchitis and pneumonia, and even life-threatening [6–13]. Furthermore, HAdV55 has the potential to spread widely and cause severe epidemics in view of the lack of herd immunity and its higher tendency in causing severe ARD than other adenoviruses [7]. This status highlights the need for vaccine development against HAdV55 infection. HAdV55 was first identified as HAdV-B11a from an

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Electronic Supplementary Information

Identification of Camphor Derivatives as Novel M2 Ion Channel Inhibitors of Influenza A Virus

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呼吸疾病国家重点实验室

Biological experiments

Patch Clamp Assay.

The inhibitors were tested via patch clamp assay using A/M2 expressed 293Trex cells and membrane currents were recorded as in a previous report (Hu et al., 2010).

Plaque Reduction Assay.

A monolayer of MDCK cells were infected with 0.01 MOI influenza A viruses for 1 h at 37 °C. The inoculums were then removed, and the cells were washed twice with phosphate-buffered saline (PBS). The cells were then overlaid with 1% agar DMEM-containing amantadine or one of the synthesized compounds in the presence of 2 μg/mL trypsin and 0.3% BSA. Two to three days after infection, the monolayers were fixed and stained with 0.1% crystal violet solution.

Viral Inhibition Assay.

MDCK cells were grown to confluence in 96-well microtiter plates, the medium was removed, and the cells were covered with 50 μL of medium containing various amounts of amantadine or one of the synthesized compounds in the presence of 1

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Case Report

IgG4-related lung disease manifested as pneumonia in puerperium: a case report

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Abstract: IgG4-related lung disease (IgG4-RLD) is recently emerging entity. Several reports concerned with the clinicopathologic feature have been described, but this disease in puerperium has not been reported previously. Here, we report a 24-year-old woman diagnosed as IgG4-RLD in puerperium, who developed dry cough, low fever and exertional dyspnea following the delivery. The inflammatory markers and pulmonary lesions of the patient suggested pneumonia. However, there was no improvement after antibiotic treatment. The infiltration of IgG4-positive lymphoplasmacytes was found in lung biopsy by video-assisted thoracic surgery (VATS). And the serum IgG4 level was high. The patient was effectively treated with corticosteroids. This unique case highlights the occurrence of IgG4-RLD in puerperium and underscores it should be taken into consideration as a possible differential diagnosis when dense lymphoplasmacytic infiltration was found in pulmonary consolidation in complex puerperal respiratory cases.

Keywords: IgG4-related lung disease, pulmonary nodule, lymphoplasmacyte, puerperium

Introduction

IgG4-related lung disease (IgG4-RLD), a condition characterized by IgG4-positive lymphoplasmacytic cells infiltration in lung and elevated serum IgG4 concentration in most patients, is a recently emerging entity [1]. Reports indicated IgG4-RLD has multiple forms of lung lesions, which is more than previously thought [2-9], but the full spectrum of clinicopathologic feature has not been well described, it appears to be rather nonspecific, so, it is easy to be misdiagnosed as pneumonia with pulmonary consolidations. In addition, the disease always occurs in adults, male predominance [3]. To date, no description of IgG4-RLD in puerperium has been published to our knowledge. Herein, we describe a case of IgG4-RLD in puerperium, who manifested inflammatory conditions and was misdiagnosed to pneumonia.

Case report

A 24-year-old woman was administrated for management of delivery at 38 weeks of gestation at six weeks ago (gravida 1, para 1), who gave birth by spontaneous delivery and had uneventful antenatal follow-up period. The female newborn had a birth of 3,203 grams and Apgar scores of 8. No obvious deficits were noted during delivery. Three weeks following the delivery, she was admitted to our hospital because of dry cough, coexisting with fever and exertional dyspnea. She had a history of allergic rhinitis. Her body temperature was 38 degree centigrade, and there were no any signs in chest physical examination. Laboratory findings showed erythrocyte sedimentation rate (ESR) was 105 mm/1 H (normal range, 0-20 mm/1 H) and C reaction protein (CRP) was 28.74 mg/L (normal range, ≤10 mg/L). The total count and classification of white blood cells were 11.47×10^9/L (normal range, 4.0-10.0×10^9/L) and 70.1%. Serum IgG (1860 mg/dl, normal range, 700-1600 mg/dl) and IgM (290 mg/dl, normal range, 50-270 mg/dl) were mildly increased. Other laboratory tests including IgA, IgE, interleukin-6 (IL-6), carcino-embryonic antigen (CEA), carbohydrate antigen-125 (CA-125), CA-153, CA-199, Antinuclear antibodies (ANA), rheumatoid factors (RF), anti-neutrophil cytoplasmic antibody (ANCA) were normal.

国家重点实验室

IL-13 receptor α2 is a negative prognostic factor in human lung cancer and stimulates lung cancer growth in mice

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Keywords: *lung cancer, IL13Rα2, TAZ, PI3K*

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ABSTRACT

IL-13 receptor subunit alpha-2 (IL13Rα2) is associated with poor prognosis in some cancers. However, the role of IL13Rα2 in lung cancer remains unknown. We showed that IL13Rα2 overexpression was associated with late stages of disease progression and shorter disease-free survival (DFS) as well as overall survival (OS) in resected lung cancer patients. IL13Rα2 promoted the migration, invasion and anoikis resistance of lung cancer cells *in vitro*. Silencing of IL13Rα2 in lung cancer cells decreased invasion *in vitro* and lung metastasis *in vivo*. IL13Rα2 activated phosphatidylinositol 3 kinase (PI3K), Akt, and transcriptional coactivator with PDZ-binding motif (TAZ). Inhibition of PI3K attenuated activation of TAZ and its downstream target genes by IL13Rα2. We suggest that inhibition of IL13Rα2 is a potential therapeutic approach in lung cancer.

INTRODUCTION

Chemokine-mediated inflammation participates in tumor growth, invasion, and metastasis [1]. The presence of proinflammatory molecules as interleukins (ILs) are typical features of cancer-related inflammation [2]. IL-13 is a proinflammatory, Th2-derived cytokine which is associated to different pathological conditions, such as asthma, autoimmune diseases, and ulcerative colitis [3]. IL-13 binds to two receptor subunits, IL-13 receptor subunit alpha-1 (IL13Rα1) and IL-13 receptor subunit alpha-2 (IL13Rα2). IL13Rα2 has been shown to be highly expressed in many tumor types, such as colon, glioblastoma, ovarian, head and neck, kidney, and mesothelioma, but not by most normal cells such as immune cells or endothelial cells [4–9]. IL13Rα2 is also associated with poor prognosis in human cancers and a target for cancer therapy [10–11]. IL-13 binding to IL13Rα2 increased tumor migration and invasion. Silencing of IL13Rα2 prolonged mice survival in mouse glioblastoma xenograft models [12]. IL13Rα2 participated in signal transduction, triggering the activation of several signaling proteins, such as MAPK and TGF-β1 [13–14]. However, little was known about the role of IL13Rα2 during lung cancer progression.

Toxins such as IL13-PE38QQR (the recombinant cytotoxin composed of IL-13 and a truncated form of pseudomonas aeruginosa exotoxin) have been designed to inhibit the IL-13 receptor. The phase III trial (PRECISE study) showed that IL13-PE38QQR mediated similar effects to Gliadel Wafer, a FDA approved drug. The trial failed to achieve its objective of superiority over Gliadel Wafer due to non-selective patients based on IL-13 receptor expression, catheter positioning, and poor drug distribution. The clinical toxicity of IL13-PE38QQR was likely because of non-selective binding of the toxin to

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Impact of short term forced oral breathing induced by nasal occlusion on respiratory function in mice

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ABSTRACT

Inconsistent findings regarding the experimental nasal obstruction on respiratory functions in small animals have been reported. The purpose of this study was to investigate the impact of short term forced oral breathing on respiratory functions as well as the therapeutic implication of esophageal intubation in BALB/c mice. Thirty BALB/c mice were randomized equally to two groups: an experimental group and control group. Oral breathing was induced by applying petrolatum ointment in nostrils for occlusion both nasal cavities. Esophageal tube was inserted to enlarge the oropharyngeal airway in the experimental mice. Respiratory parameters were measured by barometric whole-body plethysmography (WBP) in the following condition: normal nasal breathing; nasal breathing loading in a soft bag; forced oral breathing loading in a soft bag; forced oral breathing loading in a soft bag after undergoing esophageal intubation. After applying petrolatum ointment of nostrils, all the mice switch to oral breathing with apparent discomfort (bradypnea). Nasal occlusion was associated with a decrease in the average respiratory rate (268 ± 36 vs. 90 ± 10 breaths/min; $P < 0.01$) and an increase in Penh (0.67 ± 0.14 vs. 19.23 ± 2.12; $P < 0.01$). After undergoing esophagus intubation, these mice switched to oral breathing with less discomfort. Compared with the control mice, respiratory rate (175 ± 25 vs. 90 ± 10) was higher; the Penh (8.84 ± 1.05 vs. 18.09 ± 2.03; $P < 0.01$) was lower. Short term forced oral breathing induced by nasal occlusion caused respiratory insufficiency in mice. Stenotic oropharyngeal airway was supposed to be one of the most important factors. Enlarging oropharyngeal airway by esophagus intubation could improve the respiratory insufficiency under nasal occlusion.

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1. Introduction

Allergic rhinitis (AR) is the most prevalent allergy disease in the world (Asher et al., 2006). The most common clinical manifestations of AR are nasal obstruction, rhinorrhea, sneezing and nasal pruritus. Impaired nasal breathing results in forced oral breathing, one of the most frequent complaint from patients with AR (Bekes et al., 2011; Patou et al., 2006). Nasal obstruction is also commonly observed in many other pathological conditions, such as rhinosinusitis, adenoid hypertrophy and nasal polyps. Forced oral breathing inhales gas by-pass the nasal mucosa and increased levels of inhaled aeroallergens may reach the lower airways (Rimmer and Ruhno, 2006). Transition from nasal to oral breathing is easily accomplished in awake adults. This is not the case however with infants, in whom the close approximation of the soft palate, tongue and epiglottis makes oral breathing difficult (Bergeson and Shaw, 2001; Harding, 1986; Polgar and Kong, 1965; Shaw, 1968; Stocks and Godfrey, 1978; Swift and Emery, 1973; Trabalon and Schaal, 2012). Consequently, in children, forced oral breathing, whether or not caused by nasal obstruction, can be associated with both social and physical stress (Fensterseifer et al., 2013; Hitos et al., 2013; Jefferson, 2010).

Mouse allergic airway models have been extensively employed. A previous study conducted in the authors' laboratory showed that airway resistance (RNA) increased in the allergic rhinitis (AR) mouse model, however the phenomenon of transition from nasal to oral breathing after nasal challenge appeared to be rare (Xie et al., 2010). These results consequently posed the question of whether or not it is inherently difficult for mice to breath through the mouth. Several studies have investigated the impact of early nasal obstruction in mice. Niaki et al. (2008) found that mice with nasal occlusion that were switched to oral breathing suffered from apparent bradypnea, higher PCO_2 levels, and decreased arterial

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RESEARCH ARTICLE

Impacts of Co-Existing Chronic Rhinosinusitis on Disease Severity and Risks of Exacerbations in Chinese Adults with Bronchiectasis

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呼吸疾病国家重点实验室

Abstract

Background

Mounting evidence supports the notion of "one airway, one disease."

Objective

To determine whether chronic rhinosinusitis (CRS) poses adverse impacts on Chinese adults with bronchiectasis.

Methods

We enrolled 148 consecutive adults with clinically stable bronchiectasis. CRS diagnosed based on the 2012 EP^{3}OS criteria. We systematically evaluated the bronchiectasis etiology, radiology, lung function, sputum bacteriology, airway inflammatory biomarkers, *Bronchiectasis Severity Index*, cough sensitivity and healthcare resource utilization. All patients were prospectively followed-up for 1 year to examine the frequency of bronchiectasis exacerbations (BEs).

Results

Forty-seven patients (31.8%) were diagnosed as having CRS. Bronchiectasis etiologies did not vary statistically between CRS and no-CRS group. There was a trend towards non-statistically higher *Bronchiectasis Severity Index* [6.4±3.4 vs. 5.0(6.0), P = 0.19], a higher proportion of patients with BEs needing hospitalization before enrollment (48.9% vs. 29.7%, P = 0.13), poorer FVC [78.2±19.8% vs. 82.2(16.8)%, P = 0.54] and FEV_1 [68.2±24.8% vs. 74.8(21.2)%, P = 0.29], a higher prevalence of *Pseudomonas aeruginosa* isolated (36.2% vs. 26.7%, P = 0.27) or colonized in sputum (36.2% vs. 21.8%, P = 0.12) and greater

Original Article

Indoor Allergen Levels and Household Distributions in Nine Cities Across China

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Abstract

Objective Chinese allergic subjects have high levels of sensitization to house dust mite (HDM) and other indoor allergens. This study quantifies common indoor allergen levels in Chinese households.

Methods Dust samples were collected from nine cities. Major allergens Der p 1 and Der f 1 from *Dermatophagoides pteronyssinus and D. farinae*, and specific antigens of *Blomia tropicalis*, *Tyrophagus putrescentiae, Acarus siro*, and cockroach species *Blattella germanica* and *Periplaneta americana* were measured by ELISA.

Results HDM allergens were found in dust samples from bedding in 95% of the Chinese households. The median levels varied from <0.006 to 9.2 μg/g of dust, depending on the city. The percentages of households having HDM allergen levels associated with the risk of developing allergy sensitization and asthma were 65% and 25%, respectively. Specific antigens of the storage mite and cockroach were only found in samples from the southern and tropical regions of China. Levels of mite allergens were generally higher in samples from bedding compared to samples from the living room, even for storage mites, whereas levels of cockroach antigens were higher in the living room samples.

Conclusion HDM allergens are present in bedding dust samples from most Chinese households. Cities in southern and central China have relatively high levels of HDM major allergens compared to cities in northern and western China. Antigens of storage mites and cockroaches are not as common as HDM allergens.

Key words: *Dermatophagoides pteronyssinus*; *D. farinae*; House dust mite; Indoor allergen; Storage mite

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Biographical note of the first author: ZHENG Yi Wu, male, born in 1973, PhD, majoring in immunotherapy and immunology.

Inflammatory Responses, Spirometry, and Quality of Life in Subjects With Bronchiectasis Exacerbations

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BACKGROUND: Bronchiectasis exacerbations are critical events characterized by worsened symptoms and signs (ie, cough frequency, sputum volume, malaise). Objectives: Our goal was to examine variations in airway and systemic inflammation, spirometry, and quality of life during steady state, bronchiectasis exacerbations, and convalescence (1 week following a 2-week antibiotic treatment) to determine whether potentially pathogenic microorganisms, including *Pseudomonas aeruginosa*, were associated with poorer conditions during bronchiectasis exacerbations. METHODS: Peripheral blood and sputum were sampled to detect inflammatory mediators and bacterial densities. Spirometry and quality of life (St George Respiratory Questionnaire [SGRQ]) were assessed during the 3 stages. RESULTS: Forty-eight subjects with bronchiectasis (43.2 ± 14.2 y of age) were analyzed. No notable differences in species and density of potentially pathogenic microorganisms were found during bronchiectasis exacerbations. Except for CXCL8 and tumor necrosis factor alpha (TNF-α), serum inflammation was heightened during bronchiectasis exacerbations and recovered during convalescence. Even though sputum TNF-α was markedly higher during bronchiectasis exacerbations and remained heightened during convalescence, the variations in miscellaneous sputum markers were unremarkable. Bronchiectasis exacerbations were associated with notably higher SGRQ symptom and total scores, which recovered during convalescence. FVC, FEV_1, and maximum mid-expiratory flow worsened during bronchiectasis exacerbations (median change from baseline of −2.2%, −0.8%, and −1.3%) and recovered during convalescence (median change from baseline of 0.6%, 0.7%, and −0.7%). Compared with no bacterial isolation, potentially pathogenic microorganism or *P. aeruginosa* isolation at baseline did not result in poorer clinical condition during bronchiectasis exacerbations. CONCLUSIONS: Bronchiectasis exacerbations are characterized by heightened inflammatory responses and poorer quality of life and spirometry, but not by increased bacterial density, which applies for subjects with and without potentially pathogenic microorganism isolation when clinically stable. (ClinicalTrials.gov registration NCT01761214.) *Key words: bronchiectasis; exacerbation; potentially pathogenic microorganism; inflammation; spirometry; quality of life.*
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Introduction

Bronchiectasis is a chronic respiratory disease characterized by repetitive exacerbations[1,2] associated with significantly worsened clinical symptoms[3] that impact daily life. They are common according to previous stud-

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Supplementary material related to this paper is available at http://www.rcjournal.com.

Drs Guan and Gao are co-first authors.

Initial empirical treatment based on clinical feature of chronic cough

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Abstract

Background: An empirical therapy based on the clinical characteristics of cough had not been reported. We evaluated this strategy of empirical therapy on chronic cough.

Methods: Patients with chronic cough were initially diagnosed with corticosteroid-responsive cough (CRC), postnasal drip syndrome (PNDS) and gastroesophageal reflux-related cough (GERC) based on their medical history and clinical presentation, and received a sequential three-step empirical therapy. A successful response was required for final diagnosis.

Results: A total of 96 patients were recruited with a median duration of cough for 4 months (range, 2–100). The primary diagnosis based on history and clinical presentation was CRC in 53 patients (55.2%), PNDS in 36 (37.5%) and GERC in 7 (7.3%). Cough improved in 60 patients (62.5%) at the first step with mean time of 6.2 ± 3.3 days. Three-step empirical therapy was beneficial in 78 of 96 (81.2%) patients at last. The final spectrum and frequency of causes of cough based on therapeutic response were as follows: CRC (46.7%), PNDS (27.5%) and GERC (10.8%). Eighteen cases (18.8%) were not responsive to empirical treatment, seven of whom were identified as other causes by diagnostic tests.

Conclusions: The empirical therapy aimed at primary diagnosis on the basis of history and clinical characteristics is a more targeted approach, and leads to improvement of chronic cough more quickly in most patients. CRC is the most common cause of chronic cough.

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Key words
chronic cough – corticosteroid – diagnosis – empirical treatment

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Authorship and contributorship
Each of the authors was involved in the conception of the research and hypotheses, the design of the study, acquisition of the data, the analysis and interpretation of such information, and in writing and revising the manuscript.

Ethics
The study was approved by the Ethics Committee of Shenzhen Second People's Hospital, and all patients gave informed written consent.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Background

Chronic cough is a common symptom in respiratory clinic. The key to successful management is to establish a diagnosis and to treat the cause of cough. An anatomic diagnostic protocol, first proposed by Irwin (1) in 1981, is widely used in the clinical practice, and it has been shown to be effective in diagnosing the causes of chronic cough and leading to effective specific therapy. Nonetheless, accurate diagnosis of cough in

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ORIGINAL ARTICLE

THORACIC

Initial experience of thoracoscopic lobectomy with partial removal of the superior vena cava for lung cancers

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Abstract

OBJECTIVES: The objectives of this study were to report the surgical techniques and clinical outcome of thoracoscopic lobectomy with partial removal of the superior vena cava for lung carcinomas.

METHODS: Between January 2010 and November 2013, 1132 patients with lung cancer underwent radical surgery by thoracoscopy; 5 (0.4%) underwent thoracoscopic lobectomy with partial removal of the superior vena cava. Perioperative variables and postoperative outcomes of these cases were analysed to evaluate the technical feasibility and safety of this operation.

RESULTS: For all cases, a right upper lobectomy was performed. The average time of surgery was 260 min (range, 170–380, 260 ± 90 min). The intraoperative blood loss averaged 160 ml (range, 50–300, 160 ± 90 ml). The median postoperative hospital stay was 11 days (interquartile range, 7–15 days). Postoperatively, tracheal extubation was achieved in the recovery room without further need for mechanical ventilation. In 1 case, the patient experienced postoperative superior vena cava thrombosis; he recovered after administration of anticoagulation drugs. None of the patients developed active blood leakage postoperatively. Perioperative mortality was not observed.

CONCLUSION: Thoracoscopic lobectomy with partial removal of the superior vena cava can be considered a feasible and safe operation for selected patients with lung cancer.

Keywords: Video-assisted thoracic surgery (VATS) • Non-small-cell lung cancer • Lung surgery • Superior vena cava

呼吸疾病国家重点实验室

INTRODUCTION

Lung cancer is one of the leading causes of death worldwide. Surgery is still the first choice for selected patients with the most common type: non-small-cell lung cancer (NSCLC) [1]. NSCLC with invasion of the superior vena cava (SVC) is locally advanced lung cancer, and is generally considered a contraindication for surgery. However, several reports showed encouraging surgical results in select cases [2–4]. Generally, open thoracotomy was the surgery of choice in these cases.

Advances in the field of minimally invasive surgery have radically transformed thoracic surgical practice. In 1992, Lewis *et al*. demonstrated the technical feasibility of thoracoscopic lobectomy; however, whether thoracoscopy was a suitable approach for lung cancer surgery was still controversial [5]. McKenna *et al*. widely applied the combination of thoracoscopic lobectomy and lymph node dissection to surgical treatment of lung cancer, and demonstrated its efficacy and safety by achieving complete removal of the tumour [6].

Despite the reported advantages of thoracoscopic techniques (e.g. smaller incision, shorter hospital stay, reduced postoperative pain and bleeding, and less damage to lung function) [7–9], there was still a question as to whether video-assisted thoracoscopic surgery (VATS) was also feasible in NSCLC patients with invasion of the SVC. In the reported articles, VATS is most commonly used for peripheral lesions [10, 11]. For more complicated cases, such as lobectomy with bronchoplasty and/or removal of the pulmonary artery, the thoracoscopic approach has only been reported in a limited number of studies [12–15]. To the best of our knowledge, there are no previous reports of VATS for cases of NSCLC with invasion of the SVC.

From January 2010 to November 2013, we conducted VATS lobectomy with partial removal of the SVC for 5 patients with NSCLC. The objectives of this study were to report the surgical techniques and clinical outcome.

MATERIALS AND METHODS

Between January 2010 and November 2013, 1132 patients with lung cancer underwent radical surgery by thoracoscopy; 5 (0.4%) underwent thoracoscopic lobectomy with partial removal of the SVC. The surgical procedures were routinely recorded, and the analysis of the surgical data was based on the reviewing of these video clips.

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Commentary

Innovations in bronchoscopic techniques will go a long way for diagnosis of early-stage lung cancers

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呼吸疾病国家重点实验室

Introduction

Lung cancer is one of the most common malignancies and a leading cause of cancer-related death worldwide (1). In China, the morbidity and mortality rates of lung cancer have been increasing over the past decades along with the worsening environment (2) and concerning situation of tobacco use (3). Imaging studies and sputum cytology as the conventional diagnostic approaches for lung cancer, are in fact very limited for detecting the early-stage lesions, and therefore do not help reduce the death toll. A number of clinical practice guidelines have recommended bronchoscopy as an important common tool for diagnosis of primary lung cancers (PLCs) (4). The direct vision of bronchoscopy enables brush and puncture biopsies, and performing bronchoalveolar lavage for cytological and histological diagnosis, which contributes to significant improvement in detection rate, and ultimately, to early identification, early diagnosis and early treatment of lung cancers. With the advance and refinement in molecular biology, endoscopic and imaging techniques, current practice with bronchoscopic examination has been recognized to remarkably enhance clinical diagnosis of lung cancer, and have an extraordinary role in improving the prognosis and survival rate of patients. This article reviews the use of several diagnostic modalities related to bronchoscopic techniques in individuals with high risk for lung cancers.

Endobronchial ultrasound (EBUS)

EBUS is a relatively new technique and procedure that uses ultrasound probe along with bronchoscope to visualize the inner surface of airway and adjacent architecture in real time. Unlike the conventional bronchoscopy that can only determine with low diagnostic yield the changes inside the airway but not in bronchial walls or adjacent tissues, the high-resolution (≤4 cm) EBUS presentation improves the blurred imaging of tracheobronchial wall, the surrounding structures, and the mediastinum. Currently, recommended indications for EBUS include: hilar and mediastinal masses or lymphadenectasis to be diagnosed or lung cancer for staging; external compression to the airway; airway submucosal lesions; intratracheal lesions; peripheral pulmonary nodule or mass. Coupled with transbronchial needle aspiration (TBNA), EBUS-TBNA demonstrates high sensitivity, specificity, and accuracy in many studies (5-10), and has been widely used for diagnosis and staging of lung cancer. However, EBUS-TBNA is more complicated, less well-tolerated by patients under local anesthesia, and more costly than conventional TBNA (11). Since the manipulation of the EBUS vision can be difficult, a successful and safe EBUS-TBNA usually requires longer curve of learning and skillful expertise. Innovative efforts have been attempted to develop more efficient devices. In a study, Xiang *et al.* tested a new Fuji EBUS scope, which has a 10 degrees forward oblique view and smaller external diameter, eliminating the need of a second scope and making the TBNA with or without EBUS simpler to do and easier to learn (12). Although not recommended as routine screening methods, EBUS-TBNA is helpful to accurate pathological diagnosis of N1 and N2 PLCs in a safe manner, which is encouraged to be used in well-equipped

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Lariciresinol-4-O-β-D-glucopyranoside from the root of *Isatis indigotica* inhibits influenza A virus-induced pro-inflammatory response

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ABSTRACT

Ethnopharmacological relevance: *Isatis indigotica* is a traditional Chinese medicine. Its dried roots named "ban lan gen" in Chinese, are used for clinical treatment of virus infection, tumor, inflammation with a long history. However, its anti-influenza active ingredient and the underlying mechanism remain unclear. In this study, the anti-influenza and anti-inflammatory effects of a lignan glycoside: lariciresinol-4-O-β-D-glucopyranoside isolated from the root of *I. indigotica* on human alveolar epithelial cell line A549 infected with influenza A virus were investigated.

Materials and methods: Chemical and spectroscopic methods were employed to identify the structure of the lignan glycoside. Cytotoxicity of the lignan glycoside was analyzed using methylthiazolyltetrazolium (MTT) assay. The inhibitory activity against influenza virus of the lignan was determined by CPE inhibition assay. HEK-293 cells stably co-transfected with NF-κB responsive firefly luciferase and constitutively expressing GFP were employed for monitoring the effect of the lignan on NF-κB signal pathway activation. Nuclear export of viral ribonucleoprotein (RNP) complexes was monitored by indirect immunofluorescence. Quantitative real-time PCR was used to quantify the expression profiling of cytokines and chemokines after infection with influenza virus.

Results: We showed that the lignan glycoside treatment was effective against the influenza A virus-induced cytopathic effect (CPE) in MDCK cells. Further study demonstrated the lignan glycoside attenuated virus-induced NF-κB activation, but did not affect export of viral ribonucleoprotein (RNP) complexes from the nucleus in late stages of infection. We revealed that the lignan glycoside suppressed influenza A virus (H1N1)-induced expression of the pro-inflammatory molecules IL-6, TNF-α, IL-8, MCP-1, IP-10 and IFN-α. Moreover, the cytokines and chemokines profiles induced by H9N2 virus resembled those of influenza virus H1N1, but the lignan glycoside reduced the expression of IP-10 and TNF-α.

Conclusions: Our results suggest that the lignan glycoside is a bioactive component of *I. indigotica* which may contribute an adjunct to pharmacotherapy for influenza virus infection.

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1. Introduction

Influenza viruses are a highly contagious pathogen of both human and animal that cause seasonal epidemics and reoccurring pandemic. Annually, influenza viruses generally cause approximately 10% of the world's population infection and can be associated with 250,000 deaths (McCaughey, 2010). The recent emergence of highly pathogenic avian-origin reassortant influenza A virus subtype H7N9 has transmitted from poultry to humans, with 258 confirmed cases and mortality rate of around 38% in just a few months in China (Gao, 2014). Moreover, due to antigenic shift and

Abbreviations: IL-6, interleukin-6; IL-8, interleukin-8; MCP-1, monocytes chemotactic factor; IP-10, interferon gamma-induced protein 10; IFN-α, interferon alpha; NF-κB, Nuclear factor-κB; TNF-α, tumor necrosis factor alpha; RNP, ribonucleoprotein; MTT, methylthiazolyltetrazolium; HEK-293, human embryonic kidney 293 cells; GFP, green fluorescent protein

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Leukotriene D_4 inhalation challenge for predicting short-term efficacy of montelukast: a pilot study

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Abstract

Introduction: The convenient measure to predict efficacy of leukotriene receptor antagonist is lacking.

Objectives: To determine if leukotriene D_4 inhalation challenge predicts short-term efficacy of montelukast in asthma.

Methods: In this open-labelled 28-day trial, 45 patients with asthma were allocated to leukotriene-sensitive and leukotriene-insensitive group to receive montelukast monotherapy (10 mg, once daily) based on the positive threshold of leukotriene D_4 inhalation challenge test (4.800 nmol). Miscellaneous measurements comprised fractional exhaled nitric oxide, methacholine inhalation challenge, Asthma Control Test and Asthma Quality of Life Questionnaire. Peak expiratory flow was self-monitored throughout the treatment. End point assessments were performed 3 to 5 days after montelukast withdrawal. (Registration: http://www.clinicaltrials.gov/ct2/show/NCT01414868?term=NCT01414868&rank=1)

Results: Twenty-three patients in leukotriene-sensitive group and 10 leukotriene-insensitive group completed the study. Both groups differed neither in 28-day peak expiratory flow rate nor in maximal weekly peak expiratory flow (both $P > 0.05$). However, minimal weekly peak expiratory flow was significantly higher in leukotriene-insensitive group throughout the treatment course (all $P < 0.05$) except for week 1 ($P > 0.05$). Both groups did not differ statistically in the post-treatment improvement in forced expiratory volume in 1 s (FEV_1) predicted% prior to inhalation challenge, fractional exhaled nitric oxide or the airway responsiveness to leukotriene D_4 or methacholine (all $P > 0.05$). There was a marked increase in Asthma Control Test score and the symptom score of Asthma Quality of Life Questionnaire in both groups (both $P < 0.05$). The overall significance of Logistic regression model was unremarkable ($P = 0.467$).

Conclusion: Responsiveness to inhaled leukotriene D_4 alone might not be sufficient to predict the short-term efficacy of montelukast monotherapy in patients with asthma.

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Key words
asthma – bronchial provocation test – leukotriene D_4 – leukotriene-sensitive – montelukast

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Ethics
Ethic Committee of First Affiliated Hospital of Guangzhou Medical University.

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Leukotriene D_4 inhalation challenge for predicting short-term efficacy of montelukast: a pilot study

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Ethics
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Original Article

Leydig cell tumor with lung metastasis diagnosed by lung biopsy

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Abstract: Leydig cell tumors are very rare and account for only 3% of testicular tumors and are generally benign. Only less than 0.2% of all testicular cancers were evidenced by metastatic spread. We report a 34-year-old man visited hospital because of coughing sputum mixed with blood. His chest CT showed bilateral patch clouding opacity. He was suspected with allergic alveolitis and treated with methylprednisolone. However, his symptoms and general condition deteriorated, and he visited our hospital. He had no abnormal findings on physical examination. A chest radiograph showed pneumonia in whole lung and CT showed multiple nodules and diffused ground glass opacities in both lung fields. Lung biopsy confirmed a diagnosis of Leydig cell tumor with lung metastasis. The diagnosis is based on the histopathology and immunohistochemistry.

Keywords: Leydig cell tumors, lung metastasis, lung biopsy, immunohistochemistry

Introduction

The interstitial Leydig cells of testis, developing from the mesenchyme located between the seminiferous tubules. The majority of Leydig cell tumors are found in men, usually at 5-10 years of age or in middle adulthood (30-60 years). Leydig cell tumors (LCTs) are very rare tumors and account for 1-3% of all testicular malignancies. Majority of these tumors are benign. Malignant LCT accounts for less than 0.2% of all testicular cancers as evidenced by metastatic spread and poor survival [1, 2]. We report an interesting case of malignant LCT with lung metastasis in 34-year-old man who presented with coughing sputum mixed with blood for 7 months. The final diagnosis of LCT with lung metastasis was made by lung biopsy.

Case presentation

A 34-year-old man who had been complaining of coughing sputum mixed with blood for 7 months was admitted to a local hospital. His chest CT showed bilateral patch clouding opacity. Percutaneous lung biopsy (PCNA) was performed by the local hospital, but the result was negative. The allergic alveolitis was suspected, and administration of methylprednisolone for 2 months.

However, his symptoms and general condition deteriorated, and she was admitted to our hospital. He was diagnosed Leydig cell tumor and a high left inguinal orchiectomy was performed one month ago. He had no prior history of lung disease, and no exposure to dust or occupational hazards. Chest auscultation was normal, and there were no lymphadenopathy, skin lesions or neurological signs. The full blood count findings showed moderate anemia (red blood cells (RBCs) 3.08×10^{12}/L, hemoglobin 82 g/L) with increased white blood cells (13.0×10^{9}/L: 90.7% neutrophils, 0.4% eosinophils, 5.0% lymphocytes, and 3.1% monocytes) and normal platelets counts (262×10^{9}/L). The rest of the biochemical findings were normal. Chest X-ray showed pneumonia in whole lung (**Figure 1A**). CT showed multiple nodules and diffused ground glass opacities in both lung fields (**Figure 1B**).

Infection, rheumatic diseases and lymphoproliferative diseases were suspected as the primary

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mediated by inflammatory reaction to inhalation of an allergen. These may be organic or inorganic particles (microbes, animal or plant proteins, and certain chemicals) that form haptens by sensitized individuals. The chest CT of this disease often shows homogeneous ground-glass opacity and numerous round centrilobular opacities which is usually less than 5 mm in diameter [17, 18]. The homogeneous ground-glass opacity is bilateral and symmetric but sometimes patchy and concentrated in the middle part and base of the lungs or in a bronchovascular distribution. The chest CT of pulmonary metastases shows soft tissue attenuation well circumscribed rounded lesions, more often in the periphery of the lung. They are usually of variable size, a feature which is of some use in distinguishing them from a granuloma [19]. A prominent pulmonary vessel has frequently been noted heading into a metastasis. The ground-glass opacity representing hemorrhage can be seen, particularly surrounding haemorrhagic pulmonary metastases. In our case, the CT of the patient showed multiple nodules and diffused ground glass opacities in both lung fields. It is very difficult to distinguish allergic alveolitis and pulmonary metastases only via CT. Therefore, lung biopsy plays a very important role in the diagnosis of this lung disease.

In summary, the possibility of pulmonary metastases might be considered in some cases diagnosed as allergic alveolitis or interstitial pneumonia. It is important to encourage the use of lung biopsy by clinicians and cytopathologists for investigating an abnormality found on a chest X-ray or CT scan.

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Disclosure of conflict of interest

None.

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Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis

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Currently, limited information is available to clinicians regarding the long-term efficacy of omalizumab treatment for allergic asthma. In this report, we aimed to (i) systematically review the evidence regarding the long-term efficacy of omalizumab in patients with persistent uncontrolled allergic asthma, and to (ii) discuss the cost-effectiveness evidence published for omalizumab in this patient population. A comprehensive search for randomized controlled trials (RCTs; ≥52 weeks) was performed, and six studies met our final inclusion criteria (n = 2,749). Omalizumab was associated with significant improvements in quality of life and the Global Evaluation of Treatment Effectiveness. Omalizumab also allowed patients to completely withdraw from inhaled corticosteroid therapy and did not increase the overall incidence of adverse events. However, there was insufficient evidence that omalizumab reduced the incidence of exacerbations, and the cost-effectiveness of omalizumab varied across studies. Our data indicated that omalizumab use for at least 52 weeks in patients with persistent uncontrolled allergic asthma was accompanied by an acceptable safety profile, but it lacked effect on the asthma exacerbations. Use of omalizumab was associated with a higher cost than conventional therapy, but these increases may be cost-effective if the medication is used in patients with severe allergic asthma.

Asthma is characterized by bronchial inflammation, airway hyper-responsiveness induced by specific and nonspecific stimuli, and reversible bronchial obstruction[1–3]. An estimated 57% of these asthma patients suffer from uncontrolled asthma and a substantial proportion of severe cases are attributable to allergic immunoglobulin E (IgE)-mediated mechanisms[4–8]. Patients with persistent uncontrolled asthma are at high risk of asthma-related hospitalization and mortality, suffer significant impairments in their quality of life (QOL), and account for the majority of asthma-related costs. The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach to asthma control, with treatment being stepped up until control is achieved and maintained. However, even with the availability of these asthma guidelines and the best available treatments, approximately one third of patients continue to suffer from inadequately controlled symptoms. For patients whose asthma remains uncontrolled at this step, GINA recommends adding oral corticosteroids (OCS) or anti-IgE treatment with omalizumab[9]. However, adding OCS is associated with severe side effects. Specific targeting of IgE with an anti-IgE antibody therefore represents a promising approach to the treatment of allergic asthma[10–12]. Omalizumab is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds IgE at the same epitope on the Fc region that binds to the IgE receptor[13–15].

Although omalizumab is an effective intervention as an add-on therapy in the management of severe persistent allergic asthma, important questions remain regarding the role of omalizumab in the treatment of asthma based on current guidelines. Updated National Institute for Health and Care Excellence (NICE 2013) guidelines recommend use only in patients with inadequately controlled severe persistent allergic asthma who require continuous or frequent treatments with oral corticosteroids[16]. However, this recommendation is not strongly supported by evidence. Indeed, other international guidelines are less proscriptive and recommend this treatment

Original Article

Lower airway inflammation and hyperresponsiveness in non-asthmatic patients with non-allergic rhinitis

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Background: Potential associations between non-allergic rhinitis (NAR) and asthma have been verified epidemiologically, but these associations remain not very clear. It is necessary to further explore the possible implication of lower airway abnormities in NAR patients but without asthma. This study aims to determine lower airway hyperresponsiveness (AHR), inflammation and lung function in non-asthmatic patients with NAR.

Methods: We recruited 262 non-asthmatic patients with NAR, 377 with AR and 264 healthy subjects. All subjects were non-smokers who underwent meticulous history taking, nasal examination, allergen skin prick test (SPT), blood routine test, measurement of fractional exhaled nitric oxide (FeNO), methacholine bronchial challenge test and induced sputum eosinophil count, in this order.

Results: Compared with healthy subjects, non-asthmatic patients with NAR yielded markedly lower FEV_1/FVC, maximal mid-expiratory flow (MMEF), mid-expiratory flow when 50% of FVC has been expired ($MEF_{50\%}$) and mid-expiratory flow when 75% of FVC has been expired ($MEF_{25\%}$) (P<0.05). Differences in spirometry between group AR and NAR were unremarkable (P>0.05). Patients with NAR yielded higher rate of AHR and higher FeNO levels than healthy subjects but lower than those with AR. The proportion of lower airways disorders (sputum eosinophilia, high FeNO levels or AHR) was highest in group AR (70.8%), followed by NAR (53.4%) and healthy subjects (24.2%) (P<0.01). However, sputum eosinophils in NAR patients were not higher compared with healthy subjects (P>0.05). Sputum eosinophils and FeNO had significant correlation with positive AHR and MMEF in group AR but not in NAR.

Conclusions: Non-asthmatic patients with NAR harbor lower AHR, small airways dysfunction and inflammation, despite being less significant than those with AR. This offers clues to unravel the link between NAR and asthma.

Keywords: Non-allergic rhinitis (NAR); allergic rhinitis (AR); asthma; airway inflammation; airway hyperresponsiveness (AHR)

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POSITION PAPER

MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation

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Mapping the epitope of neutralizing monoclonal antibodies against human adenovirus type 3

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ABSTRACT

Human adenovirus type 3 (HAdV-3) has produced a global epidemic in recent years causing serious diseases such as pneumonia in both pediatric and adult patients. Development of an effective neutralizing monoclonal antibody (MAb) and identification of its neutralizing epitope is important for the control of HAdV-3 infection. In this study, three neutralizing MAbs were generated, of which MAb 3D7 had a high neutralization titer of 4096 (approximately 0.5 μg/ml) against HAdV-3 infection. In indirect enzyme-linked immunosorbent assays, all three MAbs specifically recognized HAdV-3 virus particles and hexon protein, but did not react with the virus particles or the hexon protein of HAdV-7. Analyses using a series of peptides and chimeric adenovirus particles of epitope mutants revealed that all three MAbs bound to the same exposed region (amino acid positions 244–254 of hexon) in hypervariable region 4 (HVR4), which is highly conserved among global HAdV-3 strains. The amino acids T246 and G250 may be the critical amino acids recognized by these MAbs. MAb 3D7 reduced the recombinant enhanced green fluorescent protein-expressing HAdV-3 (rAd3EGFP) load recovered in the lungs of mice at 3 days post-infection. The generation of MAb 3D7 and the identification of its neutralizing epitope may be useful for therapeutic treatment development, subunit vaccine construction, and virion structural analysis for HAdV-3.

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1. Introduction

Human adenoviruses (HAdV) can cause a broad spectrum of diseases in both pediatric and adult patients, such as acute respiratory infection, acute gastroenteritis, and epidemic keratoconjunctivitis (Lenaerts et al., 2008; Sandkovsky et al., 2014). To date, seven species including more than 68 genotypes have been characterized and defined by genomics and bioinformatics (Dehghan et al., 2012; Robinson et al., 2013). Specific species genotypes are often associated with particular clinical manifestations. HAdV species C (HAdV-1, -2, -5, and -6), species B (HAdV-3, -7, -14, and -55) and species E (HAdV-4) are most commonly found in patients with respiratory infection. Among these, HAdV-3 strains of subspecies B1 are the major epidemic strains responsible for severe respiratory disease epidemics and outbreaks worldwide (Yun et al., 2014; Lu et al., 2014; Barrero et al., 2012; Alkhalaf et al., 2015; Ampuero et al., 2012; Guo et al., 2012; Deng et al., 2013; Lai et al., 2013; Lee et al., 2015; Zhang et al., 2006).

Currently, there is no effective treatment or vaccine against HAdV-3 infection. Neutralizing monoclonal antibodies (MAb) may be a promising prophylactic or therapeutic medicine against viral disease. The creation of neutralizing MAb could also be useful for identifying neutralizing epitopes, which is of great importance in the molecular design of vaccines. The adenovirus capsid icosahedron is composed of three major structural proteins: hexon, penton base, and fiber. The hexon protein is the major antigenic determinant recognized by neutralizing antibodies (NAbs) (Tian et al., 2011; Yu et al., 2013; Wu et al., 2002). Type-specific epitopes on hexons have been proposed to reside within seven highly variable regions (HVRs), of which HVR7 can be further subdivided into three

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ORIGINAL ARTICLE

Mechanical Stress and the Induction of Lung Fibrosis via the Midkine Signaling Pathway

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Abstract

Rationale: Lung-protective ventilatory strategies have been widely used in patients with acute respiratory distress syndrome (ARDS), but the ARDS mortality rate remains unacceptably high and there is no proven pharmacologic therapy.

Objectives: Mechanical ventilation can induce oxidative stress and lung fibrosis, which may contribute to high dependency on ventilator support and increased ARDS mortality. We hypothesized that the novel cytokine, midkine (MK), which can be up-regulated in oxidative stress, plays a key role in the pathogenesis of ARDS-associated lung fibrosis.

Methods: Blood samples were collected from 17 patients with ARDS and 10 healthy donors. Human lung epithelial cells were challenged with hydrogen chloride followed by mechanical stretch for 72 hours. Wild-type and MK gene–deficient ($MK^{-/-}$) mice received two-hit injury of acid aspiration and mechanical ventilation, and were monitored for 14 days.

Measurements and Main Results: Plasma concentrations of MK were higher in patients with ARDS than in healthy volunteers. Exposure to mechanical stretch of lung epithelial cells led to an epithelial–mesenchymal transition profile associated with increased expression of angiotensin-converting enzyme, which was attenuated by silencing MK, its receptor Notch2, or NADP reduced oxidase 1. An increase in collagen deposition and hydroxyproline level and a decrease in lung tissue compliance seen in wild-type mice were largely attenuated in $MK^{-/-}$ mice.

Conclusions: Mechanical stretch can induce an epithelial–mesenchymal transition phenotype mediated by the MK–Notch2–angiotensin-converting enzyme signaling pathway, contributing to lung remodeling. The MK pathway is a potential therapeutic target in the context of ARDS-associated lung fibrosis.

Keywords: lung injury; mechanical ventilation; angiotensin-converting enzyme

Acute respiratory distress syndrome (ARDS) remains a major clinical challenge in critically ill patients (1, 2). Mechanical ventilation is often necessary, but can induce or aggravate lung injury, an entity referred to as ventilator-induced lung injury (3). Lung-protective strategies that reduce lung stretch have led to decreased ARDS mortality, likely by minimizing biotrauma, a major contributor to ventilator-induced lung injury (4, 5). However, ARDS mortality rate remains unacceptably high and there is no proven pharmacologic therapy (6).

ARDS represents a stereotypic response to lung injury with transition from exudative inflammatory responses, with epithelial–capillary barrier damage, to

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SCIENTIFIC REPORTS

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Mechanistic studies of a novel C-S lyase in ergothioneine biosynthesis: the involvement of a sulfenic acid intermediate

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Ergothioneine is a histidine thio-derivative isolated in 1909. In ergothioneine biosynthesis, the combination of a mononuclear non-heme iron enzyme catalyzed oxidative C-S bond formation reaction and a PLP-mediated C-S lyase (EgtE) reaction results in a net sulfur transfer from cysteine to histidine side-chain. This demonstrates a new sulfur transfer strategy in the biosynthesis of sulfur-containing natural products. Due to difficulties associated with the overexpression of *Mycobacterium smegmatis* EgtE protein, the proposed EgtE functionality remained to be verified biochemically. In this study, we have successfully overexpressed and purified *M. smegmatis* EgtE enzyme and evaluated its activities under different *in vitro* conditions: C-S lyase reaction using either thioether or sulfoxide as a substrate in the presence or absence of reductants. Results from our biochemical characterizations support the assignment of sulfoxide 4 as the native EgtE substrate and the involvement of a sulfenic acid intermediate in the ergothioneine C-S lyase reaction.

Glutathione, one of the most abundant natural thiols inside the cells (up to 10 mM), plays a key role in buffering the intracellular redox-state. In many organisms, there exists another important thiol, ergothioneine, which is a thio-imidazole containing amino acid (**5**, Fig. 1)[1–3] Different from glutathione, the predominant form of ergothioneine is its thione form (**5b**, Fig. 1). As a result, ergothioneine's reduction potential ($E^0 = -0.06$ V)[2] is signifi antly higher than that of glutathione ($E^0 = -0.24$ V)[4,5] Humans do not synthesize ergothioneine. However, through an ergothioneine-specific transporter (OCTN1), we enrich ergothioneine from our diets to mM concentrations in many parts of our body[6], including liver, kidneys, central nervous system, erythrocytes, eye lenses, and seminal fluids[2,7–10]. Ergothioneine has many benefic al roles to human health[2,4,11,12], especially its role as an effective scavenger for reactive oxidative species (ROS), including singlet oxygen, hydroxyl, peroxyl, peroxynitrite ($ONOO^-$), nitrosoperoxycarbonate ($ONOOCO_2^-$), and carbonate radicals[13–16].

Due to ergothioneine's benefic al roles to human health, biochemists have been searching for the ergothioneine biosynthetic pathway since the 1960 s[17–19]. The ergothioneine biosynthetic genes were discovered only very recently and there exists two different ergothioneine biosynthetic pathways (Fig. 1)[20–23]. In 2010, the ergothioneine biosynthetic gene cluster in *Mycobacterium smegmatis* was discovered[20]. The mycobacterial pathway involves five steps: EgtD catalyzes the methylation of histidine to hercynine (**2**); EgtA condenses glutamate and cysteine to form γ-glutamylcysteine (γ-Glu-Cys, **6**); EgtB is a non-heme iron enzyme, catalyzing oxidative coupling of hercynine (**2**) and γ-Glu-Cys (**6**) to introduce

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My dreams

I have seen patients suffering from chronic obstructive pulmonary disease (COPD) for many years. Once the disease develops into its late stage, generally there is no effective treatment. Too many patients only come to doctors when they cannot bear the tortures of this devastating disease any more, but that's too late. Some others with early stage COPD don't pay enough attention to it. Once the pulmonary function decreases and no action is taken, severe consequences result.

This conference* has made me think about the COPD patients I have known and treated. I have had a dream about a global effort to help COPD patients everywhere. It would be an organized person to person effort to prevent COPD where we can. For those who are already developing COPD we would conduct a far-reaching initiative to diagnose patients in the very early phase of the disease. We would do our best to help these people avoid the dangerous progression of the disease before they suffer from the debilitating symptoms and the consequent decline of health. This would take place in rich countries as well as poor countries and would locate these patients in the big cities and in the small rural villages.

My second dream is that lung doctors like me and my colleagues will work closely with GPs and primary care doctors as well as other health care professionals and patients from all the communities of the world in this quest to help COPD patients and prevent others from developing COPD. Only by working together can we accomplish the great task of monitoring patients at risk for COPD and detecting the onset of the disease. Then, working with all our colleagues and our patients, we can use the best techniques to diagnose COPD and provide the medicines needed to benefit the patients. I believe that we can all work together to make these dreams come true!

Acknowledgements

*At the end of the World Conference of COPD Patient Organizations held in Shanghai, China, in November of 2011, Monica Fletcher, RN, the Chair of the European Lung Foundation, chaired a panel discussion of COPD experts from throughout the world. She challenged each of the participants to talk about what the meeting had meant to them and how they hoped that it would influence what they would work for upon their return home. Prof. Nanshan Zhong's remarks expressed the sentiments that most deeply affected the attendees from all walks of health care and from all parts of the world. Dr. Alfred Loh, the CEO of the World Organization of Family Doctors applauded Prof. Zhong's dreams. His wish was that he could mobilize his 128 member organization of GPs to take up the challenge that Prof. Zhong described. Dr. Lawrence Grouse adapted this essay from Prof. Zhong's remarks at the World Conference.

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Supporting Information

N-(3-ethynyl-2, 4-difluorophenyl)sulfonamide Derivatives as Selective Raf Inhibitors

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呼吸疾病国家重点实验室

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Neural Respiratory Drive and Arousal in Patients with Obstructive Sleep Apnea Hypopnea

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Study Objectives: It has been hypothesized that arousals after apnea and hypopnea events in patients with obstructive sleep apnea are triggered when neural respiratory drive exceeds a certain level, but this hypothesis is based on esophageal pressure data, which are dependent on flow and lung volume. We aimed to determine whether a fixed threshold of respiratory drive is responsible for arousal at the termination of apnea and hypopnea using a flow independent technique (esophageal diaphragm electromyography, EMG_{di}) in patients with obstructive sleep apnea.

Setting: Sleep center of state Key Laboratory of Respiratory Disease.

Patients: Seventeen subjects (two women, mean age 53 ± 11 years) with obstructive sleep apnea/hypopnea syndrome were studied

Methods: We recorded esophageal pressure and EMG_{di} simultaneously during overnight full polysomnography in all the subjects.

Measurements and Results: A total of 709 hypopnea events and 986 apnea events were analyzed. There was wide variation in both esophageal pressure and EMG_{di} at the end of both apnea and hypopnea events within a subject and stage 2 sleep. The EMG_{di} at the end of events that terminated with arousal was similar to those which terminated without arousal for both hypopnea events (27.6% ± 13.9%max vs 29.9% ± 15.9%max, P = ns) and apnea events (22.9% ± 11.5%max vs 22.1% ± 12.6%max, P = ns). The Pes at the end of respiratory events terminated with arousal was also similar to those terminated without arousal. There was a small but significant difference in EMG_{di} at the end of respiratory events between hypopnea and apnea (25.3% ± 14.2%max vs 21.7% ± 13.2%max, P < 0.05].

Conclusions: Our data do not support the concept that there is threshold of neural respiratory drive that is responsible for arousal in patients with obstructive sleep apnea.

Keywords: arousal, OSA, hypopnea, diaphragm EMG, esophageal pressure

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated episodes of apnea and hypopnea during sleep and major pathophysiological features of OSA are intermittent hypoxia and frequent arousals. Recurrent arousals prevent consolidated sleep and it has been shown that daytime sleepiness in patients with OSA is more closely related to arousal than to hypoxia indices.[1] Recent studies have also suggested that arousal could interfere with the ability to effectively recruit the upper airway dilator muscles and may precipitate further obstructive respiratory events.[2–4] Thus investigating the mechanism of arousal is important to further understand the pathophysiological changes of obstructive sleep apnea and to facilitate development of new approaches for relevant treatment options.[5]

Several studies have argued, based on recordings of esophageal pressure (Pes) during overnight polysomnography,[6,7] that there is an arousal threshold of respiratory effort triggering arousal in patients with OSA. However, Pes is affected by changes in lung volume, particularly airflow,[8–10] and this fundamental physiological property could preclude accurate evaluation of neural respiratory drive in patients with OSA, which is characterized by change in airflow. We have previously shown that while EMG_{di} relates closely to Pes during apnea, this is not so once airflow resumes following an apnea[9] because pressure generation declines with increase in airway flow. It remains unclear whether the stimulus leading to arousal from sleep during obstructive apneas and hypopneas is related to central respiratory output.[4,11] Diaphragm electromyography (EMG_{di}) recorded from a multi-pair esophageal electrode can accurately assess neural respiratory drive.[8–10,12]

If the hypothesis that neural respiratory output causes arousal was correct, a given level of respiratory drive within a given stage of sleep and therefore sleep depth should reliably trigger arousal during either apnea or hypopnea events, and the converse should also apply—specifically that arousal should not occur unless neural respiratory drive exceeds a certain threshold. Since most patients with obstructive sleep apnea-hypopnea syndrome present with a mixture of apneas and hypopneas, we reasoned that the untreated sleep apnea patient provides an ideal "experiment of nature" to test this hypothesis.

METHODS

Seventeen subjects aged 37 to 76 years (2 females and 15 males, mean age 53 ± 11 years, BMI 26.4 ± 3.7 kg/m^2) with OSA were recruited from patients referred to the sleep center of Guangzhou Institute of Respiratory Disease, China; their demographic data are shown in Table 1. Patients were advised to abstain from alcohol and sedative medicines ≥ 24 h prior to the study. No patient had significant coexisting conditions

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Neutralizing epitopes mapping of human adenovirus type 14 hexon

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ABSTRACT

Human adenoviruses 14 (HAdV-14) caused several clusters of acute respiratory disease (ARD) outbreaks in both civilian and military settings. The identification of the neutralizing epitopes of HAdV-14 is important for the surveillance and control of infection. Since the previous studies had indicated that the adenoviruses neutralizing epitopes were likely to be exposed on the surface of the hexon, four epitope peptides, A14R1 (residues 141–157), A14R2 (residues 181–189), A14R4 (residues 252–260) and A14R7 (residues 430–442) were predicted and mapped onto the 3D structures of hexon by homology modeling approach. Then the four peptides were synthesized, and all the four putative epitopes were identified as neutralizing epitopes by enzyme-linked immunosorbent assay (ELISA) and neutralization tests (NT). Finally we incorporated the four epitopes into human adenoviruses 3 (HAdV-3) vectors using the "antigen capsid-incorporation" strategy, and two chimeric adenoviruses, A14R2A3 and A14R4A3, were successfully obtained which displayed A14R2 and A14R4 respectively on the hexon surface of HAdV-3 virions. Further analysis showed that the two chimeric viruses antiserum could neutralize both HAdV-14 and HAdV-3 infection. The neutralization titers of anti-A14R4A3 group were significantly higher than the anti-KLH-A14R4 group ($P = 0.0442$). These findings have important implications for the development of peptide-based broadly protective HAdV-14 and HAdV-3 bivalent vaccine.

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1. Introduction

Human adenoviruses (HAdVs) played an important role in a broad spectrum of illness in humans, including acute respiratory disease (ARD), pneumonia, epidemic keratoconjunctivitis and acute gastroenteritis [1,2]. HAdVs were typed and ordered into seven species (A–G) with greater than 65 genome types [3,4], and different HAdV species were associated with distinct diseases [5,6]. First discovered in the Netherlands in 1955 during an outbreak of acute respiratory disease (ARD) in military recruits [7], human adenovirus serotype 14 (otherwise known as "agent de Wit" or HAdV-14p) was subsequently isolated during respiratory disease outbreaks among young adults [7–10]. However, in 2006–2007, a relatively rare adenovirus serotype 14 strain caused several severe lower respiratory tract disease including at least 10 deaths and 140 respiratory illnesses in New York, Oregon, Washington and Texas, in both civilian and military settings [11–16]. The outbreaks of HAdV-14 infection were then also reported in Europe and China [5,8]. The re-emerging HAdV-14 belonged to a new genome type designated "HAdV-14p1" (also known as "14a") [17], while the most notable genetic difference between the variant and the prototype HAdV-14 strain was a deletion of 6 base pairs in the fiber knob gene [17–20].

Normal exposure to human adenoviruses leads to the presence of pre-existing immunity. Prior studies have reported a prevalence of neutralizing antibodies to HAdV-5 between 60% and 70% in some populations in Europe and USA, and up to 98% in sub-Saharan African countries and Asian (Thai) tropical countries [21,22]. As far as we know, no scientific report on the natural rates of neutralizing immunity to HAdV-14 in the human population has been published yet. According to our recent survey on large population in Guangzhou, China, the seroprevalence of neutralizing antibodies

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RESEARCH ARTICLE

New Epidemiological and Clinical Signatures of 18 Pathogens from Respiratory Tract Infections Based on a 5-Year Study

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Abstract

Background

Respiratory tract infections (RTIs) are a heavy burden on society. However, due to the complex etiology of RTIs, the clinical diagnosis, treatment, and prevention of these infections remain challenging, especially in developing countries.

Methods

To determine the epidemiological and clinical characteristics of 18 respiratory pathogens, we analyzed 12,502 patients with acute respiratory infections (ARIs) by performing polymerase chain reaction (PCR) on patient pharyngeal swabs.

Results

Samples positive for at least 1 pathogen were obtained from 48.42% of the total patients. Of these pathogen-positive patients, 17.99% were infected with more than 1 pathogen. Of the 18 pathogens analyzed, four were detected with a positive detection rate (PDR) > 5%: influenza A virus (IAV) > respiratory syncytial virus (RSV) >*Mycoplasma pneumoniae* (MP) > human coronavirus (HCoV). The pathogens with the 4 highest co-infection rates (CIRs) were as follows: HCoV > human bocavirus (HBoV) > enterovirus (EV) > parainfluenza virus (PIV). The overall positive detection rate (PDR) varied significantly according to patient age, the season and year of detection, and the disease subgroup, but not according to patient sex. The individual PDRs of the pathogens followed 3 types of distributions for patient sex, 4 types of distributions for patient age, 4 types of seasonal distributions, 2 types of seasonal epidemic trends, 4 types of yearly epidemic trends, and different susceptibility distributions in the disease subgroups. Additionally, the overall CIR showed significantly different distributions according to patient sex, patient age, and the disease subgroup, whereas the CIRs of individual pathogens suggested significant preference characteristics.

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Noggin inhibits hypoxia-induced proliferation by targeting store-operated calcium entry and transient receptor potential cation channels

Kai Yang,[1,2] Wenju Lu,[1]* Jing Jia,[1] Jie Zhang,[1] Mingming Zhao,[3] Sabrina Wang,[2] Haiyang Jiang,[2] Lei Xu,[1,2] and Jian Wang[1,2]*

[1]*Guangzhou Institute of Respiratory Disease, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China;* [2]*Division of Pulmonary and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and* [3]*Laboratory of Molecular Biology and Immunology, National Institute on Aging, Baltimore, Maryland*

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Yang K, Lu W, Jia J, Zhang J, Zhao M, Wang S, Jiang H, Xu L, Wang J. Noggin inhibits hypoxia-induced proliferation by targeting store-operated calcium entry and transient receptor potential cation channels. *Am J Physiol Cell Physiol* 308: C869–C878, 2015. First published March 4, 2015; doi:10.1152/ajpcell.00349.2014.— Abnormally elevated bone morphogenetic protein 4 (BMP4) expression and mediated signaling play a critical role in the pathogenesis of chronic hypoxia-induced pulmonary hypertension (CHPH). In this study, we investigated the expression level and functional significance of four reported naturally occurring BMP4 antagonists, noggin, follistatin, gremlin1, and matrix gla protein (MGP), in the lung and distal pulmonary arterial smooth muscle cell (PASMC). A 21-day chronic hypoxic (10% O_2) exposure rat model was utilized, which has been previously shown to successfully establish experimental CHPH. Among the four antagonists, noggin, but not the other three, was selectively downregulated by hypoxic exposure in both the lung tissue and PASMC, in correlation with markedly elevated BMP4 expression, suggesting that the loss of noggin might account for the hypoxia-triggered BMP4 signaling transduction. Then, by using treatment of extrogenous recombinant noggin protein, we further found that noggin significantly normalized *1*) BMP4-induced phosphorylation of cellular p38 and ERK1/2; *2*) BMP4-induced phosphorylation of cellular JAK2 and STAT3; *3*) hypoxia-induced PASMC proliferation; *4*) hypoxia-induced store-operated calcium entry (SOCE), and *5*) hypoxia-increased expression of transient receptor potential cation channels (TRPC1 and TRPC6) in PASMC. In combination, these data strongly indicated that the hypoxia-suppressed noggin accounts, at least partially, for hypoxia-induced excessive PASMC proliferation, while restoration of noggin may be an effective way to inhibit cell proliferation by suppressing SOCE and TRPC expression.

noggin; TRPC; store-operated calcium entry; pulmonary hypertension

PULMONARY HYPERTENSION (PH) is a disease characterized by a list of functional and structural changes in the pulmonary vasculature that lead to enhanced distal pulmonary arterial (PA) contraction and remodeling, eventually causing heart failure. During the disease process, remodeling of small vessels in the lung, due to abnormal proliferation and migration of vascular smooth muscle cells and endothelium cells, is well studied and accepted (10).

Bone morphogenetic proteins (BMPs) belong to a subgroup of the transforming growth factor-β (TGF-β) superfamily, which are a group of growth factors originally discovered by their ability to induce the formation of bone and cartilage. Recently, evidence strongly indicated that dysregulated BMP signaling is involved in the pathogenesis of PH (9, 11). BMP4, a member of BMP ligands, has been found selectively upregulated by chronic hypoxia in the lungs and plays an important role during the development of chronic hypoxia-induced pulmonary hypertension (CHPH) by regulating the proliferation and migration of pulmonary arterial smooth muscle cells (PASMC) (11, 13, 20). In mechanisms, BMP4-mediated signaling transduction is mainly regulated by two groups of molecules, the typical receptors and the extracellular soluble antagonists (3). BMP4 transduces signals by binding to type II serine-threonine kinase receptors (44), which then causes recruitment and phosphorylation of type I receptors, leading to activation of a number of cellular kinases (18).

The group of BMP antagonists belongs to naturally secreted endogenous proteins that can block the BMP ligand-receptor interaction to inhibit the BMP signaling transduction. Increasing evidence demonstrated that dysfunction of these proteins leads to excessive BMP activity and signaling transduction, which is present and may account for the development of numerous diseases. In detail, gremlin1 specifically binds to BMP2, 4, and 7 and inhibits their actions on the downstream signaling (14, 23). Evidence suggests that gremlin1 is upregulated in lungs isolated from 2-day alveolar hypoxia-exposed mice (6). The increased gremlin1 expression mostly localizes in the pulmonary endothelium, but not smooth muscle (2). Deletion of gremlin1 increases cell proliferation and migration responses in mouse embryonic fibroblasts (7). Noggin, follistatin, and matrix gla protein (MGP) are all demonstrated as BMP4 antagonists, which are found to coexpress with BMP4 at sites of oscillatory shear stress in the systemic vasculature (4). Noggin has long been known as a classic BMP antagonist with a high-affinity binding to BMP4 (25, 26, 49). Traditionally defined as an antagonist of activin protein, follistatin could also interact with BMPs (including BMP4, 5, 6, 7, and 15), though in a lower-affinity range (5, 12, 32, 35). MGP is an extracellular matrix component expressing high abundance in vascular smooth muscle cells. MGP has been defined as contributing to the development of vasculature by using MGP-deficient mice (45). MGP inhibits or activates BMPs (BMP2 and BMP4) in a concentration-dependent manner (46, 48). So far, many groups have discussed the effects of BMPs antagonists on interfering BMP signaling and participating in the development of different diseases. However, the full action of these members in CHPH remains largely unknown. We previously demonstrated that animals exposed to chronic hypoxia (CH, 10% O_2) for 21 days were used as an

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Nonintubated Video-Assisted Thoracoscopic Surgery Under Epidural Anesthesia Compared With Conventional Anesthetic Option: A Randomized Control Study

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Abstract

Objective. The purposes of this study were to evaluate the feasibility, safety, and advantages of nonintubated video-assisted thoracoscopic surgery (VATS) under epidural anesthesia, by comparing with the performance of conventional approaches. *Patients and methods*. A total of 354 patients (245 men and 109 women) were recruited in this study. The surgical procedures included bullae resection, pulmonary wedge resection, and lobectomy. The anesthetic technique (epidural vs general) was selected randomly. Patients who underwent nonintubated VATS under epidural anesthesia comprised the intervention group, and patients who received VATS under general anesthesia with double lumen tube comprised the control group. *Results*. In total, 167 patients were included in the intervention group, and 180 patients were included in the control group. The 2 treatment groups of bullae resection showed significant differences in postoperative fasting time, duration of postoperative antibiotic use depending on the time when the white blood cells decreased to normal levels, and duration of postoperative hospital stay ($P < .05$). Nonintubated VATS is associated with a decreased level of inflammatory cytokines ($P < .05$). *Conclusion*. VATS under anesthesia with nontracheal intubation is safe and feasible, and has demonstrated advantages, including shorter postoperative fasting time, shorter duration of antibiotic use, and shorter hospital stay, compared with VATS under general anesthesia with double lumen tube.

Keywords

video-assisted thoracoscopic surgery, nonintubated, anesthesia

呼吸疾病国家重点实验室

Introduction

Anesthesia for video-assisted thoracoscopic surgery (VATS) should not only achieve adequate depth but also control negative intrathoracic pressure and lung expansion during the surgery.[1] Therefore, anesthesia and lung isolation techniques are particularly important for surgeons. Lung isolation under general anesthesia with double-lumen tubes has become an indispensable part of thoracic surgery. However, intubation-associated complications, including lung infections, lung injury due to ventilation pressure or overexpansion, bronchospasm, cardiac dysfunction and arrhythmia, postoperative sore throat, and irritating cough remain problematic.[1,2] In an attempt to reduce complications related to conventional anesthesia with tracheal intubation during thoracic surgery, epidural anesthesia has been reintroduced for various VATS procedures.[3,4] In our center, we have introduced, for the first time in the mainland of China, VATS under anesthesia with nontracheal intubation.[5,6] In order to evaluate the feasibility, safety, and advantages of the technique, we conducted this study to compare the performance of this novel

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Supporting Information

Organocatalytic Enantioselective Aza-Michael Reaction of Benzotriazole to β,β-Disubstituted Nitroalkenes

Sheng-Wei Chen, Gui-Cheng Zhang, Qin-Xin Lou, Wei Cui, Sha-Sha Zhang, Wen-Hui Hu,* and Jun-Ling Zhao*[a]

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呼吸疾病国家重点实验室

Advanced Synthesis & Catalysis

Very Important Publication

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Organocatalytic Enantioselective Michael Reaction of Malononitrile with β,β-Disubstituted Nitroalkenes

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Abstract: We have developed and optimized an enantioselective Michael reaction of malononitrile with β,β-disubstituted nitroalkenes. This reaction was catalyzed by a cinchona alkaloid derived thiourea catalyst, producing products of high yields (up to 98%) and stereoselectivities (up to 93% *ee*). One of the adducts was used as an intermediate for the synthesis of dihydropyrrole derivative bearing a synthetically valuable quaternary chiral center.

Keywords: asymmetric; malononitrile; Michael reaction; organocatalysis; β,β-disubstituted nitroalkenes

The catalytic asymmetric conjugate addition reaction of nucleophiles to electron-deficient alkenes has garnered attention due to its wide applicability in the synthesis of biologically relevant compounds.[1] One of the most extensively studied asymmetric conjugate addition reactions is the Michael reaction of nitroolefins, which represents a convenient access to nitroalkanes that are versatile intermediates in organic synthesis.[2] However, the studies reported to date have primarily focused on more reactive β-monosubstituted[3] or α,β-disubstituted[4] nitroolefins. The catalytic asymmetric Michael reaction of β,β-disubstituted nitroalkenes is less studied, primarily because steric hindrance poses a potential problem. Particularly noteworthy is that the synthetically important quaternary chiral centers could be generated through the Michael reaction of β,β-disubstituted nitroolefins with nucleophiles. However, only a handful of studies have focused on this particular reaction, likely due to low activity profiles.[5–6]

α-Substituted β-nitroacrylate has recently been documented as a Michael reaction acceptor with a variety of nucleophiles, with the corresponding adduct readily transformable to β-amino acids that are an important motif for β-peptides, β-lactams, and other biologically important compounds.[7] Enones,[6a] aldehydes,[6b] indoles,[6c–e] oximes,[6f] and thiols[6g] have been documented as ideal nucleophiles for this asymmetric Michael addition process. Despite those recent advances, there is still a need for the development of new nucleophilic reagents that are capable of generating structurally diverse quaternary chiral centers through Michael reaction with α-substituted-β-nitroacrylate.

Malononitrile is an equivalent to a 1,3-dicarbonyl compound, and the nitrile group is a versatile functional group for many further transformations.[8] Organocatalytic asymmetric Michael reactions using malononitrile as the nucleophile are relatively less explored due to its high reactivity and incapability of two-point binding with the catalyst. Most of the efforts in this field have been focused on the employment of α,β-unsaturated carbonyls as electrophiles.[9] There have been very few studies using nitroolefins as Michael reaction acceptors. Takemoto[10a] and Yuan,[10b] respectively, reported the bifunctional thiourea catalyzed Michael reactions of malononitrile to nitroolefins with modest enantioselectivity. Arai[10e] synthesized a neural, chiral bis(imidazolidine)-derived NCN-type palladium pincer complex and was able to show an improved stereoselectivity. Although those impressive reports have been published about this reaction, the introduction of new electrophiles for the synthesis of structurally more diversified compounds with high enantioselectivity remains a challenging task. Taking advantage of the high reactivity of malononitrile, we envisaged that the use of the more sterically congested β,β-disubstituted nitroolefins, such as α-substituted-β-nitroacrylate (**2**), as Michael reaction acceptors might improve the stereoselectivity of this reaction.

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Palladium-catalyzed intermolecular C–H amidation of indoles with sulfonyl azides

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A new kind of intermolecular indole C–H amidation reaction catalyzed by the most frequently used palladium catalyst has been developed. Sulfonyl azide was employed as an innovative nitrogen source and environmentally benign nitrogen was produced as the only byproduct.

C–H amidation, indole, palladium, sulfonyl azide

国家重点实验室 开放资源

1 Introduction

Methods of C–N bond formation have attracted particular attention of organic chemists due to the fact that nitrogen-containing molecules are ubiquitous in pharmaceuticals, agricultural chemicals, natural products and synthetic materials [1]. Among them, Ullmann reaction [2] and Buchwald-Hartwig amination [3] have been extensively investigated as efficient strategies using readily available pre-functionalized haloarenes. In recent years, transition metal-catalyzed direct amination of C–H bonds has emerged as a powerful tool without the need for pre-functionalized arenes [4,5]. However, this process usually requires external oxidants to complete the catalytic cycles [6]. Alternatively, electrophilic aminating agents [7], such as halogenated amines, have been successfully employed in C–H amination of arenes. However, generation of stoichiometric halogenated waste cannot be avoided. Recently, Chang's group [8] has demonstrated that sulfonyl azides could be used as novel amidation agents with environment benign N_2 as the sole byproduct in the absence of additional oxidants. After that, a surge of sulfonyl azide participated C–H amidation reactions have appeared in literatures [9,10]. Typically, these reactions are catalyzed by Rh, Ru and Ir using various directing groups. Palladium, the most frequently used transition-metal in C–H activation, has been absent from the feast.

Indole and its derivatives are always hot topics because of their wide existence in biologically relevant compounds [11]. As a result, much effort has been made to synthesis of indole through either construction or decoration of the indole cores [12]. The electron-rich character of indoles allows them to undertake direct C–H bond functionalization resulting in the formation of carbon-carbon or carbon-heteroatom bonds at C2 or C3 position. Previously, we have reported palladium-catalyzed C–H functionalization of indoles followed by isocyanide insertion [13]. Considering the electronic similarity between carbene and nitrene, we envisioned that C–H amidation of indoles with sulfonyl azide might take place using palladium catalyst (Scheme 1) [14].

2 Results and discussion

To test our hypothesis, we initiated the study by investigating the reaction of 2-phenylindole **1a** with *p*-methylbenzen-

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ONLINE SUPPLEMENTAL MATERIALS

Peroxisome proliferator-activated receptor γ inhibits pulmonary hypertension targeting store-operated calcium entry

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Research paper

Polymorphism in mature *microRNA-608* sequence is associated with an increased risk of nasopharyngeal carcinoma

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ABSTRACT

Accumulative evidences indicated that microRNAs (miRNAs) can function as tumor suppressors and oncogenes, in which genetic variations are implicated in various cancer susceptibilities. However, it remains unclear whether single nucleotide polymorphisms (SNPs) in mature miRNA sequence alter nasopharyngeal carcinoma (NPC) susceptibility. In this study, we analyzed associations between eight SNPs in miRNA mature sequences (i.e., rs3746444T>C in hsa-mir-499, rs4919510C>G in hsa-mir-608, rs13299349G>A in hsa-mir-3152, rs12220909G>C in hsa-mir-4293, rs2168518G>A in hsa-mir-4513, rs8078913T>C in hsa-mir-4520a, rs11237828T>C in hsa-mir-5579, and rs9295535T>C in hsa-mir-5689) and NPC susceptibility in southern China with 906 NPC cases and 1072 cancer-free controls, and validated the significant findings in eastern China with 684 cases and 907 healthy controls. Functional assays were further performed to identify the biological effects of these polymorphisms. We found that rs4919510C>G polymorphism showed a consistent association with NPC risk in southern China (GC + GG versus CC genotype, odds ratio [OR] = 1.36, 95% confidence interval [CI] = 1.10–1.70) and eastern China (GC + GG versus CC: OR = 1.37, 95% CI = 1.08–1.74). After the two populations were merged, the ORs and 95% CI were 1.38 and 1.18 to 1.62, respectively. Moreover, the rs4919510C>G adverse genotypes significantly interacted with Epstein–Barr virus (EBV) infection on increasing NPC risk ($P = 0.001$). The functional assay further showed that the CNE-2 cell lines that transfected with miR-608-rs4919510C allele expression vector exerted more colony number formations than cell lines that transfected with miR-608-rs4919510C allele expression vector ($P = 0.001$). These data suggested that rs4919510C>G of miR-608 may be a susceptible biomarker of NPC in China.

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignant tumor in most parts of the world with an incidence under 1/100,000 person-years, but it is one of highly prevalent malignancies in south China and southeast Asia, where the incidence rates range from 15 to 50/100,000 (Parkin et al., 2010; Yu and Yuan, 2002; Lo et al., 2004). The remarkable racial and geographic distributions of NPC indicate both genetic characteristics and that NPC is a malignancy with complex etiology involving both genetic and environmental factors (Chang and Adami, 2006). Numerous epidemiology studies have revealed Epstein–Barr virus (EBV) infection (Vasef et al., 1997) and some environmental factors such as intake of preserved foods (Armstrong et al., 1998) in NPC tumorigenesis. Previous genome-wide association studies (GWAS) also have identified that several single nucleotide polymorphisms (SNPs) are associated with the risk of NPC (Bei et al., 2010; Ng et al., 2009). Although significant progress has been provided into the etiology of NPC in recent decades, it remains highly prevalent and the main cause of cancer death in China. So searching for special susceptibility biomarker for NPC remains insistent and requisite.

MicroRNAs (miRNAs) are an abundant class of small non-coding RNA molecules that function as negative gene regulators by inhibiting translation or cleavaging target mRNAs through binding to their 3′-untranslated region (UTR) (Bartel, 2004). miRNAs are initially transcribed as primary miRNAs (pri-miRNAs) with several hundred nucleotides that are further processed into hairpin-structured precursor miRNAs (pre-miRNAs) and then into mature miRNAs consisting of approximately 22–25 nucleotides (Lee et al., 2002, 2003; Ryan et al., 2010). Strongly conserved among distantly related organisms, miRNAs have been found to be involved in various biologic processes, including cell proliferation,

Abbreviations: miRNA, microRNA; NPC, nasopharyngeal carcinoma; EBV, Epstein–Barr virus; MAF, minor allele frequency; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.

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Research Article

Polymorphisms of *NFκB1* and *IκBα* and Their Synergistic Effect on Nasopharyngeal Carcinoma Susceptibility

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Nasopharyngeal carcinoma (NPC) is a multifactoral and polygenic disease with high prevalence in Southeast Asia and Southern China. Environmental factors and genetic susceptibility play important roles in NPC pathogenesis. In the present study, we tested the hypothesis that single nucleotide polymorphisms (SNPs) in nuclear factor-kappa B (*NFκB*) and its inhibitor (*IκBα*) conferred consistent risks for NPC. Four putatively functional SNPs (*NFκB1*: rs28362491del>ins ATTG; *NFκB2*: rs12769316G>A; *IκBα*: rs2233406C>T and rs696G>A) were analyzed to evaluate their associations with NPC risk in total 1590 NPC cases and 1979 cancer-free controls. We found that the rs28362491 insATTG variants (ins/del + ins/ins) in *NFκB1* conferred an increased risk of NPC (odds ratio [OR] = 1.30, 95% confidenc interval [CI] = 1.09–1.55, and $P = 2.80 \times 10^{-3}$) compared with the del/del homozygous genotype. Th rs696AA variant in *IκBα* had an increased risk of NPC (OR = 1.41, 95% CI = 1.20–1.66, and $P = 2.28 \times 10^{-5}$) by decreasing *IκBα* expression due to the modulation of microRNA hsa-miR-449a. Furthermore, both adverse genotypes of *NFκB*/*IκBα* and their interaction also exerted an increased risk on NPC. Taken together, Our findi gs indicated that genetic variants in *NFκB1* (rs28362491del>ins ATTG) and *IκBα* (rs696G>A) and their synergistic effect might contribute to NPC predisposition.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy of the head and neck that originates from the epithelial lining of the nasopharynx [1]. The e were an estimated 84,400 incident cases of NPC and 51,600 deaths in 2008, representing about 0.7% of the global cancer burden [2]. NPC is rare in most parts of the world but is a leading malignancy in Southeast Asia and Southern China, with high incidence rate (40 per 100,000 person-years) [3, 4]. This distinctively geographic and ethnic distribution of NPC indicates that NPC is a malignancy with complex etiology involving both genetic and environmental factors [5].

Accumulating researches have revealed several well-established risk factors for NPC, such as Epstein-Barr virus (EBV) infection [6], certain dietary factors [7], and family history of cancer [8]. Studies have demonstrated that EBV is involved in direct carcinogenesis by triggering various cellular responses including the activation of inflammation [9, 10]. As a crucial inflammatory mediator, nuclear factor kappa-B (*NFκB*) and its endogenous inhibitors *NFκBI* (*IκB*) provide a critical mechanistic link between infl mmation and tumor [11–14]. It has been reported that many signal transduction pathways, originating from a wide multifarious cellular stimuli, converge on the *NFκB*/*IκB* complex playing an essential role in cell angiogenesis, cell adhesion, proliferation, antiapoptosis, and repressing immune response [15]. Furthermore, the abnormalities of *NFκB* signaling pathway provide the cells with the production of growth factors as well as resistance to apoptotic and genotoxic insults, contributing to multiple carcinogenesis processes including tumor initiation, promotion, invasion, and metastasis [16, 17].

Regular Article

Population Pharmacokinetics in China: The Dynamics of Intravenous Voriconazole in Critically Ill Patients with Pulmonary Disease

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Pharmacokinetic research in China on the use of voriconazole in critically ill adult patients with different pulmonary diseases remains to be explored. This study evaluated the population pharmacokinetics of the use of voriconazole (VRC) in critically ill patients to determine covariate effects on VRC pharmacokinetics by NONMEM, which could further optimize VRC dosing in this population. A one-compartment model with first-order absorption and elimination best fit the data, giving 4.28 L/h clearance and 93.4 L volume of distribution of VRC. The model variability, described as an approximate percentage coefficient of interindividual variability in clearance and volume of distribution, was 72.94% and 26.50%, respectively. A significant association between C_{min} and drug response or grade 2 hepatotoxicity was observed (p=0.002, <0.001, respectively, 1.5–4.0 μg/mL) *via* logistic multivariate regression. Monte Carlo simulations at 100, 150, 200, and 250 mg dosage predicted effectiveness at 45.99%, 99.76%, 98.76%, and 67.75% within the 1.5–4.0 μg/mL range, suggesting that a 150 or 200 mg intravenous dose twice daily is best suited to achieve the target steady state trough concentration range in critically ill patients with pulmonary disease.

Key words voriconazole (VRC); population pharmacokinetics; effective dose; safety; critically ill patient

Voriconazole (VRC) is a synthetic triazole derivative from fluconazole with better oral bioavailability and broader antifungal spectrum. VRC is the first-line agent in the treatment of infections caused by common fungal pathogens like *Aspergillus*, *Candida*, *Cryptococcus neoformans*, as well as less common pathogens as *Fusarium* and *Pseudallescheria*[1–3] in both normal fungal infected patients, and critically ill patients.[4] However, because of its large variability of plasma exposure,[5] VRC is criticized for its clinical inefficacy or toxicities in liver, central nervous system, ocular, and potential dose-related adverse reactions.[6] Previous studies showed that critically ill patients were confronted by increasing incidence of adverse reaction due to multiple reasons such as hypoalbuminemia or moderate renal function.[7,8] Moreover, when special treatments were carried out, the pharmacokinetic profile of VRC might display significant variations in critically ill patients, like extracorporeal membrane oxygenation and continuous venous hemofiltration.[4,9–11]

Moreover, the different CYP2C19 polymorphism,[12,13] body weight,[14] and life style[15] of Chinese population may result in a varied pharmacokinetic profile of VRC compared to that of westerner's. In addition, patients in the intensive care units (ICU) are more susceptive to fungal infections,[8] and suffered more complicated antifungal treatment due to their extreme body conditions and large concomitant drugs. Thus it's necessary to describe the VRC exposure in Chinese ICU patients in order to better understand its dosage–effect and –toxicity relationship. Herein, we presented the pharmacokinetic and dynamic study of VRC in Chinese critically ill patients with pulmonary diseases so as to provide further reference for the individualized VRC adjustment.

MATERIALS AND METHODS

Ethics Statement This study was a prospective and observational study that approved by the Scientific and Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (approval No. 201211) according to good clinical practice and applicable laws, as well as the declaration of Helsinki. Written informed consent was obtained from all participants themselves or their close relatives or guardians before enrollment.

Study Design In our hospital, ICU patients diagnosed with pulmonary diseases would take VRC therapy according to the advice from infectious diseases specialists either for prophylactic, empirical therapy, or based on the microorganism results. In details, patients received a loading dose of 300 mg VRC (VFEND, Injection, 200 mg, Pfizer, Ireland Pharmaceuticals Limited) followed by maintenance dose of 200 mg intravenous infusion every 12 h. For patients with abnormal renal function, diuretics were added and the dosages of drugs which were excreted through renal or had potential renal toxicity were adjusted. For patients with creatinine clearance (*CL*) less than 50 mL/min, VRC was stopped. For patients who displayed hepatic abnormality, the dosage of drugs being metabolized by liver or had potential hepatic toxicity were adjusted and hepatic protectant was added.

In this study, we enrolled adult patients (>18 years old) who received VRC therapy from March 2012 to May 2013 to build population pharmacokinetics of VRC in this special group. For these patients, VRC therapeutic drug monitoring (TDM) was a standard clinical care and determined the VRC

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Prevalence of 7 virulence genes of *Legionella* strains isolated from environmental water sources of public facilities and sequence types diversity of *L. pneumopila* strains in Macau

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Summary **In this study, we analyzed 7 virulence genes in 55 *Legionella* species (including 29 *L. pneumophila* and 26 non-*L. pneumophila* strains) which isolated from environmental water sources of the public facilities in Macau by using PCR and real-time PCR. In addition, 29 *Legionella pneumophila* isolates were subjected to genotyping by sequence-based typing scheme and compared with the data reported. The detection rate of *flaA*, *pilE*, *asd*, *mip*, *mompS*, *proA* and *neuA* genes in the *L. pneumophila* were 100.0%, respectively. The *neuA* gene was not detected in the non-*L. pneumophila* strains, but *flaA*, *pilE*, *asd*, *mip*, *mompS*, and *proA* genes could be amplified with a positive rate of 15.4%, 15.4%, 53.8%, 38.5%, 15.4%, and 38.5%, respectively. The results from real-time PCR were generally consistent with that of PCR. Those *L. pneumophila* strains were assigned into 10 sequence types (STs) and ST1 (9/29) was the dominant STs. Four new STs were found to be unique in Macau. The analysis of population structure of *L. pneumophila* strains which isolated from Macau, Guangzhou and Shenzhen indicated that the similar clones were existed and ST1 was the most prevalent STs. However, the distribution of the subtypes isolated from Macau was not the same extensive as those from Guangzhou and Shenzhen. The different detection rates of the 7 virulence genes in different species of *Legionella* might reflect their own potential for environmental adaptability and pathogenesis. And the data analyzed from STs diversity indicated the Macau *L. pneumophila* possessed obvious regional specificity and high genetic diversity.**

Keywords: Sequence-based typing, population structure, phylogenetic relationship

呼吸疾病国家重点实验室

1. Introduction

Legionella species, commonly found in the environment, are the major causative agents of Legionnaire's disease and Pontiac fever. They have been found to not only induce lung infection, but also to cause dysfunction of other organs, such as the heart, kidney and central nervous system (*1*). To date, more than 50 species of *Legionella* have been described (*2*). Among of them, 20 species are recognized as human pathogens. *L. pneumophila* was identified as primary culprit for Legionnaire's disease. In recent years, several studies related to the presence of *Legionella* have been reported in southern Chinese cities, such as Guangzhou, Shenzhen, Jiangmen and Hong Kong (*3,4*). However, no data of *Legionella* from Macau were published. In May of 2010, a case of *Legionella* infection emerged, which was vigorously suspected to be caused by local *Legionella* species since the patient did not previously travel abroad. We investigated and detected the existence of *Legionella* in natural and artificial water environments in Macau in the summer (from May to July) of the same year. A total of 55 isolates of *Legionella* were isolated from air conditioning cooling towers, fountains and

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Review Article

Prevention and Management of Lung Cancer in China

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Lung cancer is the leading cause of cancer-related death worldwide. In China, the incidence of lung cancer has grown rapidly, resulting in a large social and economic burden. Several researchers have devoted their studies to lung cancer and have demonstrated that there are many risk factors for lung cancer in China, including tobacco use, environmental pollution, food, genetics, and chronic obstructive pulmonary disease. However, the lung cancer incidence is still growing rapidly in China, and there is an even higher incidence among the younger generation. One explanation may be the *triple-neglect* situation, in which medical policies that neglect *prevention*, *diagnosis*, and *supportive care* have increased patients' mortality and reduced their quality of life. Therefore, it is necessary to enhance the efficiency of prevention and early diagnosis not only by focusing more attention on treatment but also by drawing more attention to supportive care for patients with lung cancer. ***Cancer* 2015;121:3080-8**. © *2015 American Cancer Society.*

KEYWORDS: chronic obstructive pulmonary disease, lung cancer, management, prevention.

INTRODUCTION

Lung cancer is the most common cancer worldwide, with more than 1.8 million new cases and almost 1.6 million deaths estimated in 2012.[1] Greater than one-third of all newly diagnosed lung cancers occurred in China, representing a heavy burden for the patients, families, society, and country. In China, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death. The risk factors associated with lung cancer have been well studied under limited conditions by medical staff engaging in lung cancer prevention. However, diagnosis often occurs so late that approximately two-thirds of patients have lost the opportunity for radical surgery. These patients usually die within 1 to 2 years. The 5-year survival rate was very low in 2008, and the estimated age-standardized (world) mortality rate in that year for lung cancer was 28.7 per 100,000 population in China, which was significantly higher than the world average (19.4 per 100,000 population).[2,3] One explanation for this discrepancy may be the *triple-neglect* situation, which indicates medical policies that neglect *prevention*, *diagnosis*, and *supportive care*, an approach that affects the mortality and quality of life of patients with lung cancer. Therefore, it is necessary to enhance the efficiency of prevention and early diagnosis not only by paying more attention to treatment but also by paying more attention to supportive care for patients with lung cancer.

The Incidence of Lung Cancer Has Been Growing Rapidly, Leading to High Social and Economic Burdens

Rapidly Growing Incidence

Although the massive registration of patients with lung cancer based on populations throughout the country has been difficult to conduct because of limited resources, many individuals have done a great deal of work. Cancer information is reported to the cancer registries from local hospitals and community health centers, including the Basic Medical Insurance Program for urban residents and the new Rural Cooperative Medical System. In 2008, the National Cancer Registry Program was launched by the Ministry of Health of China. Since then, the National Central Cancer Registry of China has

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Original Article

Prognosis and status of lymph node involvement in patients with adenocarcinoma in situ and minimally invasive adenocarcinoma—a systematic literature review and pooled-data analysis

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Background: Adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) have been brought up that substitute for bronchioloalveolar carcinoma (BAC), according to the new classification of lung adenocarcinoma. There has been increasing opinions that argues for the adjustment of lymph node disposition in patients with such early stage tumors. Therefore, we sought to overview the prognosis and status of lymph node involvement in AIS/MIA patients.

Methods: PubMed, Springer and Ovid databases were searched for relevant studies. Data was extracted and results summarized to demonstrate the disposition of lymph nodes in AIS/MIA.

Results: Twenty-three studies consisting of 6,137 lung adenocarcinoma were included. AIS/MIA accounted for 821 of the total 6,137. All included patients received curative surgery. After a review of the summarized data we found that only one patient (with MIA) had N1 node metastasis, N2 disease was not found in any of the included patients. In concordance with this, studies that reported 5-year disease free survival (5-year DFS) have almost 100% rate.

Conclusions: Our findings indicated that patients with AIS/MIA have good survival prognosis after surgical resection, and that recurrence and lymph node metastasis in these patients is rare. Therefore, we strongly encouraged further studies to determine the role of different lymph node disposition strategies.

Keywords: Adenocarcinoma in situ (AIS); minimally invasive adenocarcinoma (MIA); lymph node involvement

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Introduction

Lung cancer is the leading course of cancer-related mortality worldwide, and lung adenocarcinoma represents the most common histological subtype of lung cancer (1). In the past decade, numerous advances have taken place within various fields for lung adenocarcinoma, particularly in molecular biology with the discovery that EGFR and ALK biomarkers are responsive to targeted drugs. However, surgical resection is still the best option for patients with localized non-small cell lung cancer (NSCLC).

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Prognosis of synchronous and metachronous multiple primary lung cancers: Systematic review and meta-analysis

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ABSTRACT

Background: With the development of imaging technology, an increasing number of multiple primary lung cancers (MPLC) are diagnosed in recent years. However, there is still ambiguity in the stage classification rules for patients with MPLC. Our purpose was to access the prognosis of synchronous and metachronous MPLC.

Methods: A systematic literature search was performed on four databases (EBSCO, Pubmed, OVID and Springer) to obtain relevant articles. We used published hazard ratios (HRs) of overall survival (OS) if available or estimates from the published survival data.

Results: There were 1796 patients with MPLC in 22 relevant studies, who were eligible for analysis. We found that the OS of patients with synchronous MPLC was inferior to the one of metachronous MPLC patients when starting from the diagnosis of the first metachronous tumor (HR 3.36, 95% CI 2.39–4.74; $p < 0.001$). However, there was no difference when starting from the diagnosis of the second metachronous tumor (HR 1.19, 95% CI 0.86–1.66; $p = 0.29$). From further analysis we found the OS of patients with MPLC was superior to that of patients with intrapulmonary metastasis (HR 2.66, 95% CI 1.30–5.44; $p = 0.007$). Besides, we found no difference in OS between synchronous (HR 1.39, 95% CI 0.98–1.96; $p = 0.06$) and metachronous (HR 1.05, 95% CI 0.75–1.47; $p = 0.77$) patients, in spite of the histology. In terms of unilateral and bilateral MPLC patients, the OS had no difference either (HR 1.30, 95% CI 1.00–1.69; $p = 0.05$).

Conclusion: We found that MPLC had better OS than the lung cancer patients with intrapulmonary metastasis. And despite the tumor-free interval, the OS for metachronous MPLC was as good as that for synchronous MPLC. Furthermore, there was no difference of OS in different subgroups, including histology and position.

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1. Introduction

MPLC (multiple primary lung cancer) is classified as synchronous (occurring at the same time) and metachronous (occurring at different times). In 1924, Beyreuther et al. [1] first identified and reported two separate pulmonary lung cancers in one patient with tuberculosis, after that the incidence and diagnostic criteria for this condition were reported by others. The most commonly accepted criteria was outlined by Martini and Melamed [2] and modified by Antakli [3] (Table 1). In 2007, the American College of Chest Physicians [4] updated the diagnostic criteria, by adding additional clinical assessments such as lymph node and systemic metastasis, and revising the proposed interval between metachronous MPLC as at least 4 years.

Unfortunately the classification of MPLC has not reached consensus amongst three major lung cancer research institutes (American Joint Committee On Cancer (AJCC), Union for International Cancer Control (UICC), and International Association for the Study of Lung Cancer (IASLC)). The IASLC states that "multiple synchronous primary tumors should be staged separately" [5]. However, the following guideline documents present that, "The highest T category and stage of disease should be assigned and the multiplicity of the number of tumors should be indicated in parenthesis, e.g. T2(m) or T2(5)" [5]. Therefore the guideline in

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OPEN

Prognostic Significance of Programmed Cell Death 1 (PD-1) or PD-1 Ligand 1 (PD-L1) Expression in Epithelial-Originated Cancer

A Meta-Analysis

Yaxiong Zhang, MD, Shiyang Kang, MD, Jianfei Shen, MD, Jiaxi He, MD, Long Jiang, MD, Wei Wang, MD, Zhihua Guo, MD, Guilin Peng, MD, Gang Chen, MD, Jianxing He, MD, and Wenhua Liang, MD

Abstract: The expression of programmed cell death 1 (PD-1) and its ligand (PD-L1) has been observed in various epithelial-originated malignancies. However, whether the expression of PD-L1 on tumor cells or the expression of PD-1 on tumor-infiltrating lymphocytes (TILs) is associated with patients' survival remains controversial.

Electronic databases were searched for eligible literatures. Data of hazard ratio (HR) for overall survival (OS) with 95% confidence interval (CI) according to the expression status of PD-L1 or PD-1 evaluated by immunohistochemistry were extracted. The outcomes were synthesized based on random-effects model. Subgroup analyses were proposed.

Twenty-nine studies covering 12 types of epithelial-originated malignancies involving 7319 patients (2030/3641 cases for PD-L1 positive/negative, 505/1143 cases for PD-1 positive/negative) with available data of the outcome stratified by PD-L1/PD-1 status were enrolled. Epithelial-originated cancer patients with positive expression of PD-L1 on tumor tissues were associated with significantly poorer OS when compared to those with negative expression of PD-L1 (HR 1.81, 95% CI 1.33–2.46, $P < 0.001$). Similarly, patients with PD-1 positive expression on TILs had significantly shorter OS than the PD-1 negative group (HR 2.53, 95% CI 1.22–5.21, $P = 0.012$). In analyses of PD-L1, all subgroups showed consistent trends toward unfavorable prognoses of patients with positive PD-L1 expression, regardless of antibodies and evaluation cutoffs. Subgroup analyses on PD-1 were not available due to limited data.

PD-L1 or PD-1 expression status is a significant prognostic factor in epithelial-originated malignancies.

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Abbreviations: BC = breast cancer, CC = cervical carcinoma, CI = confidence interval, CRCC = clear cell renal cell carcinoma, CRC = colorectal cancer, EC = esophageal cancer, GC = gastric carcinoma, HCC = hepatocellular carcinoma, HR = hazard ratio, IFN-γ = interferon gamma, IL-2 = interleukin-2, MHC = major histocompatibility complex, NCRCC = nonclear cell renal cell carcinoma, NSCLC = nonsmall cell lung cancer, OS = overall survival, PC = pancreatic cancer, PD-1 = programmed cell death 1, PD-L1 = PD-1 ligand 1, SCLC = small cell lung cancer, TILs = tumor-infiltrating lymphocytes, TNF-α = tumor necrosis factor alpha, UCC = urothelial carcinoma.

INTRODUCTION

Improved understanding of the molecular mechanisms that govern the host response to tumors has led to the identification of checkpoint signaling pathways that limit the anticancer immune response.[1] Currently, blockade of the programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) signaling pathway has been proved one of the most promising immunotherapeutic strategies in boosting the immune system to fight against cancer.[2,3] Blocking PD-1 on tumor-infiltrating lymphocytes (TILs) or blocking PD-L1 on tumor cells results in the restoration of the functions of tumor-specific T cells. The reactivated T cells can initiate direct killing of tumor cells and secretion of immunostimulatory cytokines such as interferon gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor alpha (TNF-α).[4]

PD-L1 expression has been observed in various epithelial-originated malignancies, including carcinomas of the esophagus, gastrointestinal tract, pancreas, breast, lung, and kidney.[5,6] Several studies have found PD-L1 expression on tumor cells correlated with poor prognosis[7,8]; however, not all reports agree with this phenomenon.[9,10] In addition, the association between PD-1 expression on TILs and the survival of patients in several tumor types was also controversial.[11,12]

Therefore, whether the expression of PD-L1 on tumor cells or the expression of PD-1 on TILs is associated with the prognosis of epithelial-originated cancer remains unclear. A

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YZ, JH, and WL conceived and designed the experiments. YZ, SK, and JS carried out the search. JH, LJ, and WW extracted the data. ZG, GP, and GC assessed the quality of included studies. YZ and SK conducted the statistical analyses. YZ, JH, and WL wrote the manuscript. All of the authors conducted a primary revision.
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ORIGINAL ARTICLE

Prognostic value of ERCC1, RRM1, and TS proteins in patients with resected non-small cell lung cancer

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Abstract
Purpose Recent clinical trials showed that expression of excision repair cross-complementation group 1 (ERCC1), ribonucleotide reductase M1 (RRM1), and thymidylate synthase (TS) proteins was able to predict the effects of non-small cell lung cancer (NSCLC) to chemotherapy. However, it remains unknown whether the adjuvant chemotherapy based on expression of the three proteins has survival significance in Chinese NSCLC patients.
Methods We investigated 128 Chinese patients receiving chemotherapy after tumor resection for expression of these proteins using immunohistochemistry. Based on protein expression, patients were assigned to two groups for different adjuvant chemotherapy regimes. The disease-free survival (DFS) data were collected and analyzed using Kaplan–Meier curves and Cox models.
Results We found that DFS of these patients with carboplatin and a third-generation agent (gemcitabine or pemetrexed) stratified by protein expression showed no statistical difference between individual treatment versus non-individuation treatment analyzed using Kaplan–Meier method ($P = 0.143$, median 23.9 vs. 30.8 months). Furthermore, the multivariate analysis showed that histology and tumor stages were independent predictors for DFS in these patients.
Conclusions The results suggest that chemotherapy based on ERCC1, RRM1, and TS expression did not have significant impact on DFS of patients with resection of NSCLC.

Keywords Non-small cell lung cancer · Excision repair cross-complementation group 1 · Ribonucleotide reductase M1 · Thymidylate synthase · Chemotherapy

Introduction

Lung cancer is one of the most significant worldwide health problems [1]. Up to 80 % of lung cancer is non-small cell lung cancer (NSCLC), and NSCLC patients are usually diagnosed at the advanced stages of disease, which leaves curable surgery impossible [2]. Nevertheless, many clinical trials demonstrated that patients with complete NSCLC resection also benefited from cisplatin-based adjuvant chemotherapy [3]. To further improve the effects of the adjuvant therapeutic regimens, numerous hypotheses have emerged to increase prognosis by association of the treatment selections with tumor stage [4] or with pathology [5], while another adjuvant chemotherapy trial was based on expression of molecular biomarkers for selection of patients for treatment regimes [6]. Indeed, more and more studies indicate that molecular markers did help physician to stratify the patients for treatment options and showed treatment benefit [7–10]. Toward this end, different studies showed that expression of excision repair cross-complementation group 1 (ERCC1), ribonucleotide reductase M1

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AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology

Proton Channel Activity of Influenza A Virus Matrix Protein 2 Contributes to Autophagy Arrest

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Influenza A virus infection can arrest autophagy, as evidenced by autophagosome accumulation in infected cells. Here, we report that this autophagosome accumulation can be inhibited by amantadine, an antiviral proton channel inhibitor, in amantadine-sensitive virus infected cells or cells expressing influenza A virus matrix protein 2 (M2). Thus, M2 proton channel activity plays a role in blocking the fusion of autophagosomes with lysosomes, which might be a key mechanism for arresting autophagy.

Influenza viruses cause significant morbidity and mortality in humans (1, 2). An outstanding feature of the virus is its ability to regulate host cellular pathways for its benefit (3). Recent studies showed that influenza A virus perturbs the autophagy process in infected cells (4–6). Autophagy is an intracellular degradation process that can be divided into two stages. The first is the formation of autophagosomes in which the cytoplasmic materials, including cellular organelles, protein aggregates, and pathogens, are directed to the double-membrane vesicles. In the second, the matured autophagosomes fuse with lysosomes to form autolysosomes to degrade their contents (7). Autophagy is involved in both the sensing of and resistance to viruses invading the host. As a result, the viruses appear to have evolved mechanisms to subvert the autophagy response for their own benefit (8–10). Although influenza A virus has been shown to modulate the autophagy process (4, 5, 11–13), the underlying mechanism has remained not well defined.

To observe the effect of influenza A virus on autophagy, we used influenza viruses A/Hong Kong/8/68 (H3N2) and A/Wisconsin/33(H1N1) to infect HEK293 cells at a multiplicity of infection (MOI) of 5. We measured the relative amounts of autophagosome marker light chain 3 (LC3) proteins (lipidated LC3-II [16 kDa] and nonlipidated LC3-I [18 kDa]) in the cells at 12 h after infection. At that time point, the cells appeared healthy, without obvious signs of cell death. We also used a cell line stably expressing a green fluorescent protein (GFP)-LC3 fusion protein for easy observation of autophagosomes (14). Both influenza viruses A/Hong Kong/8/68 (H3N2) and A/Wisconsin/33 (H1N1) increased the autophagosome marker LC3-II level (Fig. 1A) and induced punctate LC3 perinuclear localization (Fig. 1B). These results demonstrated that influenza A virus infection can induce autophagosome accumulation, which was consistent with a previous report (4). We then used amantadine, an influenza A virus M2 proton channel blocker, and oseltamivir, an influenza A virus neuraminidase inhibitor, to assess if these two antiviral agents have any effect on autophagosome accumulation at the early stage of infection. Amantadine or oseltamivir was added at 3 h, and cells were harvested at 12 h postinfection for analysis. Surprisingly, amantadine can significantly block autophagosome accumulation in influenza virus A/Hong Kong/8/68(H3N2)-infected cells but not in influenza virus A/Wisconsin/33(H1N1)-infected cells (Fig. 1A and B). It is worth noting that influenza virus A/Hong Kong/8/68(H3N2) is sensitive to amantadine and influenza virus A/WS/33 (H1N1) is resistant to amantadine because of an S31N mutation on M2 (15). Oseltamivir showed no effect on autophagosome accumulation in response to both influenza A viruses, indicating that neuraminidase plays no role in autophagosome accumulation, at least in the early stage of infection (Fig. 1A and B). Our study suggested that the proton channel activity of M2 might play a role in modulation of the autophagy process, in contrast to a previous report that showed that its proton channel activity was not involved in autophagy arrest (4). To further investigate whether M2 proton channel activity is sufficient to induce autophagosome accumulation and because the constitutive expression of M2 is lethal to the cells, we generated TREx-293 cell lines carrying an amantadine-sensitive (S31) or -resistant (N31) mutant form of avian influenza A virus H5N1/Vietnam/1194/2004 M2 under the control of a tetracycline-inducible promoter (15, 16). These inducible M2-expressing cell lines enabled us to observe the sole effect of M2 without the interference of influenza A virus replication or other viral proteins. Upon the expression of either H5M2 (S31) or H5M2 (N31) with induction of tetracycline, we observed remarkable autophagosome accumulation in the cells, as shown by the increase in LC3-II in a Western blot assay (Fig. 1C). Consistent with influenza A virus infection, amantadine could inhibit the increase in LC3-II and perinuclear localization induced by amantadine-sensitive H5M2 (S31) (Fig. 1C and D). In GFP-LC3-transfected cells expressing H5M2(S31), both punctate LC3 in the perinuclear region and LC3 distribution to the plasma membrane could be observed if cells were weakly permeabilized

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CHEST

Quality Assessment of Clinical Practice Guidelines for Respiratory Diseases in China

A Systematic Appraisal

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BACKGROUND: There has been a significant increase in the publication of clinical practice guidelines (CPGs) for respiratory diseases in China. However, little is known about the quality and potential impacts of these CPGs. Our objective was to critically evaluate the quality of Chinese CPGs for respiratory diseases that were published in peer-reviewed medical journals.

METHODS: A systematic search of scientific literature published between 1979 and 2013 was undertaken to identify and select CPGs that were related to respiratory diseases. Four Chinese databases (the Chinese Biomedical Literature database [CBM], the China National Knowledge Infrastructure [CNKI], the VIP database, and the WANFANG database) were used. The quality of eligible guidelines was assessed independently by four reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The overall agreement among reviewers was evaluated using an intraclass correlation coefficient.

RESULTS: A total of 109 guidelines published in 27 medical journals from 1979 to 2013 were evaluated. The overall agreement among reviewers was considered good (intraclass correlation coefficient, 0.838; 95% CI, 0.812-0.862). The scores of the six AGREE domains were low: 57.3% for scope and purpose (range, 4.2%-80.5%), 23.8% for stakeholder involvement (range, 2.8%-54.2%), 7.7% for rigor of development (range, 0%-27.1%), 59.8% for clarity and presentation (range, 22.2%-80.6%), 10.9% for applicability (range, 0%-22.9%), and 0.6% for editorial independence (range, 0%-16.7%). Scores for all guidelines were below 60%, and only three guidelines (2.8%) were recommended for clinical practice with modifications.

CONCLUSIONS: The quality of the guidelines was low, and stakeholder involvement, rigor of development, applicability, and editorial independence should be considered in the future development of CPGs for respiratory diseases in China. CHEST 2015; 148(3):759-766

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ABBREVIATIONS: AGREE = Appraisal of Guidelines for Research and Evaluation; CPG = clinical practice guideline

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Case Report

Refractory Hyperlactatemia with Organ Insufficiency in Lipid Storage Myopathy

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Abstract

Lipid storage myopathy is a metabolic disorder characterized by abnormal lipid accumulation in muscle fibers and progressive muscle weakness.

Here, we report the case of a 17-year-old woman with progressive muscle weakness, refractory hyperlactatemia, and multiple organ insufficiency. Severe pneumonia was the initial diagnosis. After anti-infective treatment, fluid resuscitation, and mechanical ventilation, the patient's symptoms improved but hyperlactatemia and muscle weakness persisted. She was empirically treated with carnitine. Biochemical tests, electromyography, and muscle biopsy confirmed lipid storage myopathy. After 7 weeks of treatment, the patient resumed normal daily life.

An empirical treatment with carnitine may be beneficial for patients before an accurate diagnosis of lipid storage myopathy is made.

Key words: Carnitine, hyperlactatemia, lipid storage myopathy, respiratory failure, septic shock

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Introduction

Circulating free fatty acids are the major energy source for the muscle. Disorders of lipid metabolism can result in various metabolic myopathies and lead to muscle dysfunction. An example is lipid storage myopathy (LSM), which presents clinically as a globally progressive muscle weakness, sometimes accompanied by muscle atrophy. Pathologically, LSM is characterized by prominent lipid accumulation in muscle fibers.[1] Without typical symptoms, LSM is often misdiagnosed and mistreated. A definitive diagnosis requires careful pathological examinations that may take much time.

Here, we report the case of a 17-year-old woman with refractory hyperlactatemia, septic shock, multiple organ insufficiency, and progressive muscle weakness history. The patient was empirically treated with carnitine before LSM was histologically confirmed. The patient fully recovered after 7 weeks of treatment. Based on our experience, we recommend early empirical treatment with carnitine for patients suspected of LSM, prior to the pathologically confirmed diagnosis. Most metabolic myopathies respond poorly to treatment, but LSM can be effectively cured if diagnosed in a timely fashion. Timely treatment can effectively shorten the disease process, reduce complications, and decrease the economic burden of patients.

Case report

A 17-year-old female was admitted to our hospital after an 8-month history of pitting edema and weakness in the lower limbs with muscle soreness and occasional palpitation, exacerbated since one week ago. During the eight months, her blood creatine kinase (CK) levels were consistently elevated. A myogram suggested peripheral neurogenic damage, possibly resulting from polymyositis or Guillain-Barré syndrome. The patient was previously treated with high-dose steroid, γ-globulin, cyclophosphamide (Cytoxan) (2 months before admission to our hospital), as well as other supportive therapy. Her symptoms did not improve. She was slightly underweight, without coughing.

Physical examination revealed a heart rate of 125 beats/min, non-pitting edema of the lower limbs, slight edema of both hands, grade-4 strength in the upper limb muscles and grade 3 in the lower limb muscles. Lab tests showed lactic acid levels >12.0 mmol/L (normal, 0.7–2.1 mmol/L), pH 7.235–7.405, HCO_3 8.2–14.7 mmol/L, CK 734 U/L (normal, 10–190 U/L), and lactate dehydrogenase 1274 U/L (normal, 109–255 U/L). The chest X-ray was normal. The electrocardiogram showed sinus tachycardia and T wave changes. The ultrasonic cardiogram and cardiac function test revealed backflow through the tricuspid valve (median), pulmonary arterial hypertension (48 mmHg), slight pericardial effusion, ejection fraction 60%, and normal contraction. The myogram indicated neurogenic muscle damage. A diagnosis of polymyositis and bronchitis was made.

The patient experienced dyspnea five days after admission. Lab tests showed a NT-proBNP of 3294 pg/mL (normal, <155 pg/mL) and refractory hyperlactatemia. Arterial blood gas analysis indicated metabolic acidosis and respiratory alkalosis with pH 7.32, $PaCO_2$ 18.9 mmHg, PaO_2 121 mmHg, and HCO^-_3 9.4 mmol/L. Chest X-ray showed heart enlargement, pneumonia in double lower lobes of lung, pulmonary edema, and pericardial effusion. The patient was then transferred to the intensive care unit. Her muscle weakness, limb edema, and shortness of breath were aggravated. On admission to the ICU, physical examination revealed respiratory rate 30/min, heart rate 120–138 beats/min, SpO_2 100% (mask oxygenation <4 L/min), moist rales in double lower lungs, and negative pathological signs. Neurological exam-

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ORIGINAL PAPER

Risk factors shared by COPD and lung cancer and mediation effect of COPD: two center case–control studies

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Abstract
Purpose To reveal the shared risk factors for chronic obstructive pulmonary disease (COPD) and lung cancer, and to analyze the mediation effect of COPD during lung carcinogenesis.
Methods We conducted four independent case–control studies included 1,511 COPD patients and 1,677 normal lung function controls and 1,559 lung cancer cases and 1,679 cancer-free controls during 2002–2011 in southern and eastern Chinese.
Results Eight factors were observed to be consistently associated with both diseases risk, including pre-existing tuberculosis, smoking, passive smoking, occupational exposure to metallic toxicant, poor housing ventilation, biomass burning, cured meat consumption, and seldom vegetables/fruits consumption. Furthermore, smoking and biomass burning conferred significantly higher risk effects on lung cancer in individuals with pre-existing COPD than those without. COPD also had significant mediation effects during lung carcinogenesis caused by smoking, passive smoking, and biomass burning, which explained about 12.0 % of effect, 3.8 % of effect, and 6.1 % of effect of these factors on lung tumorigenesis in turn.
Conclusion Our study mapped a shared spectrum of etiological factors for both COPD and lung cancer in Chinese, and COPD acts as a mediator during lung cancer development. These observations should be in consideration for the prevention of both diseases.

Keywords COPD · Lung cancer · Case–control study · Risk factor · Mediation effect

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are the most striking lung diseases with high and increasing morbidity and mortality worldwide [1, 2]. In China, COPD has achieved a prevalence of 8.2 % in adults

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Ritonavir-boosted indinavir but not lopinavir inhibits erythrocytic stage *Plasmodium knowlesi* malaria in rhesus macaques

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ABSTRACT

The inhibitive activities of the human immunodeficiency virus protease inhibitors ritonavir (RTV) boosted indinavir (IDV) and RTV boosted lopinavir (LPV) for erythrocytic stage malaria were evaluated in rhesus macaques. The IDV/RTV regimen effectively inhibits the replication of *Plasmodium knowlesi* with clinically relevant doses, whereas the LPV/RTV regimen did not show activity against plasmodium infection.

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Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) and malaria are among the most prevalent infectious diseases worldwide. Approximately 35 million people were living with HIV in 2013. Sub-Saharan Africa is the most affected region, and seventy percent of HIV infected people are living in this region.[1] In 2013, an estimated 198 million cases of malaria caused 584,000 deaths, and most of the cases and deaths also occurred in sub-Saharan Africa.[2] Because the endemic regions of HIV and malaria overlap extensively, coinfection with both is common. Therefore, integrated control programs for these two diseases are particularly important.[3]

Previous studies have demonstrated that most HIV protease inhibitors (PIs) exert antimalarial effects in antiretroviral therapy (ART) regimens.[4–7] Among these, lopinavir (LPV) boosted by ritonavir (RTV) is actively used in malaria patients at clinically relevant doses.[4,5,8,9] Therefore, PI-containing antiretroviral regimens were presumed to have prophylactic activity against malaria in HIV-infected patients. Recently, Achan et al. reported that the incidence of malaria was lower among children receiving the LPV/RTV-based regimen than among those receiving the nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based regimen, as was the risk of a recurrence of malaria after treatment with artemether–lumefantrine in a clinical trial conducted in HIV-infected children who were 2 months to 5 years old.[10] However, Skinner-Adams and Porter reported that the frequency of malaria is similar among women receiving either LPV/RTV or nevirapine-based antiretroviral treatment, and that LPV/RTV had no apparent beneficial effect on the incidence of clinical malaria among HIV-infected adult women.[11,12] The discrepancies of published studies likely have to do with differences in study design, transmission intensities, statistical power, age ranges, etc.

Plasmodium knowlesi (*Pk*) is a monkey malaria parasite closely related to *Plasmodium vivax*,[13] and it causes a lethal infection in macaques and severe quotidian malaria in humans.[14,15] To investigate the antimalarial effect of LPV, *Pk* infected Chinese rhesus macaques were used in this study. We previously reported that indinavir (IDV) had anti-*Pk* infection potency in rhesus macaques,[16] therefore we compared the activities of LPV and IDV in current study. To mimic the clinical regimen, ritonavir (RTV)-boosted LPV or IDV combinations were used. In clinical regimens, the oral dosage of LPV/RTV is typically 800 mg/200 mg once daily, while IDV/RTV is typically administered at 800 mg/100 mg twice daily (note: RTV has no antimalarial activities at these dosages). Thus, we converted these clinical dosages to monkey dosages.[17] For the monkeys, LPV/RTV doses of 40 mg/kg and 10 mg/kg were administered intragastrically once daily, and IDV/RTV doses of 40 mg/kg and 5 mg/kg were administered twice daily. Treatment with LPV/RTV and IDV/RTV (Fig. 1) was initiated five days before the parasite inoculation, and was successively administered for sixty-three days. Malaria was initiated by an intravenous injection

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国家重点实验室

Original Article

Role of a Serum-Based Biomarker Panel in the Early Diagnosis of Lung Cancer for a Cohort of High-Risk Patients

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BACKGROUND: This study applied a combined cancer biomarker panel to clinically identify small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC) in a high-risk population. **METHODS:** The serum levels of 4 biomarkers (progastrin-releasing peptide [ProGRP], carcinoembryonic antigen [CEA], squamous cell carcinoma antigen [SCC], and cytokeratin 19 fragment [CYFRA21-1]) were determined in 153 patients with a high risk of lung cancer (12 with a new diagnosis of SCLC, 52 with NSCLC, and 89 without lung cancer). Information about diagnosis delays was collected through interviews of all participants. **RESULTS:** Significantly higher serum levels of ProGRP ($P<.0001$) were found among the SCLC patients versus the rest of the population. A receiver operating characteristic curve analysis established the cutoff values of ProGRP, CEA, SCC, and CYFRA21-1 as 300 pg/mL, 7.3 ng/mL, 3 ng/mL, and 6.5 ng/mL, respectively. The sensitivity and specificity of ProGRP in diagnosing SCLC were 75% and 100%, respectively. Among the 14 lung cancer patients with a false-negative computed tomography (CT) result, the diagnostic panel detected 8 additional cancers. **CONCLUSIONS:** This panel increased the diagnostic specificity for high-risk subjects (those with renal failure being excluded), and auxiliary to a CT scan, it increased the sensitivity for patients with lung cancer. These results might be applied to shorten the diagnosis delay at health care institutions in China. ***Cancer*** **2015;121:3113-21.** *© 2015 American Cancer Society.*

KEYWORDS: biomarker, delayed diagnosis, non–small cell lung cancer, progastrin-releasing peptide (ProGRP), small cell lung cancer.

INTRODUCTION

Currently, lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide.[1] Lung cancer has replaced liver cancer to become the top killer among malignant tumors in China for the past 3 decades, during which the registered mortality rate for lung cancer increased by 465%.[2,3] Among lung cancer deaths, 87% are attributable to cigarette smoking.[4] The mortality rate of lung cancer is approximately 23 times higher for current male smokers and 13 times higher for female smokers versus lifelong nonsmokers.[5] A population-based, cross-sectional study estimated the total number of lung cancer deaths in China to be 493,348 (338,346 males and 155,002 females) in 2008.[6] The variations in lung cancer mortality rates between males and females seen in China and across other countries reflect differences in the stages and degrees of the tobacco epidemic.[7-10]

Diagnosis of Lung Cancer

The early diagnosis and accurate staging of lung cancer for early and appropriate treatment are among the main strategies for improving the dismal 5-year survival rates[11]; however, several studies have investigated the diagnostic delay for lung

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Da-Wei Yang, Yong Zhang, and Qun-Ying Hong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Da-Wei Yang contributed to the study design, laboratory work, intellectual discussion of the results, statistical analysis, and writing of the article and approved the submitted article. Yong Zhang contributed to the study design and subject recruitment and approved the submitted article. Qun-Ying Hong contributed to the subject recruitment and laboratory work and approved the submitted article. Jie Hu, Chun Li, and Qun Wang contributed to the subject recruitment and approved the submitted article. Bai-Shen Pan, Fei-Hong Ding, Jia-Xian Ou, Fang-Lei Liu, Dan Zhang, and Jie-Bai Zhou contributed to the laboratory work and approved the submitted article. Yuan-Lin Song contributed to the study design and intellectual discussion of the results and approved the submitted article. Chun-Xue Bai contributed to the application for the study grant, study design, subject recruitment, and intellectual discussion of the results and approved the submitted article.

The first 3 authors contributed equally to this article.

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Role of *folP1* and *folP2* Genes in the Action of Sulfamethoxazole and Trimethoprim Against Mycobacteria

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The combination of trimethoprim (TMP) and sulfamethoxazole (SMX) has been shown to be active against *Mycobacterium tuberculosis* (Mtb) in clinical tuberculosis (TB) treatment. However, the mechanism of action of TMP-SMX against Mtb is still unknown. To unravel this, we have studied the effect of TMP and SMX by deleting the *folP2* gene in *Mycobacterium smegmatis* (Msm), and overexpressing the Mtb and Msm *folP1/2* genes in Msm. Knocking out of the *folP2* gene in Msm reduced the minimum inhibitory concentration of SMX 8-fold compared with wild type. Overexpression of the *folP1* genes from Mtb and Msm increased the MICs by 4- and 2-fold in Msm for SMX and TMP, respectively. We show a strong correlation between the expression of *folP1* and *folP2* genes and TMP-SMX resistance in mycobacteria. This suggests that a combination of FolP2 inhibitor and SMX could be used for TB treatment with a better outcome.

Keywords: Mycobacteria, sulfamethoxazole, trimethoprim, *folP1*, *folP2*

呼吸疾病国家重点实验室

Introduction

Tuberculosis (TB) is a chronic disease caused by *Mycobacterium tuberculosis* (Mtb). The emergence of multidrug resistance (MDR), defined as resistance to at least the two main first-line anti-TB drugs, rifampicin and isoniazid; extensively drug resistance (XDR), defined as MDR strains that are also resistant to a fluoroquinolone and at least one second-line injectable agent such as amikacin, kanamycin (KAN), or capreomycin; and the more severe totally drug resistance (TDR), defined as Mtb strains resistant to all first- and second-line anti-TB drugs, is an urgent medical and public health concern, as the available anti-TB drugs exhibit limited efficacy [20, 26]. Development of new drugs is time-consuming, difficult, and expensive. However, if already existing clinically established effective drugs could be used for treatment of TB, then faster and cheaper drug development coupled with effective TB management would be attained.

Sulfamethoxazole (SMX) and trimethoprim (TMP) are such potential candidates for TB treatment, having been used in drug regimens for the treatment of various bacterial infections of the respiratory, urinary, and gastrointestinal tracts for more than 40 years [1, 10]. TMP and SMX target successive steps of the folate biosynthesis pathway. SMX inhibits the dihydropteroate synthase (DHPS) activity, which catalyzes the addition of dihydropterindiphosphate to *p*-aminobenzoic acid (PABA), a structural analog of SMX. The product of DHPS, 7,8-dihydropteroate (DHP), reacts with glutamate to form dihydrofolate (DHF), which is reduced to tetrahydrofolate (THF) by dihydrofolate reductase (DHFR), the target of TMP (Fig. 1). Bacteria, fungi, and plants synthesize folate *de novo*, but mammals lack DHPS and therefore cannot produce folate. THF is an essential co-factor involved in the transfer of a one-carbon unit and is implicated in the biosynthesis of purines and pyrimidines and in the biosynthesis and catabolism of some amino acids. The combination of TMP and SMX

Original Article

Screening for pectus excavatum among primary students and establishment of a pectus excavatum screening program in Dongguan, China

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Objective: To carry out pectus excavatum (PEx) screening among primary school students in Dongguan, with an attempt to establish a PEx screening program and provide epidemiological evidences for developing guidelines on the diagnosis and treatment of PEx for young children.

Methods: A total of 479,402 primary school students who were already in school in 2012 or newly enrolled in 2013 from 422 primary schools in 32 towns in Dongguan, Guangdong Province were screened for PEx. Meanwhile, about 420 medical staff from the infirmaries of 422 primary schools were provided with a serial of training, with an attempt to establish a PEx screening program and network.

Results: Valid screening results were obtained from 477,627 pupils (99.62%) from 406 primary schools in 31 towns. These students aged 4-15 years (mean: 8.78 years), among whom there were 244,545 males (N_1; mean age: 8.22 years) and 233,082 females (N_2; mean age: 8.89 years). Totally 257 PEx patients were identified, yielding a prevalence of 0.583%, among whom there were 176 males (N_3; mean age: 8.79 years) and 81 females (N_4; mean age: 8.77 years). With the PEx patients as the PEx group and the healthy children as the control group, chi square test with gender as the dependent variable showed that the incidence of PEx was significantly different between male and female students (P=0.00) (N_3:N_4 =2.172:1). In addition, 410 medical staff from the school infirmaries were trained, and a PEx screening program and network was established.

Conclusions: The screening for PEx was successfully performed among pupils who were already in school in 2012 or newly enrolled in 2013 from 422 primary schools in Dongguan, Guangdong Province. Statistical analysis showed that the incidence of PEx differed between male and female pupils. A stable effective PEx screening program was established, which will provide personal and technical supports for the early diagnosis and treatment of this condition.

Keywords: Pectus excavatum (PEx); census; screening network

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Original Article

Screening for pectus excavatum among primary students and establishment of a pectus excavatum screening program in Dongguan, China

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Objective: To carry out pectus excavatum (PEx) screening among primary school students in Dongguan, with an attempt to establish a PEx screening program and provide epidemiological evidences for developing guidelines on the diagnosis and treatment of PEx for young children.

Methods: A total of 479,402 primary school students who were already in school in 2012 or newly enrolled in 2013 from 422 primary schools in 32 towns in Dongguan, Guangdong Province were screened for PEx. Meanwhile, about 420 medical staff from the infirmaries of 422 primary schools were provided with a serial of training, with an attempt to establish a PEx screening program and network.

Results: Valid screening results were obtained from 477,627 pupils (99.62%) from 406 primary schools in 31 towns. These students aged 4-15 years (mean: 8.78 years), among whom there were 244,545 males (N_1; mean age: 8.22 years) and 233,082 females (N_2; mean age: 8.89 years). Totally 257 PEx patients were identified, yielding a prevalence of 0.583%, among whom there were 176 males (N_3; mean age: 8.79 years) and 81 females (N_4; mean age: 8.77 years). With the PEx patients as the PEx group and the healthy children as the control group, chi square test with gender as the dependent variable showed that the incidence of PEx was significantly different between male and female students (P=0.00) (N_3:N_4 =2.172:1). In addition, 410 medical staff from the school infirmaries were trained, and a PEx screening program and network was established.

Conclusions: The screening for PEx was successfully performed among pupils who were already in school in 2012 or newly enrolled in 2013 from 422 primary schools in Dongguan, Guangdong Province. Statistical analysis showed that the incidence of PEx differed between male and female pupils. A stable effective PEx screening program was established, which will provide personal and technical supports for the early diagnosis and treatment of this condition.

Keywords: Pectus excavatum (PEx); census; screening network

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Review Article

Sepsis and ARDS: The Dark Side of Histones

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Despite advances in management over the last several decades, sepsis and acute respiratory distress syndrome (ARDS) still remain major clinical challenges and the leading causes of death for patients in intensive care units (ICUs) due to insuffici t understanding of the pathophysiological mechanisms of these diseases. However, recent studies have shown that histones, also known as chromatin-basic structure proteins, could be released into the extracellular space during severe stress and physical challenges to the body (e.g., sepsis and ARDS). Due to their cytotoxic and proinfl mmatory effects, extracellular histones can lead to excessive and overwhelming cell damage and death, thus contributing to the pathogenesis of both sepsis and ARDS. In addition, antihistone-based treatments (e.g., neutralizing antibodies, activated protein C, and heparin) have shown protective effects and have signific ntly improved the outcomes of mice suffering from sepsis and ARDS. Here, we review researches related to the pathological role of histone in context of sepsis and ARDS and evaluate the potential value of histones as biomarkers and therapeutic targets of these diseases.

1. Introduction

Over the last several decades, severe sepsis and acute respiratory distress syndrome (ARDS) have been the most common causes of mortality in critically ill patients [1–3]. During these years, a growing number of advanced interventions and strategies have been applied to critically ill patients. Pharmacological interventions, including antithrombin III [4], tifacogin [5], vasoactive drugs [6, 7], and activated protein C [8], have been proven to be helpful. Moreover, the strategies of mechanical ventilation are of vital importance. With an increasing use of noninvasive positive-pressure ventilation, a reduction in tidal volume, and an increase in applied positive end-expiratory pressure [9], the mortality of critically ill patients with sepsis and ARDS has gradually decreased over the last decade [9, 10]. However, the mortality rates still remain unacceptably high, with a 20 to 30% mortality rate from sepsis [11] and a mortality rate greater than 40% from ARDS [12].

Despite advanced developments in life support management (e.g., ventilators, dialysis, and extracorporeal membrane oxygenation), these interventions are not specifi for blocking or targeting the pathogenic processes of these diseases. Therefore, a comprehensive treatment for critical illness should include not only alleviating the pain but also targeting the underlying pathological mechanism. However, the underlying mechanisms of ARDS and sepsis remain largely unknown. Sepsis and ARDS result from complex events such as infections, trauma, burning, and acid aspiration [13], which trigger innate and adaptive immune responses. Th complexity of these processes involves complement system activation, neutrophil infiltration, vascular endothelial system damage, coagulation cascades promotion, and barrier dysfunction [14, 15]. Therefore, for a better understanding of the pathophysiological process of sepsis and ARDS, additional molecular mechanisms need to be explored.

It appears to be widely accepted that investigating the targets that are abnormally expressed in critically ill patients and in animal models holds promise for identifying new underlying molecular mechanisms. Recently, it has been reported that histones, as basic and important structural

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Clinical Cancer Research

Sequence Variation in Mature MicroRNA-499 Confers Unfavorable Prognosis of Lung Cancer Patients Treated with Platinum-Based Chemotherapy

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Abstract

Purpose: This study was implemented to investigate the associations between SNP in mature microRNA (miRNA) sequence and lung cancer prognosis and to verify the function of those SNP.

Experimental Design: Eight SNPs (rs3746444T>C in hsa-mir-499, rs4919510C>G in hsa-mir-608, rs13299349G>A in hsa-mir-3152, rs12220909G>C in hsa-mir-4293, rs2168518G>A in hsa-mir-4513, rs8078913T>C in hsa-mir-4520a, rs11237828T>C in hsa-mir-5579, and rs9295535T>C in hsa-mir-5689) were analyzed in a southern Chinese population with 576 patients with lung cancer, and the significant results were validated in two additional cohorts of 346 and 368 patients, respectively. A series of experiments were performed to evaluate the relevancies of those potentially functional SNPs.

Results: We found that the microRNA-499 rs3746444T>C polymorphism exhibited a consistently poor prognosis for patients with lung cancer in the discovery set [HR, 1.24; 95% confidence interval (CI), 1.02–1.49; $P = 0.028$], in the validation set I (HR, 1.31; 95% CI, 1.01–1.71; $P = 0.048$) and in the validation set II (HR, 1.45; 95% CI, 1.12–1.86; $P = 0.004$). The adverse effect of CT/CC variants was more remarkable in patients receiving platinum-based chemotherapy. Further functional assays demonstrated that the rs3746444C variant allele influences the expression of several cancer-related genes and affects lung cancer cells' proliferation and tumor growth *in vivo* and *in vitro* via the cisplatinum resistance.

Conclusion: Our findings suggested that the rs3746444T>C polymorphism in mature miR-499 sequence could contribute to poor prognosis by modulating cancer-related genes' expression and thus involve tumorigenesis and anti-chemotherapy, which may be a useful biomarker to predict lung cancer patients' prognosis. *Clin Cancer Res; 1–12. ©2015 AACR.*

Introduction

Lung cancer is one of the most fatal human malignancies, which ranks the No. 1 incidence and cancer-related death among tumors in the world and China (1). Despite of much research effort in treatment for lung cancer in recent decades, the 5-year survival rate is still poor as less than 20% (2). Evidences revealed that patients with lung cancer with similar stages or histologic classifications have dramatically different responses to anticancer therapies and distinct survival outcomes, likely due to heterogeneity of gene/protein expression profiles (3). Established methods for predicting prognosis include the tumor, node, and metastasis (TNM) staging system; however, accumulating studies indicated that genetic biomarkers might play a vital role in cancer prognosis, according to their influences on cancer progression and treatment efficiency (4, 5). Therefore, seeking distinctive molecular biomarkers and genetic variants of the key genes involved tumor initiation and progression may promote improving survival outcomes for human cancers.

MicroRNAs (miRNA) are an abundant class of small noncoding, single-stranded RNAs of 21 to 24 nucleotides gene products, which has been conjectured miRNAs regulating the expression of approximately one third of human genes (6, 7), by distinctive mechanisms of perfect or imperfect base pairing with target mRNAs at the 3′-untranslated region(UTR) or protein-coding sequences(CDS), leading to mRNA cleavage or translational repression (8, 9). The biogenesis of miRNAs is a complex process and miRNAs are initially transcribed into a long noncoding RNA known as the primary miRNA (pri-miRNA) that are then processed in the nucleus into about 70-nt miRNA precursor (pre-miRNA) with hairpin-shaped. Pre-miRNAs are further processed into 21 to 24 nt mature miRNAs (10–12). Emerging evidences have indicated that miRNAs are involved in a wide diversity of biologic processes, including cell-cycle regulation, differentiation, proliferation, development, and apoptosis (13–15). Furthermore, miRNAs have been extensively associated with the etiology and clinical outcome of human malignancies, which

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Original article

Six-minute walk test in Chinese adults with clinically stable bronchiectasis: association with clinical indices and determinants

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Abstract

Background:
The profiles of 6-minute walk distance (6MWD) in adults with clinically stable bronchiectasis in Chinese adult patients with bronchiectasis are unclear.

Objectives:
To delineate the 6MWD by stratification of clinical indices, and to investigate the factors associated with reduced 6MWD in Chinese adults with clinically stable bronchiectasis.

Methods:
We recruited 141 adult bronchiectasis patients (mean age: 44.3 ± 13.9 years). Demography, radiology, spirometry, diffusing capacity, etiology, sputum bacteriology, modified Medical Research Council dyspnea scale (MMRC) and quality of life were assessed. The safety profile of the measurement was also examined.

Results:
Lower levels of 6MWD were associated with older age (>50 years), higher HRCT total score, presence of cystic bronchiectasis, bilateral bronchiectasis, reduced diffusing capacity, higher MMRC score, and higher SGRQ scores. Correlation coefficients between 6MWD and spirometry and quality of life scores were different in patients with 6MWD higher and lower than lower limit of normal. D_LCO being less than 80% predicted (OR = 3.13, 95% CI: 1.32–7.43, $P = 0.01$) and MMRC scale between 1 and 4 (OR = 6.42, 95% CI: 2.27–18.18, $P < 0.01$) were the factors associated with 6MWD being less than the lower limit of normal (80% predicted value). No severe adverse events were reported.

Conclusion:
The 6MWD could be safely measured in adult patients with bronchiectasis and is poorly associated with clinical parameters. D_LCO less than 80% predicted and higher MMRC scale are independent predictors of 6MWD below the lower limit of normal. Our findings will provide a reference for management of bronchiectasis patients in mainland China.

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Skp1 in lung cancer: clinical significance and therapeutic efficacy of its small molecule inhibitors

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国家重点实验室

ABSTRACT

Skp1 is an essential adaptor protein of the Skp1-Cul1-F-box protein complex and is able to stabilize the conformation of some ubiquitin E3 ligases. However, the role Skp1 plays during tumorigenesis remains unclear and Skp1-targeting agent is lacking. Here we showed that Skp1 was overexpressed in 36/64 (56.3%) of non-small cell lung cancers, and elevated Skp1 was associated with poor prognosis. By structure-based high-throughput virtual screening, we found some Skp1-targeting molecules including a natural compound 6-*O*-angeloylplenolin (6-OAP). 6-OAP bound Skp1 at sites critical to Skp1-Skp2 interaction, leading to dissociation and proteolysis of oncogenic E3 ligases NIPA, Skp2, and β-TRCP, and accumulation of their substrates Cyclin B1, P27 and E-Cadherin. 6-OAP induced prometaphase arrest and exerted potent anti-lung cancer activity in two murine models and showed low adverse effect. These results indicate that Skp1 is critical to lung cancer pathogenesis, and Skp1 inhibitor inactivates crucial oncogenic E3 ligases and exhibits significant therapeutic potentials.

INTRODUCTION

The S phase kinase-associated protein 1 (Skp1)–Cullin 1 (Cul1)–F-box protein (SCF) complexes are multi-protein E3 ubiquitin ligase complexes that promote the ubiquitination and degradation of a large number of regulatory proteins involved in diverse processes [1]. Accumulative evidence demonstrates that components of SCF complexes play pivotal roles in tumorigenesis [2]. For example, Cul1 is increased in melanoma and breast and lung cancers, and is able to promote cancer cell proliferation [3, 4, 5]. Many of the F box proteins function as oncoproteins (e.g., Skp2, NIPA and β-TRCP) or tumor suppressors (e.g., Fbxw7) [1, 2]. Skp2 is overexpressed in human cancers [6] and is able to promote degradation of p27 [7] and activation of Akt, leading to cancer initiation and progression [8, 9]. β-TRCP activates NFκB by mediating ubiquitination and degradation of IκBα [10], and enhances β-Catenin transcriptional activity [11]. Skp1 is the essential adaptor protein linking the F-box protein and Cul1 [12, 13,

Sleep apnoea: a major and under-recognised public health concern

Sleep-related breathing disorders, particularly obstructive sleep apnoea syndrome (OSAS), are highly prevalent and represent an increasing part of clinical respiratory practice. OSAS represents something of a paradox in clinical medicine. On the one hand, the clinical disorder has been widely recognised only in recent decades, although the sleeping characteristics of OSAS have been recognised in the medical and classical literature for centuries. On the other hand, OSAS is now recognised to be highly prevalent with recent prevalence figures approaching those of asthma and chronic obstructive pulmonary disease (1,2), and there is increasing evidence that OSAS is associated with many adverse sequelae, both behavioural and physical. Behavioural features include daytime sleepiness, impaired memory and concentration, whereas physical consequences include cardiovascular and metabolic disorders (3). Although sleep apnoea was first described as a specific clinical entity in the late 1950s, there are several descriptions in earlier clinical journals that clearly refer to the disorder. The sleeping characteristics of obstructive apnoea were clearly described by Broadbent (4) in the late nineteenth century: "there will be perfect silence through two, three, or four respiratory periods, in which there are ineffectual chest movements; finally air enters with a loud snort, after which there are several compensatory deep inspirations".

In 1965, Gastaut and co-authors (5) provided the first comprehensive account of OSAS, describing polysomnography in obese hypersomnolent patients with frequent nocturnal apnoeas. During the following decade, the clinical (6) and pathophysiological (7) features of OSAS were described and it became clear that the pathophysiological basis of obstructive apnoea fundamentally relates to a narrowed upper airway. This narrowing is partly genetic in origin, but acquired factors such as obesity also contribute (8). Upper airway narrowing compromises the balance between collapsing forces affecting the upper airway during inspiration and the counteracting forces of upper airway dilating muscles (9). Although early research focused on clinical and pathophysiological aspects, more recent research has increasingly focused on genetic and molecular factors (10,11), particularly in the development of comorbid conditions, such as cardiovascular and metabolic disease. Although much has been learnt, substantial knowledge deficits remain, and the basic mechanisms and consequences of OSAS represent an exciting area for future research.

The relatively recent clinical and pathophysiological descriptions of OSAS are surprising given that the disorder is so highly prevalent, affecting up to 10% of adult males and 3% of adult females in the developed world (2), and this prevalence is growing in parallel with the growing prevalence of obesity. However, many of these cases are clinically unsuspected, since the two most common symptoms of loud snoring and a tendency to fall asleep during the daytime are often considered normal variants, and patients frequently do not seek medical attention. Unfortunately, many patients who do seek medical attention are dismissed as having no significant illness, without formal assessment, and it is very common for patients who have been symptomatic for many years to present to sleep clinics (12).

The failure to recognize clinically significant OSAS is particularly unfortunate for many reasons. First, the condition carries significant morbidity and mortality, and is associated with an increased risk of heart attack and stroke (13), in addition to a significant risk of automobile accidents and injury in the workplace as a consequence of excessive sleepiness (14). Secondly, the condition is very treatable, and severe forms of OSAS can respond dramatically well to the continued home use of nocturnal nasal continuous positive airway pressure (CPAP) therapy. Additional clinical challenges in the assessment and management of OSAS include the presentation of sleep apnoea without sleepiness and the differing clinical presentations of sleep apnoea in the elderly (15), in children (16), and in females (17). Although OSAS has traditionally been regarded as a disease affecting males, there is increasing recognition that the disease is also prevalent in females, particularly after the menopause, and that the clinical manifestations may differ from those in males (17). Sleep apnoea is very prevalent in the elderly population, but affected patients appear to be relatively less symptomatic (15), and the disorder may have less severe clinical consequences in this age group.

The physical morbidity of OSAS relates principally to the cardiovascular system (13) although there is increasing evidence of independent associations with metabolic disease also, particularly diabetes mellitus (18). Systemic hypertension occurs in

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Perspective

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Small Molecule Discoidin Domain Receptor Kinase Inhibitors and Potential Medical Applications

Miniperspective

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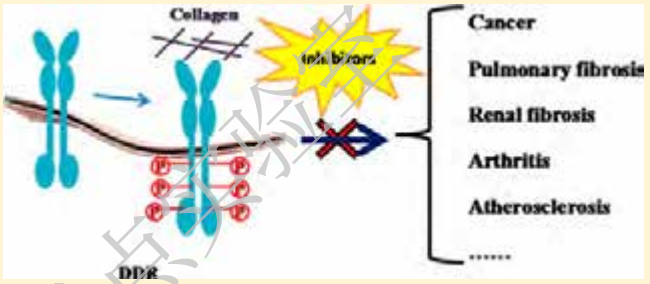
ABSTRACT: Discoidin domain receptors (DDRs) are members of the transmembrane receptor tyrosine kinase (RTK) superfamily which are distinguished from others by the presence of a discoidin motif in the extracellular domain and their utilization of collagens as internal ligands. Two types of DDRs, DDR1 and DDR2, have been identified with distinct expression profiles and ligand specificities. These DDRs play important roles in the regulation of fundamental cellular process, such as proliferation, survival, differentiation, adhesion, and matrix remodeling. They have also been closely linked to a number of human diseases, including various fibrotic disorders, atherosclerosis, and cancer. As a consequence, DDRs have been considered as novel potential molecular targets for drug discovery and increasing efforts are being devoted to the identification of new small molecule inhibitors targeting the receptors. In this review, we offer a contemporary overview on the discovery of DDRs inhibitors and their potential medical application for the treatment of cancer and inflammation related disorders.



INTRODUCTION

Discoidin domain receptors (DDRs) are members of the transmembrane receptor tyrosine kinase (RTK) superfamily discovered in the early 1990s.[1] They are structurally distinguished from other RTKs by the presence of a discoidin motif in the extracellular domain. Two types of DDRs, DDR1 and DDR2, with distinct expression profiles and ligand specificities have been identified. DDR1 has five splice variants, DDR1a, DDR1b, DDR1c, DDR1d, and DDR1e, generated by alternative splicing or deletion of exons, while DDR2 has only one isoform. DDR1a, DDR1b, and DDR1c encode full-length enzymatically active receptors,[1g,2] but DDR1d and DDR1e are predicted as kinase-deficient receptors because of their truncated or kinase deficient cytosolic fragment (Figure 1).[3]

Typical RTKs use peptide-like growth factors as ligands, but DDRs are activated by various types of triple-helical collagens which are the most abundant components of the extracellular matrix (ECM).[4] Specifically, DDR1 can bind to essentially almost all types of collagens identified to date, while DDR2 shows a preference for type I, II and III fibrillar collagens, and nonfibrillar type X collagen.[4,5] In addition to their ligand specificities, DDR1 and DDR2 also display distinct expression profiles. DDR1 is widely expressed in epithelial cells in lung, kidney, colon, and brain, whereas DDR2 is primarily expressed in mesenchymal cells including fibroblasts, myofibroblasts, smooth muscle cells, and chondrocytes in kidney, skin, lung, heart, and connective tissues.[1]

Studies have demonstrated that both DDR1 and DDR2 are important for the regulation of fundamental cellular processes, such as proliferation, survival, differentiation, adhesion, and matrix remodeling.[6] Dysregulation of the receptors is closely related to a number of human diseases, including fibrotic disorders (e.g., renal fibrosis and pulmonary fibrosis, etc.), atherosclerosis, and cancer.[6] Thus, DDR1 and DDR2 have been considered as novel potential molecular targets for drug discovery, and development of small molecule DDR inhibitors may lead to new and attractive therapeutic strategies for the treatment of cancer or various inflammation-related disorders. This review provides an updated overview on the discovery of DDR inhibitors and their potential application to the treatment of cancer and inflammation-related disorders. Audiences are also encouraged to read the recent comprehensive reviews to get extensive knowledge on the biological background of DDRs.[6]

STRUCTURAL DETAILS OF DDRS

Similar to the structural arrangement of classic RTKs, DDR1 and DDR2 consist of three fundamental elements: an extracellular domain, a transmembrane domain, and an intracellular domain with intrinsic enzymatic activity (Figure 1). Distinctively, DDRs contain, in the extracellular region, a

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Small-Molecule BET Inhibitors in Clinical and Preclinical Development and Their Therapeutic Potential

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Ke Ding

Abstract: Lysine acetylation is a pivotal mechanism in chromatin processes and the regulation of gene transcription. The acetylated lysine residues of histones are exclusively recognized by bromodomains (BRDs) known as epigenetic reader. Proteins containing BRDs undergo a post-translational modification (PTM) with development of cellular signaling and disease biology. The bromo and extra-terminal (BET) proteins are the second subfamily, which play important roles in cellular proliferation, cell cycle progression and chromatin compaction. Recently, a variety of small molecules have been reported to interact with the BET family proteins and accelerate the validation of BET proteins as druggable targets for treatment of cancers, inflammation and related diseases. In this review, we will summarize the small-molecule inhibitors in clinical and preclinical studies of the BET family bromodomains and their medicinal implications.

Keywords: Acetyl-lysine (KAc) binding pocket, Bromodomain (BRDs), Bromo and extra-terminal (BET) proteins, Medicinal implications, Selectivity, Small-molecule inhibitors.

1. INTRODUCTION

Epigenetics is "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states" [1]. Epigenetic events are mainly driven by DNA methylation, histone modifications and nucleosome remodeling. Histone modifications (also referred to as "histone code") undergo epigenetic alterations through post-translational modifications (PTMs) such as acetylation, methylation, phosphorylation, ribosylation, ubiquitination, sumoylation and acylation [2, 3]. Histone code, leading to the idea of "writers" (PTM marks), "readers" (recognition of the marks) and "erasers" (removal of the marks), plays important roles in epigenetic regulations [4]. Among a variety of histone modifications, lysine acetylation is a widespread protein modification that regulates chromatin biology and gene transcriptions. The acetylation of lysine leads to neutralization of charge of this amino acid, which significantly affects protein functions [5]. The bromodomain (BRD) family of proteins known as epigenetic readers exclusively recognizes the acetylated lysine residues of histones [5]. Especially , the bromo and extra-terminal (BET) proteins (BRD2, BRD3, BRD4, and BRDT), which are the second subfamily of bromodomains, have increasingly received much attention [6]. On the account of the therapeutic potential in cancer, inflammatory and infectious disease, considerable efforts have been made to develop BET selective\ small-molecule bromodomains inhibitors since the first two selective nanomolar inhibitors almost simultaneously reported [7, 8]. In this review, we seek to summarize the small-molecule inhibitors in clinical and preclinical studies of the BET family bromodomains and their medicinal implications.

2. BIOLOGY

2.1. Bromodomains Structure

Bromodomains are firstly named after the *Drosophilia* gene *brahma* [9], and they contain approximately 110 amino acid motifs. There are 61 BRDs within 46 distinct proteins encoded in human genome, which cluster into eight families based on structure or sequence similarity. Bromodomains have been identified in a variety of nuclear proteins like histone acetyltransferases (HATs), ATP-dependent chromatin-remodeling complexes, helicases, methyltransferases, transcriptional coactivators, transcriptional mediators, nuclear-scaffolding proteins, and the BET family (Table **1**) [10].

The first three-dimensional structure of BRD disclosed by Dhalluin and colleagues is the transcriptional co-activator p300 /CBP associated factor (PCAF) [11]. Almost all bromodomains contain a conserved fold of a left-handed bundle of four helices (α_Z, α_A, α_B, and α_C), which are connected by a hydrophobic pocket formed by the ZA loop (a long loop between helices α_Z, and α_A) and BC loop (the loop linking helices α_B, and α_C) (Fig. **1A**). The sequence similarity of the large bromodomain family in ZA loop and BC loop is not very high with the major sequence variations. ZA loop is more structurally flexible and is connected to the dynamic binding with acetyl-lysine, and BC loop comprises a hydrophobic pocket serving to stabilize the structure as well as to

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Spirometric Reference Values for Healthy Han Children Aged 5–15 Years in Guangzhou, Southern China

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Summary. Background: Reliable interpretation of spirometry rests on appropriate reference values, but there are few published reference values for healthy children in China. Objective: To develop the updated spirometric normative values for healthy children aged 5–15 years in Guangzhou, southern China, and to explore the differences by comparison with published reference values. Methods: In this cross-sectional study, health questionnaire and physical examination conducted for screening healthy Han children. Spirometry was performed by well-trained technicians according to American Thoracic Society guidelines. Using Lambda-Mu-Sigma (LMS) algorithm, predicted equations for the median and lower limits of normal were derived for forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), and maximal mid-expiratory flow ($FEF_{25–75\%}$). Predicted values were compared with other published spirometric reference equations. Results: Data were obtained from 422 healthy children (226 boys and 196 girls) aged 5–15 years. Spirometric parameters showed moderate-to-strong positive correlations with age, height, and weight in both genders, with height being the most crucial predictor. There were significant differences between spirometric values and other published reference values. Spirometric values were comparable with the data derived from the same area population in 2002, with exception of increased height and weight in the equivalent age groups. Conclusions: The present spirometric reference equations are feasible for assessment of lung function among children in southern China. Further studies for establishment of reference values for Chinese children in other regions are needed. **Pediatr Pulmonol. 2015;50:1009–1016.**

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Key words: children; lung function; normative value; reference equations; spirometry.

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INTRODUCTION

Spirometry plays a pivotal role in the clinical evaluation and management of respiratory diseases. It is a relatively simple, non-invasive, and useful method to assess children with pulmonary disorders, and has been applied in the early detection of pediatric respiratory diseases and monitoring normal growth. The interpretation of spirometric results rests largely on the reference values,[1] therefore their accuracy has important implications for individuals and health-care practice.[2]

It has been well documented[3–6] that spirometric reference values varied across different ethnic groups. China is a large country with a vast territory and a wide variety of ethnic groups. To avoid incorrect interpretation of spirometry in a population by using predicted values derived from a different ethnicity, establishment of reference values based on specific populations in different geographical regions is warranted.[2] However, there have been few published spirometry reference values for healthy children in China and currently available

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Conflict of interest: None.

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Sputum bacteriology in steady-state bronchiectasis in Guangzhou, China

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SUMMARY

BACKGROUND: The impact of potentially pathogenic micro-organisms (PPMs) on Chinese patients with steady-state bronchiectasis is unknown.

METHODS: Peripheral blood and sputum were sampled to determine inflammatory markers and sputum bacterial density. Spirometry and diffusing capacity were measured. Quality of life was assessed using the St George's Respiratory Questionnaire.

RESULTS: Of 144 patients with steady-state bronchiectasis, *Pseudomonas aeruginosa* was isolated in 44 cases (30.6%). Compared with other PPMs, *P. aeruginosa* had a more pronounced influence on airway inflammation and spirometry, but not on systemic inflammation or quality of life. The impact of PPMs other than *P. aeruginosa* on clinical indices was similar. Bacterial density was not correlated with most clinical parameters. Factors associated with PPM isolation included bronchiectasis symptoms for ⩾10 years (OR 2.13) and ⩾4 bronchiectatic lobes (OR 2.82). Having ⩾4 exacerbations within 2 years (OR 2.18) and cystic bronchiectasis (OR 2.23) was associated with the colonisation of PPMs, i.e., isolating an identical PPM on at least two occasions within 1 year.

CONCLUSION: In patients with steady-state bronchiectasis in Guangzhou, *P. aeruginosa* is the most common organism causing heightened airway inflammation and poor lung function. PPM isolation or colonisation should be suspected in case of longer duration of symptoms, multilobar bronchiectasis, frequent exacerbation and cystic bronchiectasis.

KEY WORDS: bronchiectasis; *Pseudomonas aeruginosa*; bacterial density; airway inflammation; systemic inflammation; lung function

BRONCHIECTASIS IS DRIVEN by the vicious cycle of 'infection–inflammation–airway destruction'[1] frequently triggered by bacteria. Clinically, potentially pathogenic micro-organisms (PPMs) isolated from bronchiectasis patients primarily comprise *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*.[2] These bacteria trigger airway inflammation,[3–6] biofilm formation[7] and oxidative stress,[8,9] which promote progressive airway destruction, possibly via the release of matrix metalloproteinases into bronchial mucosa.[10–12] Mucoid *P. aeruginosa* strains were associated with more significantly increased levels of airway matrix metalloproteinase-8 and -9, which are synergistically related to poorer lung function and frequent exacerbations (Guan et al., unpublished data). However, different PPMs elicit various effects on bronchiectasis. *P. aeruginosa* has been associated with pronounced airway inflammation and poorer lung function.[13,14]

In bronchiectasis, host-immune responses, environmental factors and ethnicity may be responsible for the differences in PPM acquisition and clearance. Cystic fibrosis patients are frequently colonised with *S. aureus*[2] and immunocompromised subjects with *P. aeruginosa*.[15] *H. influenzae* was isolated from 32∼40% of sputum samples in Western countries[16,17] and 7.5∼12.8% in Hong

WJG, YHG and GX contributed equally to the study.

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国家重点实验室

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ORIGINAL ARTICLE

Sputum matrix metalloproteinase-8 and -9 and tissue inhibitor of metalloproteinase-1 in bronchiectasis: Clinical correlates and prognostic implications

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ABSTRACT

Background and objective: **The triplet of airway infection, inflammation and bronchial wall destruction associated with excessive matrix metalloproteinases (MMP) release and imbalance of tissue inhibitor metalloproteinase-1 (TIMP-1) is implicated in bronchiectasis. We sought to determine the associations between sputum MMP (MMP-8, MMP-9) and TIMP-1 and the severity of bronchiectasis; the utility of MMP in predicting risks of future bronchiectasis exacerbations (BE); and the changes in MMP levels during BE.**

Methods: **We recruited 102 patients with stable bronchiectasis and 22 healthy subjects. For bronchiectasis patients, baseline measurements consisted of sputum inflammation and MMP measurements, bacterial culture, spirometry and chest high-resolution computed tomography (HRCT). Bronchiectasis patients were followed up for 1 year to determine the frequency of BE. Changes in MMP levels during BE were assessed in 36 bronchiectasis patients.**

Results: **Sputum MMP-8, MMP-9 and MMP-9/TIMP-1 ratio in bronchiectasis patients were significantly increased compared with healthy subjects. MMP-8 and MMP-9 levels, but not TIMP-1, were positively correlated with clinical measures, including HRCT scores, spirometry and *Bronchiectasis Severity Index*. Seventy-nine bronchiectasis patients were included in survival analyses of BE. Lower levels of baseline MMP-9 were associated with reduced risks of and a longer time to the first BE during follow-up. MMP-8 and MMP-9, but not TIMP-1 or MMP-9/TIMP-1 ratio, were significantly heightened during BE.**

Conclusions: **Sputum MMP might be useful biomarkers for the assessment of bronchiectasis severity and the prediction of future risks of BE. Our results provide the rationales for the future clinical application of MMP inhibitors.**

SUMMARY AT A GLANCE

Excessive MMP release and the imbalance of their inhibitors are implicated in bronchiectasis pathogenesis. Our study showed that MMP-8 and MMP-9 levels significantly correlated with clinical measures of bronchiectasis, and that baseline MMP-9 levels predicted future risks of exacerbations, which may offer rationales for future clinical application of MMP inhibitors.

Key words: Bronchiectasis, bronchiectasis exacerbation, disease severity, lung function, matrix metalloproteinase.

Abbreviations: BE, bronchiectasis exacerbation; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL, interleukin; MMP, matrix metalloproteinases; TIMP-1, tissue inhibitor metalloproteinase-1; TNF, tumour necrosis factor

INTRODUCTION

Bronchiectasis is a chronic airway suppurative disease that harbours the triplet of airway infection, inflammation and bronchial wall destruction[1] associated with excessive matrix metalloproteinase (MMP) release in airways.[2] Markedly increased MMP-8 and MMP-9 (markers closely linked to neutrophilic inflammation) in bronchoalveolar lavage fluid[3] and bronchial lamina propria[4] have been detected in bronchiectasis. Increased MMP have been associated

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Original Article

Study on risk factors and phenotypes of acute exacerbations of chronic obstructive pulmonary disease in Guangzhou, China—design and baseline characteristics

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Background: To describe a study design that focuses on risk factors and patterns of chronic obstructive pulmonary disease (COPD) exacerbations.

Methods: A 2-year, single centre, observational study was conducted in Guangzhou in China. The study enrolled 318 subjects with COPD aged 40-79 years, stratified into different but equally sized groups according to global initiative for chronic obstructive lung disease (GOLD) stage (including Stage 0) and 86 lung healthy controls. An assessment each year was scheduled including questionnaires, lung function testing, Chest X-ray and blood collection. A sub-group, called sub-group X, consisting of 203 subjects with COPD and 51 lung healthy controls, was selected to answer a symptom questionnaire daily (EXACT-PRO) via a BlackBerry Personal Digital Assistant (PDA) device. Upon an alert that indicated a change in daily symptom pattern, the patients were contacted by the clinic to decide whether they had experienced an exacerbation and should have an extra visit within 24-48 hours. At an extra visit, nasal and throat swabs, induced sputum and blood were collected. Air pollution, temperature and humidity were also monitored daily. A subset of sub-group X, called sub-group M that consisted of 52 COPD patients and 15 healthy controls was dedicated to measure muscle strength and a dexa scan.

Results: More than 78 % of the enrolled patients completed the study successfully. There appeared a difference between the patient groups and the controls in gender, age, body mass index (BMI), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC and smoking at baseline. In sub-group X 90 out of 203 (44.4%) selected COPD patients developed one or more exacerbations in the 2-year observation period. They were more severe COPD patients according to GOLD stage at study start. On average most exacerbations occurred in the month March and the least number of exacerbations occurred in October.

Conclusions: This study with the obtained patient dataset will allow a better insight in many aspects of exacerbations in COPD (e.g., the identification, the risk factors, phenotypes and the biomarkers).

Keywords: Chronic obstructive pulmonary disease (COPD); exacerbations; study design; demographics; China

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Surface Confined Retro Diels–Alder Reaction Driven by the Swelling of Weak Polyelectrolytes

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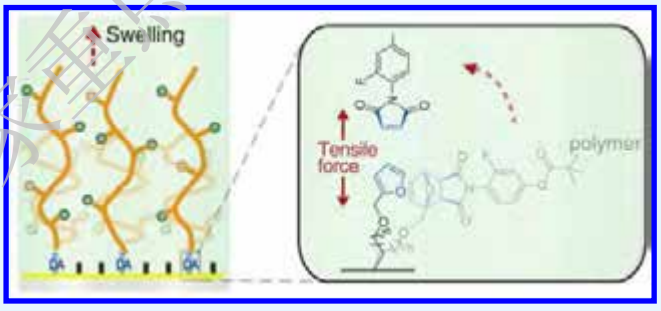
Supporting Information

ABSTRACT: Recently, the type of reactions driven by mechanical force has increased significantly; however, the number of methods for activating those mechanochemical reactions stays relatively limited. Furthermore, in situ characterization of a reaction is usually hampered by the inherent properties of conventional methods. In this study, we report a new platform that utilizes mechanical force generated by the swelling of surface tethered weak polyelectrolytes. An initiator with Diels–Alder (DA) adduct structure was applied to prepare the polyelectrolyte-carboxylated poly(OEGMA-r-HEMA), so that the force could trigger the retro DA reaction. The reaction was monitored in real time by quartz crystal microbalance and confirmed with atomic force microscopy and X-ray photoelectron spectroscopy. Compared with the conventional heating method, the swelling-induced retro DA reaction proceeded rapidly with high conversion ratio and selectivity. A 23.61 kcal/mol theoretical energy barrier supported the practicability of this retro DA reaction being triggered mechanically at ambient temperature. During swelling, the tensile force was controllable and persistent. This unique feature imparts this mechanochemical platform the potential to "freeze" an intermediate state of a reaction for in situ spectroscopic observations, such as surface-enhanced Raman spectroscopy and frequency generation spectroscopy.



KEYWORDS: *mechanochemistry, retro Diels–Alder reaction, polyelectrolyte, polymer brush, quartz crystal microbalance*

INTRODUCTION

Mechanically facilitated chemical deformations in polymers, such as bond dissociation and isomerization, have been realized with various methods.[1−5] However, the understanding of the mechanisms of the mechanochemical deformations has been lagging behind, largely due to the difficulty in monitoring reactions in real time. As for the solution-state methods such as sonication and flow fields, reactions are usually characterized ex situ with optical/fluorescent spectroscopy, such as the gel permeation chromatography or nuclear magnetic resonance spectroscopy.[6,7] Efforts have been taken to monitor reaction dynamics, but entirely in situ analyses are still highly wanted.

In the current study, we report a new mechanochemical platform that is potentially compatible with in situ analyzing techniques. In this platform, the target bond was embedded into the chains of surface-tethered weak polyelectrolyte brush–carboxylated poly(OEGMA-r-HEMA), which was tethered on gold surface on one end (Scheme 1a). When exposed to salt solutions, the ionized polyelectrolyte chains would repulse to each other and extend perpendicularly to the surface due to electrostatic interactions, which is referred to as the swelling

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RESEARCH ARTICLE

Surveillance for Seasonal Influenza Virus Prevalence in Hospitalized Children with Lower Respiratory Tract Infection in Guangzhou, China during the Post-Pandemic Era

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files. The data points used to determine any summary statistics presented in the figures and tables have been included.

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Abstract

Background

Influenza A(H1N1)pdm09, A(H3N2) and B viruses have co-circulated in the human population since the swine-origin human H1N1 pandemic in 2009. While infections of these subtypes generally cause mild illnesses, lower respiratory tract infection (LRTI) occurs in a portion of children and required hospitalization. The aim of our study was to estimate the prevalence of these three subtypes and compare the clinical manifestations in hospitalized children with LRTI in Guangzhou, China during the post-pandemic period.

Methods

Children hospitalized with LRTI from January 2010 to December 2012 were tested for influenza A/B virus infection from their throat swab specimens using real-time PCR and the clinical features of the positive cases were analyzed.

Results

Of 3637 hospitalized children, 216 (5.9%) were identified as influenza A or B positive. Infection of influenza virus peaked around March in Guangzhou each year from 2010 to 2012, and there were distinct epidemics of each subtype. Influenza A(H3N2) infection was more frequently detected than A(H1N1)pdm09 and B, overall. The mean age of children with influenza A virus (H1N1/H3N2) infection was younger than those with influenza B (34.4 months/

Predictive value of *BRCA1* expression on the efficacy of chemotherapy based on anti-microtubule agents: a pooled analysis across different malignancies and agents

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Contributions: (I) Conception and design: Q He, J He, W Liang; (II) Administrative support: None; (III) Provision of study materials or patients: M Zhang, J Zhang, S Zhong, Y Liu, J Shen, J He; (IV) Collection and assembly of data: M Zhang, J Zhang, S Zhong, Y Liu, L Jiang, C Yang, Y Zeng, M Guo, X Chen; (V) Data analysis and interpretation: Q He, X Chen, W Liang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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呼吸疾病国家重点实验室

Background: Breast cancer susceptibility gene 1 (*BRCA1*) expression has been suggested as a predictor in anti-neoplastic treatment with anti-microtubule agents. However, the existing evidence is conflicting. Consulting the literature, we sought to examine the true impact of *BRCA1* expression on the efficacy of anti-microtubule agents.

Methods: Medline by PubMed and Embase databases were searched for eligible studies. The primary endpoints were objective response rate (ORR) and progression free survival (PFS). Additional subgroup analyses stratified for detection methods, regimen, and patient origin were also performed.

Results: A total of 13 relevant studies involving a total of 1,490 cases were enrolled. Involved agents included paclitaxel, docetaxel and vinorelbine. Malignancies included non-small cell lung cancer, gastric cancer, esophageal carcinoma, ovarian carcinoma, malignant pleural mesothelioma, breast cancer, and small cell lung cancer. Through meta-analyses, we observed a potentially greater ORR in the population with high *BRCA1* expression *vs.* low *BRCA1* expression (OR 1.63, 95% CI: 0.92 to 2.88, P=0.09) but the heterogeneity is severe (P=0.01; I^2=61%). Similar results were observed in PFS (high *vs.* low expression, HR 0.93, 95% CI: 0.75 to 1.15, P=0.49; heterogeneity, P<0.01, I^2=75%). After stratification by testing methods, a significantly higher ORR in the population with high *BRCA1* expression was shown in the subgroup using mRNA as a quantitative method (OR 2.90, 95% CI: 1.92 to 4.39, P<0.01; I^2=0) whereas the difference in the subgroup using immunohistochemistry (IHC) was not significant (OR 0.60, 95% CI: 0.33 to 1.10, P=0.10; I^2=0). Stratification by regimen (platinum-based *vs.* non platinum-based) and patient origin (Asian *vs.* Caucasian) did not reduce the heterogeneity.

Conclusions: Although the predictive value of *BRCA1* expression on the anti-microtubule chemotherapy remained uncertain based on overall results, our exploratory analyses suggested that detection using mRNA might be a preferred technique, however, further validation is required to substantiate our findings.

Keywords: Breast cancer susceptibility gene 1 (*BRCA1*); anti-microtubule agents; meta-analysis

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Synthesis and biological evaluation of 3,5-disubstituted-4-alkynylisoxozales as a novel class of HSP90 inhibitors

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ABSTRACT

A series of 3,5-disubstitute-4-alkynylisoxazole derivatives were designed and synthesized through palladium(II)–copper(I) catalyzed Sonogashira cross-coupling reaction of an alkynyl moiety and an isoxazole scaffold as novel HSP90 inhibitors. The resultant compounds displayed moderate to potent binding affinity to HSP90 proteins, and also demonstrated good cell growth inhibitory activity against various cancer cell lines (A549, K562, MCF-7, DU145 and Hela). Some compounds (**18d**, **18e**, **19a**, **19d**, **20c** and **20q**) show similar or better binding affinity towards HSP90α and HSP90β comparing to NVP-AUY922. In addition, compounds **18e**, **19a** and **20q** exhibited potent inhibitory activity against various human cancer cell lines.

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Heat shock proteins (HSPs) are a family of stress proteins that act as protective factors against misfolding of various essential proteins involved in maintaining cell functionality. Among the HSPs, HSP90 is a ubiquitous ATP-dependent molecular chaperone that represents about 1–2% of total proteins in normal cells. However, it may increase up to 4–6% under stress conditions, such as in tumors.[1–4] There are two subtypes of HSP90, HSP90α and HSP90β. Functionally, both subtypes are similar, having both tissue and substrate specificity.[5] It is well established that HSP90 plays a vital role in maintaining the stability, conformation and function of a variety of signaling proteins that are involved in pathways associated with cell cycle progression, cellular proliferation, invasion and metastasis. Furthermore, many of the client proteins of HSP90 including AKT, vascular endothelial growth factor (VEGF), human epidermal growth factor receptor 2 (Her2), MET, and ALK, are involved in signal transduction, cell cycle regulation and apoptosis. HSP90 is associated with a variety of co-chaperones and ATP to form a mature complex. When the competitive inhibitors occupy the ATP-binding site of HSP90, the complex is disrupted and the client proteins are degraded. Some client proteins of HSP90 are key oncogenic proteins, which make it an attractive therapeutic target for cancer therapy.[6–9] HSP90 is also essential for homodimerization and binding of client proteins, co-chaperones and other accessory proteins operating in a chaperone cycle.[10] Inhibition of HSP90 triggers disruption of folding cycle, leading to proteasomal degradation of client proteins, which causes loss of function and, thus, inhibition of cell growth.[11–13]

HSP90 has higher ATPase activity with higher binding affinity to HSP90 inhibitors in tumor cells than in normal cells.[14] Although a variety of HSP90 inhibitors have been identified since the clinical evaluation of natural-product-based HSP90 inhibitor, Geldanamycin analogs 17-AAG and 17-DMAG (Fig. 1). Many of these compounds have been reported to have unwanted side effects.[15–24] It is therefore desirable to develop new and potent inhibitors with improved specificity for HSP90.

NVP-AUY922, a 4,5-diarylisoxazole-based HSP90 chaperone inhibitor developed by Vernalis, entered clinical trials in 2007.[25] Various analogues of NVP-AUY922 were also evaluated for their binding affinities to HSP90α protein and their cell growth inhibitory activities against various tumor cell lines, such as HCT-116, NCI-H460 or A549. Several of the analogues displayed potent HSP90 binding affinity and cell growth inhibitory activity (Fig. 1).[26–29] Based on these results, we designed and synthesized a series of new alkynes-linked isoxazole scaffolds to investigate their inhibitory activities for human HSP90α and HSP90β proteins, and further to determine their anti-proliferative activity against tumor cell lines. While maintaining the interactions of the resorcinol OH groups and C-3 amide, we speculated that the introduction

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The cystic fibrosis transmembrane conductance regulator as a biomarker in non-small cell lung cancer

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Abstract. An increased risk of non-small cell lung cancer (NSCLC) in cystic fibrosis (CF) patients and carriers of CF transmembrane conductance regulator (CFTR) mutations has been proposed. However, the role of CFTR in lung cancer remains controversial. In the present study, CFTR expression was assessed in 165 NSCLC tumors and 22 normal lung samples with validation in an independent series of 131 samples. The effect of gain and loss of CFTR on the malignant behavior of NSCLC was examined. The effect of CFTR manipulation on tumor metastasis was examined in a mouse model. Expression of CFTR was downregulated in NSCLC (P=0.041). Low CFTR expression was correlated with advanced stage (P<0.001) and lymph node metastasis (P=0.009). Low CFTR expression was significantly associated with poor prognosis (overall survival: 45 vs. 36 months, P<0.0001; progression-free survival: 41 vs. 30 months, P=0.007). Knockdown of CFTR in NSCLC cells enhanced malignant behavior (epithelial-mesenchymal transition, invasion and migration); in contrast, overexpression of CFTR suppressed cancer progression *in vitro* and *in vivo*. The tumor-suppressing effect of CFTR was associated with inhibition of multiple uPA/uPAR-mediated malignant traits in culture. These results show that CFTR plays a role in inhibition of NSCLC metastasis and suggest that CFTR may serve as a novel indicator for predicting adverse prognosis and metastasis in NSCLC patients.

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Key words: lung cancer, cystic fibrosis transmembrane conductance regulator, epithelial-mesenchymal transition, prognosis

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignancies with increasing incidence worldwide (1-3). Despite the advances in early detection and improvements in the treatment, long-term survival from NSCLC still remains poor. Tumor relapse and metastasis are the main factors influencing patient prognosis. The identification of biomarkers that can predict the risk of recurrence and metastasis is therefore clinically important.

The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-activated anion channel which is expressed ubiquitously in epithelial tissues. Germline mutations in the gene encoding CFTR cause recessive cystic fibrosis (CF) (4,5). Over the last three decades, long-term survival rate for CF patients has significantly improved but an elevated risk of cancer is being recognized to be associated with survivorship. Intriguingly, an increased risk of cancer, primarily of the gastrointestinal tract, has been reported in some, but not all studies in the carriers of CFTR mutations (6-10). Hypermethylation of the CFTR promoter is frequently seen in a number of different tumor types, including lung cancer (11-13), suggesting DNA methylation-mediated transcription silencing of CFTR may influence cancer development (9,14,15). Of note, both mutation and hypermethylation of CFTR have been identified in NSCLC patients (12,16).

By analyzing a series of tumors from 296 lung cancer patients we have shown that aberrant CFTR expression level is significantly associated with NSCLC progression, metastasis and poor prognosis. We have also shown that suppression of

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The draft genome, transcriptome, and microbiome of *Dermatophagoides farinae* reveal a broad spectrum of dust mite allergens

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Background: A sequenced house dust mite (HDM) genome would advance our understanding of HDM allergens, a common cause of human allergies.

Objective: We sought to produce an annotated *Dermatophagoides farinae* draft genome and develop a combined genomic-transcriptomic-proteomic approach for elucidation of HDM allergens.

Methods: A *D farinae* draft genome and transcriptome were assembled with high-throughput sequencing, accommodating microbiome sequences. The allergen gene structures were validated by means of Sanger sequencing. The mite's microbiome composition was determined, and the predominant genus was validated immunohistochemically. The allergenicity of a ubiquinol-cytochrome c reductase binding protein homologue was evaluated with immunoblotting, immunosorbent assays, and skin prick tests.

Results: The full gene structures of 20 canonical allergens and 7 noncanonical allergen homologues were produced. A novel major allergen, ubiquinol-cytochrome c reductase binding protein–like protein, was found and designated Der f 24. All 40 sera samples from patients with mite allergy had IgE antibodies against rDer f 24. Of 10 patients tested, 5 had positive skin reactions. The predominant bacterial genus among 100 identified species was *Enterobacter* (63.4%). An intron was found in the 13.8-kDa *D farinae* bacteriolytic enzyme gene, indicating that it is of HDM origin. The Kyoto Encyclopedia of Genes and Genomes pathway analysis revealed a phototransduction pathway in *D farinae*, as well as thiamine and amino acid synthesis pathways, which is suggestive of an endosymbiotic relationship between *D farinae* and its microbiome.

Conclusion: An HDM genome draft produced from genomic, transcriptomic, and proteomic experiments revealed allergen genes and a diverse endosymbiotic microbiome, providing a tool for further identification and characterization of HDM allergens and development of diagnostics and immunotherapeutic vaccines. (J Allergy Clin Immunol 2015;135:539-48.)

Key words: *House dust mite, allergen, genome, microbiome, transcriptome, proteome, ubiquinol-cytochrome c reductase binding protein, Der f 24,* Enterobacter *species*

Allergic diseases, which affect 30% to 40% of the world's population and are increasing in prevalence internationally, particularly among young people, have negative effects on patients' work and social lives and have become a costly global health problem.[1,2] House dust mites (HDMs) are predominant sources of inhalant allergens, with more than 50% of allergic disease cases being attributed to them.[3-5] Decades of research have revealed 23 HDM allergen groups, with the canonical group 1 and 2 allergens being the most clinically important because they possess IgE-binding activity in most sera of patients with mite allergy.[5-7] Group 1 and 2 allergens induce T_H2 immune responses by encoding cysteine proteases and by facilitating Toll-like receptor 4 signaling, respectively.[8,9]

It remains a perplexing question why HDMs are seemingly teeming with allergenic components. The identities of the full spectrum of HDM allergenic components are not yet known. Allergen-specific immunotherapy represents the only currently available therapy that has long-lasting effects on allergic diseases.[10] HDM allergen vaccines are generally made from extracts of purified mite bodies, which include components of microbes that inhabit mites.[11,12] It is difficult to ensure the lot-lot consistency of the vaccine because of its complex components. Distinguishing the effective components of vaccines

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The duration of cough in patients with H1N1 influenza

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Abstract

Background: Cough is one of common symptoms of influenza, the cough duration and prevalence of postinfectious cough (PIC) after viral upper respiratory tract infection has not been well described.

Objectives: We aim to investigate the duration of cough and prevalence of PIC and its relation with acute symptoms, airway inflammation and cough sensitivity in patients with H1N1 influenza.

Methods: Patients with acute symptoms of H1N1 influenza were enrolled and followed up until cough relived. Spirometry, induced sputum test, capsaicin challenge test were conducted in patients with PIC. Cough sensitivity was presented as logarithm of provocative concentration inducing five or more coughs (logC5).

Results: A total of 141 cases with H1N1 influenza were enrolled. In patients with H1N1 influenza, 97.2% of them complained cough. The duration of cough was as following: <1 week (73.0%); 1–2 weeks (7.8%); 2–3 weeks (7.8%); ≥3 weeks (8.5%). Twelve (8.5%) patients had cough lasting more than 3 weeks (PIC), 4 (2.8%) patients developed chronic cough (>8 weeks). Acute symptoms, spirometry, bronchial responsiveness and sputum differential cell count were similar between patients with PIC and those without PIC, however, there was a higher prevalence of previous PIC (58.3% vs 14.7%, $P < 0.05$) and elevated cough sensitivity (lgC5: 1.18 ± 0.58 vs 2.73 ± 0.33, $P < 0.01$) in patients with PIC as compared with the patients without PIC.

Conclusions: Acute cough is common in patients with H1N1 PIC, only a few of patients develop chronic cough. Acute symptoms cannot predict PIC which is related with previous PIC and increased cough sensitivity.

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Abbreviations

BHR	bronchial hyperresponsiveness
FEV1	forced, expiratory volume in 1 s
FVC	forced vital capacity
PIC	postinfectious cough
RT-PCR	reverse transcription polymerase chain reaction

Key words
cough – cough sensitivity – influenza – postinfectious cough

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Authorship and contributorship
Ke-Fang Lai designed the study, participated in the experiments, wrote and revised the manuscript. Zi-Feng Yang participated in the experiments and was responsible for virus diction. Ling Lin, Yang-Qin Zhan and Wei Luo enrolled subjects and patients, assisted in data analysis and drafting the manuscript. Ru-Chong Chen participated in the presentation of data and interpretation. Bao-Juan Liu, Jia-Yu Pan and Fang Yi participated in the presentation of data and assisted in English writing of the manuscript. All authors read and approved the final manuscript.

Ethics
This study was approved by The Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine. The IRB approval number is 2008GL-15.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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The effect of statins on chronic obstructive pulmonary disease exacerbation and mortality: a systematic review and meta-analysis of observational research

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The objective of this study is to assess whether statin use is associated with beneficial effects on COPD outcomes. We conducted a systematic review and meta-analysis of all available studies describing the association between statin use and COPD mortality, exacerbations and cardiovascular events. Medline, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials were searched, with no restrictions. The hazard ratio (HR) with 95% confidence interval (CI) was estimated. Fifteen studies with a total of 238,459 patients were included. Nine articles provided data on all-cause mortality (124,543 participants), and they gave a HR of 0.62 (95% CI 0.52 to 0.73). Three studies provided data on cancer mortality (90,077 participants), HR 0.83 (0.65 to 1.08); four studies on COPD mortality (88,767 participants), HR 0.48 (0.23 to 0.99); and three studies on cardiovascular mortality (90,041 participants), HR 0.93 (0.50 to 1.72). Six articles provided data on COPD exacerbation with or without hospitalization (129,796 participants), HR 0.64 (0.55 to 0.75). Additionally, the use of statins was associated with a significant reduction risk of myocardial infarction, but not for stroke. Our systematic review showed a clear benefit of statins in patients with COPD.

Statins, 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, are commonly used in clinical practice to treat dyslipidemia[1]. In addition to the lowering of serum cholesterol, recent data indicated that statins have potent anti-inflammatory and immunomodulatory properties called "pleiotropic effects"[2]. Due to these properties, it has been suggested that these drugs may have benefic al effects in patients with chronic obstructive pulmonary disease (COPD)[3–5]. Most population-based observational studies have reported associations between statins and a reduced risk of mortality and hospitalization among COPD patients[6–20]. *In vitro* and animal studies convincingly show that statins can reduce airway inflammation by mechanisms that are unrelated to their effects on cholesterol metabolism[21,22].

There is an increasing interest in determining whether statins improve the prognosis of patients with COPD. In 2009, two reviews suggested that statins might have a benefic al role in the treatment of COPD[23,24]. Since then, several additional trials have been conducted in this setting[7–9,11,12,17,19,20,25]. Overall, the results of some of the trials showed a benefic al effect, but the results were inconsistent when all trials were considered. We therefore conducted a systematic review and meta-analysis of all available studies

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The evaluation of clinical usefulness of transbrochoscopic lung biopsy in undefined interstitial lung diseases: a retrospective study

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Abstract

Background and Aims: Previous studies mostly focused on the diagnostic accuracy of transbronchoscopic lung biopsy (TBLB) in the diagnosis of interstitial lung diseases (ILDs). We aimed to explore the clinical usefulness of TBLB results in the diagnostic procedure of undefined ILDs.

Methods: The retrospective analysis included patients undergoing TBLB for the diagnosis of undefined ILDs from January 2007 to December 2010. The clinically useful TBLB was defined as that lead to a specific histopathological diagnosis or that was consistent with the working diagnosis based on existing clinical and radiological data.

Results: A total of 664 patients were included in the study. TBLB failed to obtain lung parenchyma in 155 cases (23.3%). TBLB was considered clinically helpful in 202 procedures (30.4%), including 114 cases that provided definitive histopathological diagnoses and 88 cases that were consistent with working diagnoses. Among 202 cases of clinically useful TBLBs, the majority were diagnosed as pulmonary alveolar proteinosis (PAP) (67 cases, 33.2%), connective tissue disease-related ILDs (CTD-ILDs) (65, 32.2%) and idiopathic pulmonary fibrosis (IPF) (33, 16.3%). Although TBLB could provide definitive histopathological diagnoses in all cases diagnosed as PAP, only few cases of IPF (7, 21.2% of IPF diagnoses) and CTD-ILDs (9, 13.8% of CTD-ILD diagnoses) could be identified by TBLBs.

Conclusion: The clinical usefulness of TBLB, in conjunction with thorough clinical and radiological data, in the diagnosis of ILDs may be varied depending on different subtypes. The use of histopathological analysis and the type of biopsy employed should therefore be considered on a case-by-case basis.

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Key words
idiopathic interstitial pneumonia – idiopathic pulmonary fibrosis – interstitial lung diseases – pulmonary alveolar proteinosis – transbronchoscopic lung biopsy

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Rongchang Chen conceived the study, Qian Han collected data, co-analysed the data and drafted the manuscript; Qun Luo supervised the data collection and critically revised the manuscript; Xiaobo Chen collected data; Jiaxing Xie contributed to data analysis and Lulu Wu contributed to data collection.

Ethics
The study protocol was approved by Ethics Committee of Guangzhou Medical University. All patients authorized their records to be reviewed.

Conflicts of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Han Qian and Luo Qun contributed equally to this article.

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ORIGINAL RESEARCH

The Functional Copy Number Variation-67048 in *WWOX* Contributes to Increased Risk of COPD in Southern and Eastern Chinese

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Abstract

Recent studies have recognized the genetic variants in the WW domain-containing oxidoreductase (*WWOX*) gene as genetic determinants of lung function, reflecting that the *WWOX* gene may be a susceptible factor of chronic obstructive pulmonary disease (COPD), which characters as poor lung function. We have previously showed that the copy number variation-67048 (CNV-67048) of *WWOX* was associated with lung cancer risk. Here, we hypothesized that the CNV-67048 affects COPD susceptibility. Based on a two-stage case-control study with a total of 1791 COPD patients and 1940 controls of southern and eastern Chinese, we found that the loss genotypes (0-copy and 1-copy) of CNV-67048 harbored a significantly increased risk of COPD, with an odds ratio (OR) as 1.29 (1.11–1.49) when compared with the common 2-copy genotype. The pre-forced expiratory volume in one second (pre-FEV_1) to pre-forced vital capacity (pre-FVC) of carriers with loss genotypes (0.729 ± 0.130) was significantly lower than carriers with 2-copy genotype (0.747 ± 0.124; $p = 7.93 \times 10^{-5}$). However, no significant difference was observed on pre-FEV_1, pre-FVC and the annual decline of pre-FEV_1 between the loss genotypes and 2-copy genotype carriers. Our data suggest that the loss genotypes of CNV-67048 in *WWOX* predispose their carriers to COPD, which might be a genetic biomarker to predict risk of COPD in Chinese.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most strikingly increasing lung diseases that threatens the life and health of world people. According to the latest WHO estimates, about 64 million people have COPD worldwide and more than 3 million people died of COPD in 2004–2005, which accounted for 5% of all deaths globally that year (1). In China, approximate 8.2% of subjects who were 40 years and older suffer COPD (2). COPD is now prevalent in China and it will grow exponentially in the coming years, driven by the high smoking rate and the aging of Chinese population, which is going to cause high burden on Chinese society.

Although COPD is most commonly caused by tobacco smoke, the heritable factor has a determinant role on etiology of COPD, because only a small portion of smokers develop COPD (3–5). Recently, multiple epidemiological studies, including genome-wide and candidate association studies, have revealed several susceptible loci in human genes for COPD (6–8). These loci, most of which are single nucleotide polymorphisms (SNPs), are more or less associated with COPD or phenotypes of COPD, such as the forced expiratory volume in 1 second (FEV_1), FEV_1 to forced vital capacity ratio (FEV_1/FVC)

Keywords: COPD, copy number variation, missing heritability, WW domain-containing oxidoreductase

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The Impact of Visceral Pleural Invasion In Node-negative Non-small-cell Lung cancer: A Systematic Review and Meta-analysis

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RESEARCH ARTICLE

The Pneumonia Severity Index as a Predictor of In-Hospital Mortality in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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呼吸疾病国家重点实验室

Abstract

Objective

To determine whether the pneumonia severity index (PSI) can predict in-hospital mortality for AECOPD patients and compare its usefulness with the CURB65 and BAP65 indexes to predict mortality.

Methods

Demographics, clinical signs and symptoms, comorbidities, and laboratory and radiographic findings of hospitalized AECOPD patients were obtained. Univariate and multiple logistic regression analyses were used to identify the risk factors for in-hospital mortality. The PSI, CURB65 and BAP65 scores were calculated. Receiver operating characteristic (ROC) curve analysis was used to identify the PSI, CURB65 and BAP65 scores that could discriminate between non-survivors and survivors. To control for the confounding factor of invasive mechanical ventilation (IMV) regarding the mortality of AECOPD, subgroup analysis was performed when excluded patients who had met the criteria of IMV but who had not received the cure of IMV according to their wishes.

Results

During the in-hospital period, 73 patients died and 679 patients recovered. Age, PaO_2<60 mmHg, pH < 7.35, PaCO2≥50 mmHg, nursing home residency, congestive heart failure, liver disease, sodium<130 mmol/L, lower FEV1% and altered mental status were risk factors for in-hospital mortality. The areas under the ROC curves (AUCs) of the PSI for death were 0.847 (95% CI: 0.799-0.895). The cut-off value was 116.5 with a sensitivity of 82.2% and a specificity of 77.6%. However, the AUCs of the CURB65 and BAP65 for death were only 0.744 (95% CI: 0.680-0.809) and 0.665 (95% CI: 0.594-0.736), respectively. Subgroup

CHEST

Quality Assessment of Clinical Practice Guidelines for Respiratory Diseases in China

A Systematic Appraisal

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BACKGROUND: There has been a significant increase in the publication of clinical practice guidelines (CPGs) for respiratory diseases in China. However, little is known about the quality and potential impacts of these CPGs. Our objective was to critically evaluate the quality of Chinese CPGs for respiratory diseases that were published in peer-reviewed medical journals.

METHODS: A systematic search of scientific literature published between 1979 and 2013 was undertaken to identify and select CPGs that were related to respiratory diseases. Four Chinese databases (the Chinese Biomedical Literature database [CBM], the China National Knowledge Infrastructure [CNKI], the VIP database, and the WANFANG database) were used. The quality of eligible guidelines was assessed independently by four reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The overall agreement among reviewers was evaluated using an intraclass correlation coefficient.

RESULTS: A total of 109 guidelines published in 27 medical journals from 1979 to 2013 were evaluated. The overall agreement among reviewers was considered good (intraclass correlation coefficient, 0.838; 95% CI, 0.812-0.862). The scores of the six AGREE domains were low: 57.3% for scope and purpose (range, 4.2%-80.5%), 23.8% for stakeholder involvement (range, 2.8%-54.2%), 7.7% for rigor of development (range, 0%-27.1%), 59.8% for clarity and presentation (range, 22.2%-80.6%), 10.9% for applicability (range, 0%-22.9%), and 0.6% for editorial independence (range, 0%-16.7%). Scores for all guidelines were below 60%, and only three guidelines (2.8%) were recommended for clinical practice with modifications.

CONCLUSIONS: The quality of the guidelines was low, and stakeholder involvement, rigor of development, applicability, and editorial independence should be considered in the future development of CPGs for respiratory diseases in China. CHEST 2015; 148(3):759-766

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ABBREVIATIONS: AGREE = Appraisal of Guidelines for Research and Evaluation; CPG = clinical practice guideline

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RESEARCH ARTICLE

The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies

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呼吸疾病国家重点实验室

Abstract

Background

Previous studies have suggested that asthmatic patients often have comorbid depression; however, temporal associations remain unclear.

Objectives

To determine whether depression predicts asthma and, conversely, whether asthma predicts depression.

Methods

A literature search was conducted without language restrictions using Pubmed, Embase, Cochrane and PsycINFO for studies published before January, 2015. Papers referenced by the obtained articles were also reviewed. Only comparative prospective studies with reported risk estimates of the association between depression and asthma were included. In order to investigate whether one of these conditions was predictive of the other, studies were excluded if enrolled participants had pre-existing depression or asthma. A random-effects model was used to calculate the pooled risk estimates for two outcomes: depression predicting asthma and asthma predicting depression.

Results

Seven citations, derived from 8 cohort studies, met our inclusion criteria. Of these, six studies reported that depression predicted incident adult-onset asthma, including 83684 participants and 2334 incident cases followed for 8 to 20 years. Conversely, two studies reported that asthma predicted incident depression. These studies involved 25566 participants and 2655 incident cases followed for 10 and 20 years, respectively. The pooled adjusted relative

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RESEARCH ARTICLE

The Role of *Cryptococcus* in the Immune System of Pulmonary Cryptococcosis Patients

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Abstract

Objectives

To investigate the role of *Cryptococcus* in the immune system of immunocompetent patients with pulmonary cryptococcosis (PC) by analysing the dynamic changes of patients' immune status before and after antifungal therapy.

Methods

The level of the serum interferon-γ (IFN-γ) and interleukin (IL)-2, -4, -10 and -12 was measured before and after 6-months of treatment. Peripheral blood samples were obtained from 30 immunocompetent PC patients and 30 age- and gender-matched healthy controls. Peripheral blood mononuclear cells (PBMCs) were isolated and incubated with recombinant human IL-12 (rhIL-12) for 48 h. Then the concentrations of IFN-γ and IL-4 in the supernatant were analysed.

Results

Baseline serum IFN-γ level was significantly lower in the PC patients as compared with the control group ($P < 0.001$). The serum IL-2 and IFN-γ of PC patients were significantly increased after appropriate treatments ($P < 0.05$ and $P < 0.001$ when compared to their baseline levels). The productions of IFN-γ in the culture supernatant of PBMCs showed no significant difference between the control and PC patients both before and after antifungal treatments. RhIL-12 is a potent stimulus for IFN-γ production. Culture PBMCs collected from PC patients before treatments had a smaller increase of IFN-γ production in the present of rhIL-12 than the control ($P < 0.01$); PBMCs from PC patients completing 6-months of treatment showed a comparable increase of IFN-γ production by rhIL-12 stimulation to the control group.

Original Article

The role of SOX-2 on the survival of patients with non-small cell lung cancer

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Background: Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death worldwide. Observational studies on the prognostic role of SOX-2 in non-small-cell lung cancer (NSCLC) are controversial.

Methods: To clarify the impact of SOX-2 in NSCLC survival, we performed this meta-analysis that included eligible studies. The combined hazard ratios and their corresponding 95% confidence intervals (95% CI) were calculated in terms of overall survival.

Results: A total of seven studies with 1,944 patients were evaluable for this meta-analysis. The studies were categorized by histology, disease stage and patient race. Our results suggested that SOX-2 overexpression had a favorable impact on survival of patients with NSCLC, the HR (95% CI) was 0.57 (0.48 to 0.65). However, highly significant heterogeneity was detected among these studies (I^2=76.7%, P=0.000).

Conclusions: SOX-2 overexpression indicates a favorable prognosis for patients with NSCLC.

Keywords: SOX-2; prognosis; lung cancer; meta-analysis

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呼吸疾病国家重点实验室

Introduction

Lung cancer remains the most lethal cancer worldwide, despite improvements in diagnostic and therapeutic techniques. Its incidence has not peaked in many parts of world, particularly in China, which has become a major public health challenge all the world (1). The prognosis for lung cancer patients is generally poor, with an overall 5-year survival rate of approximately 15%, and it has shown little improvement in recent decades (2,3). Several independent prognostic factors for survival have been identified: performance status (PS), disease stage, age, sex and amount of weight lost (4). Some of these factors are useful when choosing treatment options for an individual, principally disease stage and PS. However, the discriminant value of most potential prognostic biological markers is insufficient to predict the optimal therapeutic course for an individual (5,6).

SRY (sex determining region Y)-box 2, also known as SOX-2, is one of the key transcriptional factors that control the unique properties of stem cells self-renewal and pluripotency (7,8) and play a critical role inmaintaining the stem cell-like phenotype in cancer cells (9-12). Over-expression of SOX2 in NSCLC cells stimulates cellular migration and anchorage-independent growth while SOX-2 knockdown impairs cell growth (13,14).

Recently, a number of studies have reported the contribution of SOX-2 to tumorigenesis and its correlation with clinical progression of various types of tumors, including lung cancer. However, no consensus has been reached; conflicting results have been reported from different laboratories. We therefore carried out a meta-

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CHEST

The Role of Viral Infection in Pulmonary Exacerbations of Bronchiectasis in Adults

A Prospective Study

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BACKGROUND: Although viral infections are a major cause of exacerbations in patients with chronic airway diseases, their roles in triggering bronchiectasis exacerbations in adults remain unclear. Therefore, we prospectively investigated the incidence and clinical impacts of viral infection in adults with bronchiectasis exacerbations.

METHODS: The study cohort of 119 adults with bronchiectasis was followed up prospectively for 12 months. Nasopharyngeal swabs and sputum samples were assayed for 16 respiratory viruses, using polymerase chain reaction assays. Symptoms, spirometry, quality of life, bacterial cultures, and inflammatory markers were assessed during steady-state bronchiectasis and exacerbations.

RESULTS: A total of 100 exacerbations were captured from 58 patients during 1-year follow-up. Respiratory viruses were found more frequently in nasopharyngeal swabs and sputum during bronchiectasis exacerbations (49 of 100, 49.0%) than during steady state (11 of 58, 18.9%; $P < .001$). The most common viruses found in patients experiencing exacerbations were coronavirus (19 of 65, 39.2%), rhinovirus (16 of 65, 24.6%), and influenza A/B viruses (16 of 65, 24.6%). Virus-positive exacerbations were associated with a greater increase in markers of systemic and airway inflammation (serum IL-6 and tumor necrosis factor-α; sputum IL-1β and tumor necrosis factor-α) compared with virus-negative exacerbations, but the differences in spirometric indexes, quality of life, and bacterial density were unremarkable. In receiver operating characteristics analysis, serum interferon-γ-induced protein 10 yielded an area under curve of 0.67 (95% CI, 0.53-0.77; $P = .018$). Furthermore, a greater proportion of patients with virus-positive exacerbations received IV antibiotics.

CONCLUSIONS: Prevalence of viral infections, detected by polymerase chain reaction assay, is higher in cases of bronchiectasis exacerbations than in steady-state bronchiectasis, suggesting that respiratory viruses play crucial roles in triggering bronchiectasis exacerbations. The potential mechanisms of virus-induced bronchiectasis exacerbations merit further investigations.

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ABBREVIATIONS: BE = bronchiectasis exacerbation; BSI = Bronchiectasis Severity Index; CAT = COPD Assessment Test; CFU = colony-forming unit; CRP = C-reactive protein; HCoV = human coronavirus; HRCT = high-resolution CT; IP-10 = interferon-γ-induced protein 10; IQR = interquartile range; LCQ = Leicester Cough Questionnaire; NPS = nasopharyngeal swab; PCR = polymerase chain reaction; QoL = quality of life; SGRQ = St. George's Respiratory Questionnaire; TNF = tumor necrosis factor

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URGCP promotes non-small cell lung cancer invasiveness by activating the NF-κB-MMP-9 pathway

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ABSTRACT

Invasion and metastasis are main traits of tumor progression and responsible for the poor prognosis of advanced non-small cell lung cancer (NSCLC). The molecular mechanisms underlying the malignant behaviors of NSCLC remain incompletely understood. The present study demonstrate that up-regulator of cell proliferation (URGCP), a recently identified tumor-promoting gene found in several tumor types, is markedly overexpressed in human NSCLC cell lines and clinical NSCLC samples. URGCP upregulation correlates significantly with the progression and poor prognosis of this disease. *In vitro* and *in vivo* studies demonstrate that increasing URGCP expression accelerates invasion, migration, and distant metastasis of NSCLC cells whereas downregulating URGCP suppresses these malignant traits. Notably, silencing URGCP expression almost completely abrogates the metastatic ability of NSCLC cells. At the molecular level, URGCP markedly promotes MMP-9 expression by activating NF-κB signaling. Additionally, URGCP and MMP-9 expression are positively correlated in various cohorts of human NSCLC specimens, and NF-κB-activated MMP-9 expression contributes to URGCP-induced invasiveness of NSCLC cell lines. Collectively, these findings indicate that URGCP plays an important role in promoting NSCLC cell invasion and metastasis by enhancing NF-κB-activated MMP-9 expression and may serve as a potential therapeutic target and prognostic marker.

INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality and morbidity worldwide, with an estimated 1.7 million new cases annually and more than 1.4 million deaths per year [1]. Over 80% of lung cancer cases are non-small cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma and large cell carcinoma. The combined 5-year overall survival (OS) rate for all stages and subtypes of NSCLC remains as low as 15%; however, the overwhelming number of lung cancer-related deaths are due to metastatic diseases [2]. Moreover, it is estimated that more than half of NSCLC patients show local invasion or distant metastasis at the time of diagnosis and that only approximately 2% of advanced NSCLC patients survive 5 or more years, with a median survival time of 7 months [3, 4]. Although considerable improvements have been made in NSCLC patient management, tumor invasion and metastasis continue to greatly limit treatment options, and no cure for NSCLC patients with advanced disease is currently available [5, 6].

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Original Article

Utility of contrast-enhanced ultrasound with SonoVue in biopsy of small subpleural nodules

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Abstract: Objectives: This study aimed to evaluate the diagnostic accuracy and complication rates of contrast-enhanced ultrasound (CEUS)-guided biopsy of small subpleural nodules with SonoVue. Methods: CEUS-guided biopsies with SonoVue and conventional ultrasound were performed to determine nodule size, texture and biopsy route. After baseline ultrasonography, all patients received an intravenous injection of 4 mL of SonoVue, followed by 5 mL of saline flush. CEUS was obtained using a convex probe and contrast-specific imaging software. The lesion was observed using a contrast agent. Biopsies were performed during real-time visualisation of the target lesion. Results: A total of 51 patients (34 males and 17 females; average age, 54.8 ± 5.8 years) with subpleural nodules were enrolled. The median nodule size was 1.92 ± 0.75 cm (0.9-2.5 cm). Forty-eight of 51 procedures (94.1%) provided adequate material for histological analysis. Thirty patients (62.5%) were malignant and 18 patients (37.5%) were benign at the definitive diagnosis. The true positive and true negative result were 28 (58.3%) and 18 (37.5%), no false positive result was seen and two (4.2%) provided a false negative result. The sensitivity, specificity, positive and negative predictive values for the malignant diagnosis were 93.3, 100, 100 and 90%, respectively. The diagnostic accuracy was 95.8% (46/48), the standard error and the 95% CI were 2.8% and 86%-99%. An asymptomatic pneumothorax was present in one patient with no chest tube placement required. A small amount of hemoptysis was observed in another patient, which stopped spontaneously without treatment. Conclusions: CEUS-guided biopsy with SonoVue exhibits high diagnostic accuracy and low complication rates. It is especially advantageous for biopsies of small subpleural nodules.

Keywords: Contrast-enhanced ultrasound, SonoVue, biopsy, subpleural nodules

Introduction

Small subpleural nodules (less than 2.5 cm) are common in physicians' practices. However, the aetiology and diagnostic approach for these nodules are highly difficult. Definitive diagnosis relies on histological proof obtained via nodule biopsy. For subpleural nodules, CT-guided percutaneous transthoracic biopsy is a well-established technique of acquiring sufficient tissue for histopathological diagnosis [1, 2]. However, biopsies of small subpleural nodules have been reported to be technically difficult and associated with a higher risk of pneumothorax [3] if the nodules are located in the lower lobes, where nodules are subjected to major respiratory movements and/or the needle tract is obstructed by overlying bony structures [1].

Thoracic ultrasound (US) is a non-invasive and portable diagnostic tool with important application for pulmonary specialists. US is suited to visualise nodules arising from the chest wall and peripheral lung nodules abutting the chest wall or adjacent to the pleural surface [4, 5]. US-guided biopsy is effective and offers many advantages, such as real-time monitoring throughout the procedure; it can even be performed in general wards [5-8]. Despite being a validated and well-established imaging modality, US-guided biopsy is still not utilised to its full potential by pulmonary specialists. Contrast

techniques with or without CEUS. Another limitation was our small number of patients, larger studies that require more experiences are recommended.

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Disclosure of conflict of interest

None.

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Validation of human small airway measurements using endobronchial optical coherence tomography

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ABSTRACT

Background: Small airway remodeling is the cardinal feature underlying chronic airway diseases. There is no modality which identifies small airway pathological changes, which is crucial for early diagnosis, efficacy and prognostic assessment.
Objective: To evaluate the usefulness of endobronchial optical coherence tomography (EB-OCT) in assessing small airways morphology *in vivo*.
Methods: Twelve patients with pulmonary nodules scheduled for lung resection underwent spirometry, multi-detector computed tomography (MDCT) and EB-OCT. We measured D_{mean} (mean luminal diameter), Ai (inner luminal area), Aw (airway wall area) and Aw% [Aw/(Ai + Aw) × 100%] from the 3rd to 5th generation bronchi of RB9 segment by MDCT. D_{mean}, Ai, Aw and Aw% from the 3rd to 9th generation bronchi of RB9 segment were measured by EB-OCT and histology. Correlations of these parameters, measured by three different methods, were evaluated. We recruited 4 COPD patients to determine if EB-OCT could identify peripheral airway remodeling.
Results: The 4 parameters, measured by CT and EB-OCT, correlated significantly [D_{mean} ($r = 0.991$), Ai ($r = 0.997$), Aw ($r = 0.997$), Aw% ($r = 0.991$), all $P < 0.01$]. Significant correlation were found for these parameters, measured by histology and EB-OCT, from the 3rd to 5th generation bronchi [D_{mean} ($r = 0.989$), Ai ($r = 0.997$), Aw ($r = 0.999$), Aw% ($r = 0.988$), all $P < 0.01$], and from the 6th to 9th generation bronchi [D_{mean} ($r = 0.979$), Ai ($r = 0.997$), Aw ($r = 0.994$) and Aw% ($r = 0.988$), all $P < 0.01$]. Significant small airways morphological abnormalities were observed in COPD patients.
Conclusions: EB-OCT, a minimally invasive imaging modality with high-resolution, is useful and clinically practical for assessing proximal and distal airways of human compared with CT and histology.
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1. Introduction

Airway remodeling (particularly in small airways) is the cardinal pathological feature underlying various chronic airway diseases [1] (i.e., COPD, asthma and bronchiectasis). Identifying pathological changes of airway remodeling is crucial for the early diagnosis, severity and efficacy assessment and prognostic outcomes [2]. Despite the measurement of specimens derived from surgical resection or lung biopsy, little is known regarding the airway morphology of these chronic airway diseases. High-resolution computed tomography (HRCT) [3] has been a useful tool which could assess airway architecture as distal as to the 6th generation

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Will nonasthmatic eosinophilic bronchitis develop chronic airway obstruction? A prospective, observational study

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ORIGINAL RESEARCH

Breathlessness or Health Status in Chronic Obstructive Pulmonary Disease: The Impact of Different Definitions

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Abstract

Objective: **The GOLD 2011 report recommends the use of symptoms, exacerbation history, and FEV_1% predicted to categorise patients into groups A–D. We investigated the choice of mMRC or CAT on category assignment and characterization of the categories.** ***Methods:*** **Patients were prospectively recruited from tertiary hospitals in China, as part of the INTACT study, with a prior diagnosis of COPD. The GOLD categories were defined using mMRC and CAT, along with exacerbations in the previous year, and FEV_1% predicted.** ***Results:*** **1,465 patients were included. The most prevalent group was group D. However, proportions of patients categorised into groups A to D differed depending on symptom instruments. The use of CAT resulted in more patients being placed into groups B and D. Cardiac co-morbid conditions, particularly ischaemic heart disease, heart failure, and arrhythmia were highly prevalent in groups B and D. Group B appeared to have a similar burden of cardiac co-morbidities to group D, in spite of a higher FEV_1 level. Although mMRC assigned a smaller proportion of patients to groups B and D, the patients it did assign had a higher burden of cardiac co-morbidities than patients assigned by CAT. When patients were assessed according to LLN, 14.2% had normal airflow according to ECSC 1993 equations, with 12.6% having normal airflow according to GLI 2012 formulae.** ***Conclusions:*** **The choice of symptom assessment is one potential confounder impacting the patient assignment. Breathlessness may be an important marker of overall disease severity, indicating the presence of cardiac co-morbidities in the GOLD categories.**

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document proposed in 2011 a new multidimensional system for the assessment of patients with chronic obstructive pulmonary disease (COPD) that combines the assessment of symptoms with severity of airflow limitation and history of exacerbations (1). As a result, COPD patients are now classified in groups A–D that, along with the assessment of potential co-morbidities, guides the selection of their therapy (1).

However, this new multidimensional system for the assessment of COPD is an empirical proposal mostly based on expert opinion. Therefore, soon after the release of this new GOLD proposal, a number of investigators used their existing cohorts, i.e. COPDGene (2), Copenhagen (3), Cocomics (4), and ECLIPSE (5) to explore the distribution, characteristics, stability, and/or relationship with long-term outcomes of the four patient categories. Recent comparative analyses of the four different cohorts further validated the new GOLD proposal (6). However, these existing cohorts

Keywords: cardiovascular disease, chronic obstructive lung disease, COPD, dyspnea, Global Initiative for Co-morbidity

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Original Article

Cigarette smoking impairs the response of EGFR-TKIs therapy in lung adenocarcinoma patients by promoting EGFR signaling and epithelial-mesenchymal transition

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Abstract: Cigarette smoking represents for the highest risk-factor for non-small cell lung cancer (NSCLC), and a growing body of evidence suggested that smoking was associated with a high recurrence and poor therapeutic response of NSCLC as well. On the other hand, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), such as gefitinib, has been proved to be an efficient and safe strategy for treating NSCLC. Although accumulating clinical data suggested that smoking history might influence the therapeutic effects of EGFR-TKIs even in NSCLC patients harboring sensitive EGFR mutation, the exact effects of cigarette smoking on the efficacy of EGFR-TKIs treatment in NSCLC patients remain exclusive. In this study, we firstly identified the adverse effect of smoking exposure on the efficacy of EGFR-TKIs treatment against lung adenocarcinoma in mutation-positive patients by retrospective analysis of clinical data. The hypo-responsiveness of smoking patients on the therapy was accompanied with persistent activation of EGFR-downstream signal molecules ERK1/2 and AKT, which could not be inhibited by gefitinib and thus lead to the failure of EGFR-TKIs treatment. Based on our in vitro data, it was also found that long-term cigarette smoking extract (CSE) exposure induced epithelial-mesenchymal transition (EMT), which might also contribute to acquired resistance to EGFR-TKIs. Taken together, our findings suggested that cigarette smoking negatively regulated the clinical outcome of EGFR-TKIs therapy in lung adenocarcinoma patients, which was correlated with the activation of EGFR signaling and the induction of EMT.

Keywords: NSCLC, adnocarcinoma, cigarette smoking, EGFR-TKIs, EMT

Introduction

Lung cancer is the most common and leading cause of cancer deaths, resulting in over 1.4 million worldwide deaths per year. Smoking history represents for a high risk of the occurrence of lung cancer and about 80% of lung cancer cases in males and 50% in females arouse in ever-smokers [1]. Despite progress in loco regional and systemic therapies, improvement in the prognosis of advanced lung cancer remained a great challenge. Besides its role in increasing the risk of cancer occurrence, continuous smoking during the treatment of lung cancer could also lead to a higher incidence of recurrence, development of drug resistance and significantly increased mortality as shown by retrospective studies [2-4].

In recent years, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) therapy emerged as a breakthrough for treating non-small cell lung cancer (NSCLC) and has been widely used in clinical practice. Currently EGFR-TKIs drugs (gefitinib and erlotinib) have been recommended to be the first-line treatment on advanced NSCLC patients harboring somatic EGFR mutations [5, 6]. In concert with that, the responsiveness of patients to EGFR-TKIs largely depends on the somatic mutations occurring in EGFR kinase domain of cancer cells [7]. Exon 19 in-frame deletions (delE746-751) and exon 21 substitution (L858R) have been shown to be the mostly observed types of EGFR mutations, and thus were used as biologic predictors during patients selection for EGFR-TKIs treatment [8, 9]. Unfortunately,

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Correlation of increased *MALAT1* expression with pathological features and prognosis in cancer patients: a meta-analysis

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ABSTRACT. Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) has been identified as a potential cancer biomarker, yet the mechanism by which it influences the development of cancer remains unknown. In this study, we aimed to correlate *MALAT1* expression with pathological features and prognosis in cancer patients. Several databases were searched using combinations of keywords relating to *MALAT1* and cancer. After selection of relevant cohort studies according to strict criteria, a meta-analysis was conducted. Twelve studies were analyzed, involving 958 cancer patients. Elevated *MALAT1* expression was associated with poor prognosis and larger tumors [prognosis: hazard ratio = 3.11, 95% confidence interval (CI) = 1.98-4.23, P = 0.000; tumor size: odds ratio (OR) = 0.40, 95%CI = 0.21-0.74, P = 0.003]. However, no connection with histological grade, T-stage, lymph node (LN) metastasis, or distant metastasis was established (all P > 0.05). A correlation between increased

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Research Article

Epithelium-Specific Ets-Like Transcription Factor 1, ESE-1, Regulates ICAM-1 Expression in Cultured Lung Epithelial Cell Lines

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Cystic fi rosis (CF) patients suffer from chronic airway infl mmation with excessive neutrophil infi tration. Migration of neutrophils to the lung requires chemokine and cytokine signaling as well as cell adhesion molecules, such as intercellular adhesion molecule-1 (*ICAM-1*), which plays an important role in mediating adhesive interactions between effector and target cells in the immune system. In this study, we investigated the relationship between *ICAM-1* and epithelium-specifi ETS-like transcription factor 1 (*ESE-1*) and found that *ICAM-1* expression is upregulated in cell lines of CF (IB3-1) as well as non-CF (BEAS-2B and A549) epithelial origin in response to infl mmatory cytokine stimulation. Since *ESE-1* is highly expressed in A549 cells without stimulation, we examined the effect of *ESE-1* knockdown on *ICAM-1* expression in these cells. We found that *ICAM-1* expression was downregulated when *ESE-1* was knocked down in A549 cells. We also tested the effect of *ESE-1* knockdown on cell-cell interactions and demonstrate that the knocking down *ESE-1* in A549 cells reduce their interactions with HL-60 cells (human promyelocytic leukemia cell line). The e results suggest that *ESE-1* may play a role in regulating airway inflammation by regulating *ICAM-1* expression.

1. Introduction

Airway infl mmation is a hallmark of the cystic fibrosis (CF) lung disease. The airways of CF patients are initially colonized by viruses, fungi, or bacteria, including *Staphylococcus aureus*, *Haemophilus influenzae,* and *Klebsiella pneumonia* [1]. Most patients later become infected with mucoid strains of *Pseudomonas aeruginosa* and some with *Burkholderia cepacia* [2].

In CF patients, the number of neutrophils and the levels of cytokines such as tumor necrosis factor-α (TNF-α), interleukin- (IL-) 6, and IL-8 in the airways are increased compared to non-CF individuals [3, 4]. Cultured CF lung epithelial cells (IB3-1) show downregulation of the anti-infl mmatory cytokine IL-10 and an exaggerated upregulation of IL-8 in response to a variety of external stimuli, such as TNF-α and bacterial products [5, 6]. Overproduction of IL-8 is likely a major cause of excessive neutrophil infiltration, since IL-8 is a potent chemoattractant for neutrophils [7].

Neutrophil migration in response to inflammatory stimuli requires cell adhesion molecules, such as intercellular adhesion molecule-1 (*ICAM-1*, also known as CD54) [8, 9]. Migration of neutrophils out of the vascular system occurs in distinct phases: rolling, fi m adhesion, and transmigration [10].

Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Group IIE Secretory Phospholipase A_2 Regulates Lipolysis in Adipocytes

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Objective: To examine the function of group IIE secretory phospholipase A_2 (sPLA$_2$-IIE) in adipocytes and to explore the possible signaling mechanism involved.

Methods: The expression of sPLA$_2$-IIE was demonstrated using real-time PCR and Western blot analysis. Lipid accumulation was evaluated via the measurement of cellular triglycerides (TG). Lipolysis was quantified by measuring the release of free glycerol. The expressions of M-type sPLA$_2$ receptor (PLA$_2$R1) and the genes encoding adipogenic proteins were measured using real-time PCR. The activities of the Janus kinase 2 (JAK2), extracellular regulated protein kinase (ERK), and hormone-sensitive lipase (HSL) were determined using Western blot.

Results: *sPLA$_2$-IIE$^{-/-}$* mice gained significantly more epididymal fat than wild-type (WT) mice. When treated with adipogenic stimuli *ex vivo*, stromal vascular cells isolated from the adipose tissue of *sPLA$_2$-IIE$^{-/-}$* mice accumulated significantly more TG than those from WT mice. Conversely, a significant reduction in lipid accumulation and an increase of free glycerol were observed in OP9 cells overexpressing sPLA$_2$-IIE and in 3T3-L1 cells treated with sPLA$_2$-IIE protein. Moreover, sPLA$_2$-IIE significantly induced adipocyte glycerol release and HSL activity, which was inhibited by PD98059, an ERK inhibitor.

Conclusions: sPLA$_2$-IIE regulates lipolysis in adipocytes, likely through the ERK/HSL signaling pathway.

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Introduction

The secreted phospholipase A_2 (sPLA$_2$) family consists of low molecular weight, Ca^{2+}-requiring extracellular enzymes that catalyze the hydrolysis of phospholipids at the *sn*−2 position, generating free fatty acids and lysophospholipids (1,2). To date, 11 sPLA$_2$s (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA, and XIIB), which were defined based on the number and positions of disulfide bonds and their molecular structures, have been identified in mammals (1,2). Each sPLA$_2$ displays a unique expression pattern in different cell types within restricted tissues (1-3), and is involved in a variety of physiological and pathological processes via the release of arachidonic acid from membrane phospholipids or binding to specific membrane receptors (4,5).

The group IIE secretory phospholipase A_2 (sPLA$_2$-IIE) is a member of the group II sPLA$_2$ that consist of a signal peptide of 19 amino acids (6) and can promote stimulus-induced arachidonic acid release similar to those of other related heparin-binding sPLA$_2$s (7). Compared with the other isoforms of sPLA$_2$ that are broadly expressed in various tissues (2), sPLA$_2$-IIE is restricted to only a few tissues including the heart, brain, lung, and epididymal adipose tissue (2,8,9). Additionally, current evidence suggests that sPLA$_2$-IIE has a much lower catalytic activity than the other group II sPLA$_2$s, at least under the standard sPLA$_2$ assay conditions (3,6,7). Nevertheless, elevated levels of sPLA$_2$-IIE were found in damaged cells compared with normal cells, in which sPLA$_2$-IIE generally presented at low or undetectable levels (7,10,11). This finding suggests that sPLA$_2$-IIE may play fundamental roles in life-related processes; however, the functions of sPLA$_2$-IIE in related tissues have not yet been firmly established.

A previous study revealed that sPLA$_2$-IIE was upregulated in epididymal adipose tissue of a polygenic obese line of mice during delipidation elicited by conjugated linoleic acid (9); however, the roles of sPLA$_2$-IIE in adipocytes and the molecular mechanisms involved remain unclear. Because sPLA$_2$-IIE is expressed in adipose tissue, we hypothesized that it could play important roles in adipose-specific processes such as lipolysis and adipogenesis. Some members of the PLA$_2$ superfamily, e.g., PLA$_2$-XVI and PLA$_2$-X, have

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Author contributions: Hui Zhi conceived and carried out experiments and analyzed data. Linbing Qu and Fang Wu carried out experiments. Ling Chen and Jun Tao conceived experiments. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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acetaminophen; vomiting, cough, and shortness of breath also developed. He was hospitalized on day 6 of his illness and began receiving antibiotic treatment (Fig. 1A). Chest radiography revealed mild bilateral ground-glass opacities in his lower lung (Fig. 1B). Two days later, pulse oximetry showed that the arterial blood oxygen saturation levels had declined (to approximately 50 to 70%) in spite of the administration of high-flow oxygen (5 to 6 liters per minute), and invasive mechanical ventilation was commenced. A throat-swab sample was positive for influenza A virus, as assessed by means of real-time reverse-transcriptase–polymerase chain reaction (PCR), and treatment with oseltamivir (150 mg twice a day for 13 days, administered through a nasogastric tube) was initiated on day 9. On day 12 of his illness, an influenza A virus isolate, designated A/Guangzhou/39715/2014 (H5N6), was obtained from a throat-swab specimen (see the Supplementary Appendix, available with the full text of this letter at NEJM.org, for details). Influenza A(H5N6) was identified by means of subtype-specific PCR and sequencing of the virus isolate (GenBank accession numbers, KP765785 through KP765792).

On day 14, the patient was transferred to the isolation ward of the intensive care unit in the First Affiliated Hospital of Guangzhou Medical University. A chest radiograph and a computed tomographic scan showed progression of lung consolidation (Fig. 1C and 1D). Influenza A RNA was detectable by means of real-time PCR in sputum samples but not from throat-swab, blood, urine, or stool samples. The next day, virus was undetectable in throat-swab, sputum, and bronchoalveolar-fluid specimens. Multidrug-resistant *Acinetobacter baumannii* was detected in sputum but not in blood cultures. There was evidence of neutrophilia and lymphocytopenia (Table S1 in the Supplementary Appendix). Serum levels of aspartate aminotransferase, creatinine, lactate dehydrogenase, creatine kinase, and myoglobulin were within the normal range throughout his illness. Antibiotic therapy was changed to teicoplanin, meropenem, and cefoperazone–sulbactam on day 18. Low-dose methylprednisolone treatment was started on day 21 and was administered until day 42. Imaging showed resolution of the bilateral lung infiltrations. Fever recurred on day 25 in association with eosinophilia. Invasive mechanical ventilation was stopped on day 37, and the patient was later discharged (day 58). This case shows that a novel H5 clade 2.3.4.4 influenza virus can cause human infection, similar to other influenza A(H5N1) viruses.[4]

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ORIGINAL RESEARCH

LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD

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Background: The current Global initiative for chronic Obstructive Lung Disease (GOLD) treatment strategy recommends the use of one or more bronchodilators according to the patient's airflow limitation, their history of exacerbations, and symptoms. The LANTERN study evaluated the effect of the long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) dual bronchodilator, QVA149 (indacaterol/glycopyrronium), as compared with the LABA/inhaled corticosteroid, salmeterol/fluticasone (SFC), in patients with moderate-to-severe COPD with a history of ≤1 exacerbation in the previous year.

Methods: In this double-blind, double-dummy, parallel-group study, 744 patients with moderate-to-severe COPD with a history of ≤1 exacerbations in the previous year were randomized (1:1) to QVA149 110/50 µg once daily or SFC 50/500 µg twice daily for 26 weeks. The primary endpoint was noninferiority of QVA149 versus SFC for trough forced expiratory volume in 1 second (FEV_1) at week 26.

Results: Overall, 676 patients completed the study. The primary objective of noninferiority between QVA149 and SFC in trough FEV_1 at week 26 was met. QVA149 demonstrated statistically significant superiority to SFC for trough FEV_1 (treatment difference [Δ]=75 mL; $P<0.001$). QVA149 demonstrated a statistically significant improvement in standardized area under the curve (AUC) from 0 hours to 4 hours for FEV_1 (FEV_1 $AUC_{0–4h}$) at week 26 versus SFC (Δ=122 mL; $P<0.001$). QVA149 and SFC had similar improvements in transition dyspnea index focal score, St George Respiratory Questionnaire total score, and rescue medication use. However, QVA149 significantly reduced the rate of moderate or severe exacerbations by 31% (P=0.048) over SFC. Overall, the incidence of adverse events was comparable between QVA149 (40.1%) and SFC (47.4%). The incidence of pneumonia was threefold lower with QVA149 (0.8%) versus SFC (2.7%).

Conclusion: These findings support the use of the LABA/LAMA, QVA149 as an alternative treatment, over LABA/inhaled corticosteroid, in the management of moderate-to-severe COPD patients (GOLD B and GOLD D) with a history of ≤1 exacerbation in the previous year.

Keywords: COPD, long-acting β_2-agonists, long-acting muscarinic antagonist, clinical trial

Introduction

COPD is characterized by chronic airflow obstruction that interferes with normal breathing and is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.[1] COPD and, more specifically, the frequent and recurrent exacerbations experienced by patients with COPD, can result in significant health care costs, as well as causing high morbidity and mortality among this group.[2–4]

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Review Article

Link between environmental air pollution and allergic asthma: East meets West

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Abstract: With the levels of outdoor air pollution from industrial and motor vehicle emissions rising rapidly in the fastly-industrializing countries of South East Asia, the prevalence of asthma and allergic diseases has also been increasing to match those in the West. Epidemiological and experimental exposure studies indicate a harmful impact of outdoor air pollution from vehicles and factories both on the development of allergic diseases and asthma and the increase in asthma symptoms and exacerbations. The level of outdoor pollution in Asia is much higher and more diverse than those encountered in Western countries. This may increase the impact of outdoor pollution on health, particularly lung health in Asia. This review discusses the constituents of air pollution in Asia with a special focus on studies in mainland China and Taiwan where the levels of pollution have reached high levels and where such high levels particularly in winter can cause a thick haze that reduces visibility. The onus remains on regulatory and public health authorities to curb the sources of pollution so that the health effects on the population particularly those with lung and cardiovascular diseases and with increased susceptibility can be mitigated.

Keywords: Allergy; environmental air pollution; particulate matter (PM); ozone (O_3); nitrogen dioxide (NO_2); asthma

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呼吸疾病国家重点实验室

Introduction

There is increasing evidence of the negative health impact resulting from environmental air pollution, in particular that associated with respiratory diseases and allergy. The increasing prevalence of respiratory diseases and allergy such as asthma has drawn attention to the potential role of air pollution in causing this. While this has been first noticed and reported in Europe and North America, this is now being seen in many of the rapidly-growing economies of South East-Asia, particularly in China as a result of the fast pace of urbanization and increased energy consumption that occurs with rapid industrialization and the increasing number of vehicles (1). This is having a significant impact on mortality and health of Asian populations and air pollution is one of the major factors that affects the health of Asians (2). Recent data published by the *Health Effects Institute* indicate that a 10 μg/m^3 increase in PM_{10}, the coarse particulate fraction of air pollution, is associated with an increase in mortality of 0.6% in daily all natural cause mortality in major cities in India and China (3). The health effects of air pollution particularly on the common lung diseases such as asthma and COPD are also being felt particularly in Asia. The low levels of allergy and asthma that have been seen previously is now rising to match those levels observed in Western countries, and both epidemiological cohort and experimental exposure studies provide evidence to implicate a harmful impact of traffic air pollution on both the development of allergic diseases and asthma and the increase in asthma symptoms and exacerbations. Experimental exposure studies also indicate

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miR-497 and miR-34a retard lung cancer growth by co-inhibiting cyclin E1 (CCNE1)

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Keywords: CCNE1, lung cancer, miR-34a, miR-497

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ABSTRACT

Cyclin E1, encoded by the CCNE1 gene, promotes G1/S transition, chromosome instability, and oncogenesis. Here, we show that miR-497 and miR-34a target the 3′-UTR of *CCNE1*. miR-497 and miR-34a are downregulated in cancer cells and their ectopic expression inhibited cell proliferation and colony formation in vitro, and inhibited tumor growth in a xenograft model. The effect of simultaneous overexpression of miR-497 and miR-34a on the inhibition of cell proliferation, colony formation, and tumor growth, and the downregulation of cyclin E1 was stronger than the effect of each miRNA alone. The synergistic actions of miR-497 and miR-34a partly correlated with cyclin E1 levels. When cells stably expressing *CCNE1* were transfected with the Hi-miR-497/34a plasmid, there was no effect on colony formation, compared with that of cells transfected with either Hi-miR497 or Hi-miR34a. These results indicate cyclin E1 is downregulated by both miR-497 and miR-34a, which synergistically retard the growth of human lung cancer cells.

INTRODUCTION

Cancer is a complex disease caused by the progressive accumulation of genetic and epigenetic alterations in cells, which allow the cells to evade normal and environmental controls. Much progress has been made in the treatment of lung cancer in the last 10 years. Nonetheless, lung cancer is currently the most common cause of cancer-related death throughout the world, and therefore remains an unresolved medical issue. An understanding of the processes and pathogenesis of cancer at the systemic, cellular, and molecular levels is one of the most ambitious goals of cancer research. MicroRNAs (miRNAs) are epigenetic regulators that play a pivotal role in the acquisition of tumorigenic properties by cells.

miRNAs are a class of endogenous noncoding RNAs of approximately 22 nucleotides (nt) that regulate mRNA stability and translation [1-3]. A wide range of biological functions are controlled by miRNAs, including cell proliferation, differentiation, and apoptosis [4-6]. There is strong evidence that miRNAs can act as oncogenes or tumor suppressors, with key roles in cancer initiation, progression, and therapy. In an attempt to understand the mechanisms underlying cancer, an increasing number of studies have reported that individual miRNAs exert their functions in specific cancers. Many recent studies reported that some miRNAs cooperatively control a variety of biological processes, including cell development and differentiation, apoptosis, and the cell cycle [7-10]. When an mRNA or several different mRNAs involved in a specific biological process are targeted by several miRNAs, the miRNAs act cooperatively. Recent studies have demonstrated that miRNAs encoded in miRNA clusters function synergistically in cancer, e.g., the miR-17-92 cluster [11-13] and the miR-15a-16-1 cluster [14, 15]. Ventura et al. reported that miR-17-92 and miR-106b-25 double-knockout mice have a more severe phenotype than miR-17-92 single-knockout mice [16].

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Passive Immunotherapy with Dromedary Immune Serum in an Experimental Animal Model for Middle East Respiratory Syndrome Coronavirus Infection

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ABSTRACT

Middle East respiratory syndrome (MERS) is a highly lethal pulmonary infection. Serum from convalescent MERS patients may provide some benefit but is not readily available. In contrast, nearly all camels in the Middle East have been infected with MERS-CoV. Here, we show that sera obtained from MERS-immune camels augment the kinetics of MERS-CoV clearance and reduce the severity of pathological changes in infected lungs, with efficacy proportional to the titer of MERS-CoV-neutralizing serum antibody.

A decade after the emergence of the severe acute respiratory syndrome (SARS), a novel beta coronavirus was isolated from a patient with a fatal viral pneumonia in Saudi Arabia in 2012 (1). The disease is now designated Middle East respiratory syndrome (MERS), and the causative virus is MERS coronavirus (MERS-CoV). So far (as of 7 February 2015), 971 confirmed cases, 356 of them fatal, have been reported to the World Health Organization (http://www.who.int/csr/disease/coronavirus_infections/mers-5-february-2015.pdf?ua=1). Primary human cases have been reported from a number of countries in the Arabian peninsula and the Middle East region, but travel-associated cases and limited human-to-human transmission from such cases have been reported from other countries in Europe, Africa, and Asia. While clusters of human cases with limited human-to-human transmission within health care facilities or families have been reported (2), index cases in the transmission chains remain of presumed zoonotic origin.

MERS-CoV-like viruses are widespread in dromedary camels, with seroepidemiological studies indicating seroprevalence of >90% in adult animals (3). Viruses isolated from dromedaries are genetically and phenotypically closely related to viruses isolated from humans and retain the capacity to infect *ex vivo* cultures of the human airways (4). Other domestic livestock in affected areas, including cattle, goats, sheep, and equids, have no evidence of MERS-CoV infection. There is no convincing evidence of MERS-CoV in bats, although a genetically related virus, albeit with a divergent spike protein, has been detected in *Neoromicia capensis* bats from Africa (5).

Infection in dromedaries has been reported to precede human infection in a few instances (6). Given the ubiquitous nature of infection in dromedaries, human exposure to MERS-CoV must be common; however, human disease remains rare (7). Furthermore, MERS-CoV remains endemic in dromedaries in East and North Africa (3), although locally acquired human cases have not been reported in countries in these regions. It is unclear whether this represents a lack of recognition or a true absence of disease. Thus, while dromedaries are recognized as a natural host of MERS-CoV, the modes of transmission to humans remain unclear.

The apparent case fatality of MERS appears to be high (approximately 37%), with age and underlying disease conditions, including diabetes, respiratory or cardiovascular diseases, and immunocompromised status, being risk factors (8). When human case clusters have been intensively investigated, it has become apparent that milder cases are not uncommon and that such cases are probably undiagnosed in the general population (2). Thus, the overall severity of MERS may be milder than reflected from hitherto-diagnosed cases. The repeated emergence of clusters of human-to-human MERS transmission is reminiscent of the emergence of SARS in late 2002, when clusters of human cases from the animal reservoir emerged and then went extinct, until the virus finally adapted to acquire the capacity for sustained human-to-human transmission. Virus then spread globally to infect more than 8,000 persons in >28 countries or territories (reviewed in reference 9). Within the past 200 years, other animal coronaviruses have adapted to humans and have spread globally, *viz.*, human coronaviruses 229E and OC43 (10). Thus, zoonotic MERS-CoV remains a concern for global public health.

So far, no clinically effective therapeutics have been identified. Some drugs, including some licensed for human use in other clinical indications, have activity *in vitro*, but it is unclear whether their pharmacology and toxicity would allow therapeutic efficacy in humans (11, 12). Passive immunotherapy using convalescent-phase human plasma is being considered for a number of emerging infectious diseases (e.g., MERS, influenza, and Ebola) (11, 13). It was used for treatment of SARS with potentially promising re-

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ORIGINAL RESEARCH

Polo-like kinase 2 acting as a promoter in human tumor cells with an abundance of TAp73

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Background: TAp73, a member of the p53 tumor suppressor family, is frequently overexpressed in malignant tumors in humans. TAp73 abundance and phosphorylation modification result in variations in transcriptional activity. In a previous study, we found that the antitumor function of TAp73 was reactivated by dephosphorylation in head and neck squamous cell carcinomas. Polo-like kinase 2 (PLK2) displayed a close relationship with the p53 family in affecting the fate of cells. Herein, we investigate the hypothesis that PLK2 phosphorylates TAp73 and inhibits TAp73 function.

Materials and methods: Head and neck squamous cell carcinoma cell lines and osteosarcoma cell lines were used as natural models of the different expression levels of TAp73. Phosphorylation predictor software Scansite 3.0 and the predictor GPS-polo 1.0 were used to analyze the phosphorylation sites. Coimmunoprecipitation, phosphor-tag Western blot, metabolic labeling, and indirect immunofluorescence assays were used to determine the interactions between PLK2 and TAp73. TAp73 activity was assessed by Western blot and reverse transcription polymerase chain reaction, which we used to detect P21 and PUMA, both downstream genes of TAp73. The physiological effects of PLK2 cross talk with TAp73 on cell cycle progress and apoptosis were observed by flow cytometry and terminal deoxynucleotidyl transferase dUTP nick end labeling assays.

Results: PLK2 binds to and phosphorylates TAp73. PLK2 phosphorylates TAp73 at residue Ser48 and prohibits TAp73 translocation to the nucleus. Additionally, PLK2 inhibition combined with a DNA-damaging drug upregulated p21 and PUMA mRNA expression to a greater extent than DNA-damaging drug treatment alone. Inhibiting PLK2 in TAp73-enriched cells strengthened the effects of the DNA-damaging drug on both G1 phase arrest and apoptosis. Pretreatment with TAp73-siRNA weakened these effects.

Conclusion: These findings reveal a novel PLK2 function (catalyzed phosphorylation of TAp73) which suppresses TAp73 functions. PLK2 promotes the survival of human tumor cells, a novel insight into the workings of malignant tumors characterized by TAp73 overexpression, and one that could speed the development of therapies.

Keywords: antitumor therapy, DNA damaging reagent, phosphorylation, PLK2, TAp73

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Introduction

TAp73 is a member of the p53 family, the most important tumor-suppressing family, and has a structure similar to p53. It is able to activate some of the p53 target genes, such as p21 (a cell cycle inhibitor) and PUMA (a proapoptosis gene), which regulate cell survival.[1] TAp73 is frequently overexpressed in carcinomas and sarcomas[1] and is, under certain conditions, an accepted marker of malignant tumors. These mechanisms are not yet completely clear. Among the inconsistencies, we noted differences in expression levels of TAp73 between human tumor cell lines such as head and neck squamous cell carcinoma (HNSCC) cell lines originating from epithelial carcinoma

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SEE COMMENTARY

Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus

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Middle East Respiratory Syndrome (MERS) is a highly lethal pulmonary infection caused by a previously unidentified coronavirus (CoV), likely transmitted to humans by infected camels. There is no licensed vaccine or antiviral for MERS, therefore new prophylactic and therapeutic strategies to combat human infections are needed. In this study, we describe, for the first time, to our knowledge, the isolation of a potent MERS-CoV–neutralizing antibody from memory B cells of an infected individual. The antibody, named LCA60, binds to a novel site on the spike protein and potently neutralizes infection of multiple MERS-CoV isolates by interfering with the binding to the cellular receptor CD26. Importantly, using mice transduced with adenovirus expressing human CD26 and infected with MERS-CoV, we show that LCA60 can effectively protect in both prophylactic and postexposure settings. This antibody can be used for prophylaxis, for postexposure prophylaxis of individuals at risk, or for the treatment of human cases of MERS-CoV infection. The fact that it took only 4 mo from the initial screening of B cells derived from a convalescent patient for the development of a stable chinese hamster ovary (CHO) cell line producing neutralizing antibodies at more than 5 g/L provides an example of a rapid pathway toward the generation of effective antiviral therapies against emerging viruses.

MERS-CoV | neutralizing antibody | serotherapy | emerging viruses

Middle East Respiratory Syndrome coronavirus (MERS-CoV) is an emergent subgroup C betacoronavirus that was detected for the first times in June and September of 2012, when two cases of severe infections were identified in the Eastern Mediterranean region (1, 2). As of June 29, 2015, 1,379 human infections with 531 deaths have been confirmed in 26 countries in the Middle East, Europe, North Africa, Asia, and Americas, including the recent outbreak in South Korea caused by an individual who traveled to the Middle East, which caused 164 infections and 23 deaths (www.ecdc.europa.eu). MERS-CoV causes severe infection of the lower respiratory tract, similar to the Severe Acute Respiratory Syndrome CoV (SARS-CoV) that appeared in China in 2002. Several cases of human-to-human transmission have been reported in health care workers and family clusters, but at the current time there is no evidence of sustained human-to-human transmission.

SARS-CoV and MERS-CoV belong to the B and C betacoronavirus lineages and have been shown to bind to cellular receptors ACE2 and CD26 [also known as dipeptidyl peptidase 4 (DPP4)], respectively. Of note, SARS-CoV targets ciliated bronchial epithelial cells and type I and type II pneumocytes, whereas MERS-CoV infects type II pneumocytes and nonciliated bronchial cells. These differences might account for the different rates of human-to-human transmission, which was high for SARS-CoV and is moderate to low for MERS-CoV. The two viruses differ also in the duration of their epidemic, which was limited for SARS-CoV (from November 2002 to July 2003) and long-lasting for MERS-CoV, which appeared in 2012 and continues to circulate in the Middle East.

As to the zoonotic reservoir, both MERS-CoV and SARS-CoV probably originated in bats (3, 4) with dromedary camels serving as intermediate hosts for the human MERS-CoV infection and palm civets and raccoon dogs for SARS-CoV (5). Dromedary camels have a close association with humans in the affected areas. Of note, whereas in humans MERS-CoV infects the lower respiratory tract, rendering human-to-human transmission inefficient, in camels the virus infects the upper respiratory tract and is present in nasal secretions at high concentrations, which favors transmission to humans and other camels. However, the mechanisms of transmission from camels to humans and from humans to humans as well as the global incidence in humans are still unclear. Camels show no or mild symptoms, and antibodies found in banked sera samples show that the virus has been present in the animals for at least the past 20 y (6). In addition, most of the patients described appeared to have been infected in hospitals, from other MERS

Significance

Middle East Respiratory Syndrome coronavirus (MERS-CoV) causes severe respiratory disease with a high mortality rate. There is no licensed vaccine or antiviral for MERS. Here we isolated for the first time, to our knowledge, a potent MERS-CoV–neutralizing antibody from memory B cells of an infected individual. This antibody binds to a novel site on the viral Spike protein, neutralizes by interfering with the binding to the cellular receptor CD26, and is highly effective both in prophylaxis and in therapy in a relevant mouse model. This antibody can be developed for prophylaxis, for postexposure prophylaxis, or for the treatment of severe MERS-CoV infections.

Author contributions: D.C., J.Z., F.S., R.S.B., L.V., M.Z., S.P., and A.L. designed research; D.C., J.Z., M.P., L.S., S.A., C.F., B.F.-R., G.A., F.V., and R.G. performed research; M.P., L.S., S.A., M.F., C.J.L., N.A.B., and L.V. contributed new reagents/analytic tools; D.C., J.Z., M.P., L.S., S.A., M.F., R.G., and L.V. analyzed data; and D.C., J.Z., F.S., R.S.B., L.V., M.Z., S.P., and A.L. wrote the paper.

Conflict of interest statement: A.L. is the scientific founder of Humabs BioMed SA. A.L. holds shares in Humabs BioMed SA. G.A., F.V., and D.C. are employees of Humabs Biomed, a commercial company that commercializes human monoclonal antibodies.

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ORIGINAL ARTICLE

Selective killing of lung cancer cells by miRNA-506 molecule through inhibiting NF-κB p65 to evoke reactive oxygen species generation and p53 activation

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The tumor suppressor p53, nuclear factor-κB (NF-κB) and reactive oxygen species (ROS) have crucial roles in tumorigenesis, although the mechanisms of cross talk between these factors remain largely unknown. Here we report that miR-506 upregulation occurs in 83% of lung cancer patients (156 cases), and its expression highly correlates with ROS. Ectopic expression of miR-506 inhibits NF-κB p65 expression, induces ROS accumulation and then activates p53 to suppress lung cancer cell viability, but not in normal cells. Interestingly, p53 promotes miR-506 expression level, indicating that miR-506 mediates cross talk between p53, NF-κB p65 and ROS. Furthermore, we demonstrated that miR-506 mimics inhibited tumorigenesis *in vivo*, implicating that miR-506 might be a potential therapeutic molecule for selective killing of lung cancer cells.

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Keywords: miR-506; NF-κB p65; ROS; p53; lung cancer; selective killing

INTRODUCTION

MicroRNAs (miRNAs) are short noncoding RNAs of 19–25 nucleotides that are thought to modulate the expression of at least 30% of all human genes, with marked effects on fundamental biological processes such as development, cell proliferation, apoptosis, differentiation and metabolism. miRNAs exert their effects through base-pairing interactions between the seed region of the miRNA (nucleotides 2–8 from its 5′-end) and complementary sequences that usually reside in the 3′-untranslated regions (UTRs) of target mRNAs.[1,2] miRNAs appear to be involved in signal transduction pathways in most diseases, including cancer. Hence, not only protein-encoding genes but also noncoding RNAs especially miRNAs, should be considered as key factors in signaling cascades.

p53, a DNA-binding transcription factor identified in 1979,[3] has been one of the most intensively studied tumor suppressors in the past three decades. Expression of p53 is usually below detectable level in resting cells, but is activated by cellular stresses such as DNA damage, oncogene activation, hypoxia, ribosomal stress and chemotherapeutic drugs.[4] Upon stimulation, p53 enters the nucleus and induces transcription of target genes, including miRNAs.[5,6] Loss of p53 function is associated with most human cancers.[7] Consequently, modulating the stability and/or activation of p53 represents a promising anticancer strategy.[8,9]

Pro-inflammatory transcription factors such as nuclear factor-κB (NF-κB) are central mediators of immune responses in mammals. Activation of the classical NF-κB pathway and the resulting chronic inflammation[10,11] contribute to cancer development and pathology. Activation of NF-κB has been observed in human lymphomas and many types of human carcinomas.[12,13] NF-κB can be activated by many divergent stimuli, including pro-inflammatory cytokines and ionizing radiation, and chemotherapeutic agents such as tumor necrosis factor α (TNFα) and doxorubicin. Activated NF-κB binds to the NF-κB-binding elements of its target genes, including inhibition of apoptosis proteins (*IAPs*) and *bcl-2*, which mediate anti-apoptosis and chemoresistance in tumor cells.[14,15]

Lung cancer is the leading cause of cancer deaths worldwide. Approximately 50% of lung cancer patients are already at advanced stages of diagnosis,[16] making their treatment poor. Thus, it is crucial to identify better targets for lung cancer diagnosis and therapy. In advanced stages, tumors generally exhibit multiple genetic mutations and higher levels of oxidative stress than at earlier stages.[17] Persistent oxidative stress occurs in many types of cancers,[18] and while moderate levels are thought to be beneficial for tumor cells, excessive levels are anti-tumorigenic.[19] For this reason, inducing reactive oxygen species (ROS) accumulation in cancer cells is considered to be a novel therapeutic approach for preferential stimulation of apoptosis.[17,20] The key genes involved in regulation of ROS have been extensively studied; however, the role of noncoding RNAs, including miRNAs, in modulation of ROS has only recently emerged. miR-21 protects against H_2O_2-induced cell apoptosis by targeting programed cell death protein 4 (PDCD4) in cardiomyocytes.[21] miR-17–92 overexpression modulates ROS generation and reduces excessive DNA damage to a tolerable level.[22] Here, we report that human miR-506, a member of the

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Stem Cell and Idiopathic Pulmonary Fibrosis: Mechanisms and Treatment

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Wenwei Tu

Abstract: Idiopathic pulmonary fibrosis (IPF) is a progressive and lethal lung disease resulting from multiplex causes. Evidence indicates that stem/progenitor cells might play a key role in IPF pathogenesis and repair, which may provide some novel potential strategies for the future treatment of IPF. In this review, we first summarize the current understanding of the relationship between stem cells and IPF and then review the advancements made in recent clinical trials using stem/progenitor cells, especially mesenchymal stem cells, in treating IPF and their interpretations.

Keywords: Embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, pulmonary fibrosis, treatment.

1. OVERVIEW

Idiopathic pulmonary fibrosis (IPF) is a progressive and lethal lung disorder characterized by chronic and exertional dyspnea accompanied by irreversible decreases in lung function [1, 2]. In the USA, its annual prevalence is 42.7-63 per 100 000 people, while its annual incidence is 16.3-17.4 per 100 000 population estimated by broad case definitions [3-5]. IPF generally occurs in elderly adults and has a median survival time of only 3-5 years after diagnosis due to the current lack of effective therapies [3, 4]. Typical IPF features exaggerated deposition of extracellular matrix in the lung interstitium, the injured airway, and alveolar epithelial cells as well as distortion of the lung architecture [1, 6]. As a fundamental process that occurs after injury [7], the rapid and correct repair of damaged tissue after lung injury is important to the survival of patients with severe lung diseases. Thus, the reparation capacity of endogenous lung stem or progenitor cells in lung regeneration as well as their involvements in diverse respiratory diseases have recently obtained intensive attention. In addition, the roles of the abnormal repair process due to dysregulation of lung stem/progenitor cells in IPF formation have been confirmed by several studies from different research groups [8-13]. Exogenous adult and embryonic stem cells including mesenchymal stem cells (MSCs) were recently explored for use as a potential therapeutic option during IPF treatment [14-16]. In this paper, we first review several hypotheses about the pathogenesis of IPF and then discuss the role and possible clinical application of stem or progenitor cells in the treatment of IPF.

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2. EVOLVING VIEWS IN THE PATHOLOGENISIS OF IPF

2.1. Inflammatory Hypothesis

The classical inflammatory hypothesis was the first widely accepted theory in the pathogenesis of IPF and remains the main basis for current clinical treatment. This hypothesis assumed that chronic inflammation caused by unknown pathogenic factors is the main reason for persistent lung injury and pulmonary fibrosis [17, 18]. The inflammatory hypothesis was supported by a phenomenon observed in patients with IPF including type I alveolar epithelial cell and endothelial cell injuries, type II alveolar epithelial cell proliferation, alveolar structural integrity damage, interstitial cell aggregation and proliferation, and extra cellular matrix deposition. However, increasing clinical evidence shows that this does not explain all changes that occur during IPF.

In 2008, Benjamin and his colleagues [19] proposed a comprehensive role of inflammation in the pathogenesis of IPF. After injury caused by multiplex factors occurs, the balance of anti-/pro-inflammatory and fibrotic factors is disturbed, while activated inflammatory cells (i.e. eosinophils, neutrophils, monocytes, lymphocytes) are recruited to the lung by multiple chemokines such as (C-C motif) ligant 2 (CCL2), (C-C motif) ligand 3, interleukin-8, and macrophage colony stimulating factor. These inflammatory cells are then programmed to secrete some pro-inflammatory/profibrotic cytokines, such as transforming growth factor-β

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ORIGINAL ARTICLE

TBL1XR1 promotes lymphangiogenesis and lymphatic metastasis in esophageal squamous cell carcinoma

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ABSTRACT

Objective Transducin (β)-like 1 X-linked receptor 1 (TBL1XR1) plays an important role in controlling the precisely regulated switch between gene repression and gene activation in transcriptional regulation. We investigated its biological function and clinical significance in esophageal squamous cell carcinoma (ESCC).

Design Immunoblotting and immunochemistry were used to determine TBL1XR1 expression in ESCC cell lines, ESCC clinical tissues and 230 clinicopathologically characterised ESCC specimens. The role of TBL1XR1 in lymphangiogenesis and lymphatic metastasis was examined by tube formation, cell invasion and wound-healing assays in vitro, and by a popliteal lymph node metastasis model in vivo. The molecular mechanism by which TBL1XR1 upregulates vascular endothelial growth factor C (VEGF-C) expression was explored using real-time PCR, ELISA, luciferase reporter assay and chromatin immunoprecipitation.

Results TBL1XR1 expression was significantly upregulated in ESCC, positively correlated with disease stage and patient survival, and identified as an independent prognostic factor for patient outcome. We found that TBL1XR1 overexpression promoted lymphangiogenesis and lymphatic metastasis in ESCC in vitro and in vivo, whereas TBL1XR1 silencing had the converse effect. We demonstrated that TBL1XR1 induced VEGF-C expression by binding to the *VEGF-C* promoter. We confirmed the correlation between TBL1XR1 and VEGF-C expression in a large cohort of clinical ESCC samples and through analysis of published datasets in gastric, colorectal and breast cancer.

Conclusions Our results demonstrated that TBL1XR1 induced lymphangiogenesis and lymphatic metastasis in ESCC via upregulation of VEGF-C, and may represent a novel prognostic biomarker and therapeutic target for patients with ESCC.

Significance of this study

What is already known about this subject?

- Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive and lethal human malignancies. The poor outcome of patients with ESCC is attributed to the high rates of regional lymph node metastasis and distant metastasis.
- Vascular endothelial growth factor C (VEGF-C) is a putative lymphangiogenic growth factor that has been identified as an independent prognostic factor in ESCC.
- Although studies have demonstrated that TBL1XR1 controls the precisely regulated switch from gene repression to gene activation, its clinical significance and biological role in the progression of ESCC remain largely unknown.

What are the new findings?

- TBL1XR1 was upregulated in ESCC and positively correlated with ESCC progression.
- Patients with higher TBL1XR1 expression had shorter overall survival time.
- Overexpression of TBL1XR1 promoted lymphangiogenesis and lymphatic metastasis in ESCC in vitro and in vivo, whereas downregulation of TBL1XR1 suppressed these effects.
- TBL1XR1 induced VEGF-C expression by binding to the *VEGF-C* promoter.

How might it impact on clinical practice in the foreseeable future?

- By highlighting an important oncogenic role for TBL1XR1 through promotion of lymphangiogenesis and lymphatic metastasis in ESCC, our results suggest that TBL1XR1 is a potential novel prognostic marker and therapeutic target for the treatment of patients with ESCC.

INTRODUCTION

Human esophageal squamous cell carcinoma (ESCC) is one of the most aggressive and lethal malignancies.[1] Although the diagnosis, staging and treatment of ESCC have improved over the past three decades, the prognosis remains poor. The overall 5-year survival rate in patients with stage III disease is 10–15% and the median survival time in patients with stage IV disease is less than 1 year.[1–3] The poor clinical outcome of patients with ESCC is attributed to the high rates of local invasion and regional lymph node metastasis. The early occurrence of lymphatic metastasis is considered a crucial step in the development of distant metastasis in ESCC.[4 5]

Lymphangiogenesis is the growth of new lymphatic vessels and plays an important role in various physiological and pathological processes, including

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(Z)3,4,5,4′-trans-tetramethoxystilbene, a new analogue of resveratrol, inhibits gefitinb-resistant non-small cell lung cancer via selectively elevating intracellular calcium level

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Calcium is a second messenger which is required for regulation of many cellular processes. However, excessive elevation or prolonged activation of calcium signaling would lead to cell death. As such, selectively regulating calcium signaling could be an alternative approach for anti-cancer therapy. Recently, we have identified an effective analogue of resveratrol, (Z)3,4,5,4′-trans-tetramethoxystilbene (TMS) which selectively elevated the intracellular calcium level in gefitinib-resistant (G-R) non-small-cell lung cancer (NSCLC) cells. TMS exhibited significant inhibitory effect on G-R NSCLC cells, but not other NSCLC cells and normal lung epithelial cells. The phosphorylation and activation of EGFR were inhibited by TMS in G-R cells. TMS induced caspase-independent apoptosis and autophagy by directly binding to SERCA and causing endoplasmic reticulum (ER) stress and AMPK activation. Proteomics analysis also further confirmed that mTOR pathway, which is the downstream of AMPK, was significantly suppressed by TMS. JNK, the cross-linker of ER stress and mTOR pathway was significantly activated by TMS. In addition, the inhibition of JNK activation can partially block the effect of TMS. Taken together, TMS showed promising anti-cancer activity by mediating calcium signaling pathway and inducing apoptosis as well as autophagy in G-R NSCLC cells, providing strategy in designing multi-targeting drug for treating G-R patients.

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A Genetic Variant in Pre-miR-146a (rs2910164 C>G) Is Associated with the Decreased Risk of Acute Coronary Syndrome in a Chinese Population

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MicroRNAs (miRNAs) can contribute to the development of cardiovascular diseases, and single nucleotide polymorphisms (SNPs) in miRNA genes may influence disease susceptibility by altering mature miRNA expression levels. However, the effect of SNPs located in miR-146a and miR-196a2 genes on risk of acute coronary syndrome (ACS) has not been reported in the Chinese population. Two miRNA polymorphisms located in miRNA genes (miR-146a rs2910164 C>G and miR-196a2 rs11614913 T>C) were genotyped in 722 ACS patients and 721 control subjects. The CG genotype of rs2910164 was significantly associated with decreased risk of ACS [CG vs. CC, odds ratio (OR) = 0.72, 95% confidence interval (CI): 0.55-0.95, P = 0.020; dominant model, OR = 0.77, 95% CI: 0.60-0.99, P = 0.044]. We did not find any association of rs11614913 with the risk of ACS. Stratification analysis showed that the rs2910164 CG genotype was associated with decreased risk of ACS (dominant model) in males, subjects with body mass index more than 24 kg/m^2, and in hypertensive subjects. Significant combined effects were also observed between rs2910164 and blood lipids or C-reactive protein levels. In summary, this study provides the first evidence that the CG genotype of miR-146a rs2910164 is associated with a significantly decreased risk of ACS in a Chinese population. Moreover, rs2910164 and blood lipids or an inflammatory marker may have a combined effect on the onset of ACS. These findings indicate that miR-146a rs2910164 may act as a novel molecular marker for ACS susceptibility.

Keywords: acute coronary syndrome; microRNA; miR-146a; polymorphism; susceptibility
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Introduction

Acute coronary syndrome (ACS), including unstable angina and acute myocardial infarction (AMI), is the leading cause of morbidity and mortality worldwide (Lopez and Murray 1998). ACS is a clinically cardiovascular event resulting from rupture of the atherosclerotic plaque, which is caused by environmental exposure and genetic factors. Traditional risk factors for ACS have been identified, including age, sex, body mass index, hypertension, diabetes mellitus, smoking, and family history of coronary heart disease (CHD). Genome-wide association studies have uncovered numerous susceptible loci for ACS (Myocardial Infarction Genetics Consortium et al. 2009; Akerblom et al. 2014; Hirokawa et al. 2015), few of which were found to locate in microRNA (miRNA) genes.

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Original Article

A new mode of community continuing care service for COPD patients in China: participation of respiratory nurse specialists

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Abstract: *Objective:* This study explored a community nursing service mode in which respiratory nurse specialists cared for patients with chronic obstructive pulmonary disease (COPD) in a 12-week period after hospital discharge, with the aim of better preventing acute exacerbations, improving health-related quality of life (HRQOL) and reducing medical expenses in these patients. *Methods:* We carried out a prospective randomized controlled study in which 68 COPD patients discharged were recruited from a general hospital in Guangzhou, China, were randomized divided into two groups. The control group underwent conventional nursing care, and the intervention group received community continuing care by respiratory nurse specialists. The observation period was 12 weeks. The results of intervention were evaluated using the Seattle Obstructive Lung Disease Questionnaire (SOLDQ) and the COPD Self-Efficacy Scale (CSES). In addition, the frequency of acute exacerbations, emergency treatments or hospitalizations, and medical expenses were recorded in the 12-week observation period. *Results:* After six weeks, the total and subscale scores ($P < 0.05$) of SOLDQ and CSES significantly improved compared to the baseline ones in the intervention group. The control group had significantly higher scores in the treatment satisfaction (TS) of SOLDQ, the total score, and the weather/environment and behavioral risk factors of CSES. After 12 weeks, the total and subscale scores of SOLDQ and CSES showed a sustained and significant growth in the intervention group ($P < 0.05$). The control group had significantly higher scores only in the weather/environment risk factor of CSES. During the 12-week observation, the intervention group had significantly fewer acute exacerbations, emergency treatments or re-hospitalizations and significantly lower average medical expenses than the control group ($P < 0.05$). *Conclusions:* Community continuing care by respiratory nurse specialists may improve HRQOL, increase self-efficacy, reduce incidence of acute exacerbation, and lower medical expenses in patients with COPD after hospital discharge.

Keywords: Community continuing care, chronic obstructive pulmonary disease, respiratory nurse specialists, health-related quality of life (HRQOL)

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease that progresses gradually and manifests late. In China where COPD has been increasing in prevalence over the past decade and affecting over 9% of the population aged above 40 [1], a large-scale population-based survey has identified high prevalence of asymptomatic COPD [2]. High mortality and huge medical expenses related to this disorder have also been well recognized [3, 4]. In addition, COPD as a leading cause of debilitation and work loss results in heavy financial burden upon patients and their family members, and immensely interferes with their health-related quality of life (HRQOL) [5, 6].

Since COPD is not fully reversible and recurrent exacerbations may expedite decline in lung function, the major goals of clinical treatment, as proposed by Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) [7], are to improve overall health, increase exercise tolerance and reduce frequency of COPD exacerbations in the patients [8]. In many countries, post-hospital continuing care in the community for stable COPD patients has beco-

REVIEW ARTICLES

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Acoustic Analysis of Snoring in the Diagnosis of Obstructive Sleep Apnea Syndrome: A Call for More Rigorous Studies

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Background: Snoring is a common symptom of obstructive sleep apnea syndrome (OSA) and has recently been considered for diagnosis of OSA.

Objectives: The goal of the current study was to systematically determine the accuracy of acoustic analysis of snoring in the diagnosis of OSA using a meta-analysis.

Methods: PubMed, Cochrane Library database, and EMBASE were searched up to July 15, 2014. A systematic review and meta-analysis of sensitivity, specificity, and other measures of accuracy of acoustic analysis of snoring in the diagnosis of OSA were conducted. The median of apnea-hypopnea index threshold was 10 events/h, range: 5–15 or 10–15 if aforementioned suggestion is adopted.

Results: A total of seven studies with 273 patients were included in the meta-analysis. The pooled estimates were as follows: sensitivity, 88% (95% confidence interval [CI]: 82–93%); specificity, 81% (95% CI: 72–88%); positive likelihood ratio (PLR), 4.44 (95% CI: 2.39–8.27); negative likelihood ratio (NLR), 0.15 (95% CI: 0.10–0.24); and diagnostic odds ratio (DOR), 32.18 (95% CI: 13.96–74.81). χ^2 values of sensitivity, specificity, PLR, NLR, and DOR were 2.37, 10.39, 12.57, 3.79, and 6.91 respectively (All $p > 0.05$). The area under the summary receiver operating characteristic curve was 0.93. Sensitivity analysis demonstrated that the pooled estimates were stable and reliable. The results of publication bias were not significant ($p = 0.30$).

Conclusions: Acoustic analysis of snoring is a relatively accurate but not a strong method for diagnosing OSA. There is an urgent need for rigorous studies involving large samples and single snore event tests with an efficacy criterion that reflects the particular features of snoring acoustics for OSA diagnosis.

Keywords: snoring, obstructive sleep apnea syndrome, acoustic analysis, review, meta-analysis

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Obstructive sleep apnea (OSA) syndrome is a serious sleep disorder characterized by the repeated closure of the upper airway during sleep, among adults 30–70 y of age, approximately 13% of men and 6% of women have moderate to severe OSA, 14% of men and 5% of women have an apnea-hypopnea index (AHI) ≥ 5 plus symptoms of daytime sleepiness.[1] It is also being recognized as an independent risk factor for several clinical consequences, including daytime sleepiness,[2] systemic hypertension,[3] increased risk of cardiovascular and cerebrovascular disease,[4–6] traffic accidents,[7–10] and impaired quality of life.[11]

Polysomnography (PSG) is currently the gold standard of OSA diagnosis.[12,13] Unfortunately, PSG requires a full-night hospital stay in a specifically equipped sleep suite, connected to more than 15 channels of measurements requiring physical contact with sensors.[14] PSG is inconvenient, expensive, and not suitable for mass screening. The limited number of PSG facilities around the world has long waiting lists, rendering it impossible to test all the patients in need of such assessment. Approximately 80–90% of patients with OSA are believed to be undiagnosed.[15] With advances in technology and the development of portable monitors, home testing for sleep related breathing disorders is now feasible and circumvents many of the limitations of an attended in-laboratory polysomnogram. Although the portable monitors may expedite the diagnosis of OSA for many, it is essential that health care professionals using these methods recognize several inherent limitations.[16] There is an enormous need for a simplified screening instrument capable of convenient and reliable diagnosis of OSA.

Snoring is one of the common and earliest symptoms of OSA. Snoring has long been viewed as a potential indicator for monitoring OSA. It has a unique advantage over other physiological signals, in that it can be acquired conveniently with only one to two low-cost noncontact or contact microphones. Importantly, the test does not affect the patient's sleep quality. Interest in the acoustic characteristics of snores began almost 2 decades ago. Recently several papers have proposed OSA detection systems[17] and AHI estimation based on whole-night audio recording of snoring [18,19] For devices utilizing acoustic signals, the data are insufficient to determine whether the use

Acute MUS81 depletion leads to replication fork slowing and a constitutive DNA damage response

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呼吸疾病国家重点实验室

ABSTRACT

The MUS81 protein belongs to a conserved family of DNA structure-specific nucleases that play important roles in DNA replication and repair. Inactivation of the *Mus81* gene in mice has no major deleterious consequences for embryonic development, although cancer susceptibility has been reported. We have investigated the role of MUS81 in human cells by acutely depleting the protein using shRNAs. We found that MUS81 depletion from human fibroblasts leads to accumulation of ssDNA and a constitutive DNA damage response that ultimately activates cellular senescence. Moreover, we show that MUS81 is required for efficient replication fork progression during an unperturbed S-phase, and for recovery of productive replication following replication stalling. These results demonstrate essential roles for the MUS81 nuclease in maintenance of replication fork integrity.

INTRODUCTION

Faithful DNA replication is essential for the maintenance of genome stability in all organisms. The ability of cells to minimize transmission of errors arising during DNA replication to daughter cells depends not only on dedicated DNA replication factors, but also on a large number of DNA repair/DNA damage tolerance proteins. These genome maintenance proteins can act at a number of different locations during the replication process, including upstream of the advancing fork, within the replisome itself, or 'post-replicatively' behind the fork. Amongst the many replication fork repair factors are those that serve to stabilize, process or cleave replication forks stalled either by dNTP exhaustion [1, 2] or by an encounter with lesions/adducts in the template DNA [3, 4]. Failure to execute genome duplication in a timely or accurate manner can generate a cellular state often termed 'replicative stress'. This state is associated with the accumulation of markers of replication-associated DNA damage responses [5]. Importantly, in recent years it has become clear that replicative stress plays a key role during tumorigenesis [6–8]. Moreover, many solid cancers display evidence of persistent replicative stress [9, 10], and this phenotype is now widely considered to be an Achilles' heel of tumor cells than can be exploited therapeutically [11, 12].

One process that plays a critical role in restoration of productive DNA synthesis at sites of stalled or collapsed replication forks is the homologous recombination repair (HRR) pathway [13]. HRR serves to restore replication following replication fork collapse after the fork encounters a ssDNA nick in the leading strand template, often through a process known as break-induced

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Review

Adult and paediatric cough guidelines: Ready for an overhaul?

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ABSTRACT

Cough is one of the most common reasons that patients seek medical attention. Cough guidelines from numerous countries and societies are available to assist the clinician to investigate and manage patients with cough. We review some of the recent progress in the field of cough that may lead to revision of these guidelines. In adults with chronic cough, new causes such as obstructive sleep apnoea have been identified. A new terminology, cough hypersensitivity syndrome (CHS), has been proposed for patients with chronic cough, which emphasises cough reflex hypersensitivity as a key feature. New therapeutic options are now available, particularly for patients with refractory or idiopathic chronic cough, which include gabapentin, speech pathology management and morphine. There has been great progress in the assessment of cough with the development of validated quality of life questionnaires and cough frequency monitoring tools. In children, common aetiologies differ from adults and those managed according to guidelines have better outcomes compared to usual care. New diagnostic entities such as protracted bacterial bronchitis have been described. Paediatric-specific cough assessment tools such as the Parent/Child Quality of Life Questionnaire will help improve the assessment of patients. Further research is necessary to improve the evidence base for future clinical guideline recommendations. Guidelines in future should also aim to reach a wider audience that includes primary care physicians, non-specialists and patients.
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1. Introduction

Cough is a prevalent worldwide health problem. A recent survey of >10,000 subjects from specialist clinics evaluating adult patients with chronic cough from America, Europe and Asia highlighted that patients experiencing chronic cough have a strikingly similar clinical phenotype regardless of the country of origin. Patients present most commonly in middle or late age and women are twice as likely as men to suffer from chronic cough [1]. The prevalence of cough in the community has been estimated to be as high as 12% [2] and cough is one of the most common reasons for patients to consult their doctor [3,4]. Cough has been traditionally divided into acute, sub-acute and chronic categories according to its duration [5]. Acute cough and sub-acute cough typically present to primary care physicians and are usually caused by viral upper respiratory tract infections, whereas chronic cough is often referred to secondary care physicians and can be caused by a wide range of conditions. Patients often have to visit their doctor on multiple occasions before referral to an appropriate specialist and misdiagnosis is common [6]. [7] Regardless of the cause and category, cough can be very disruptive to the individual and those around them, such as parents [8], and it is often associated with an impaired health-related quality of life [6,9]. It can be associated with absence from work, social embarrassment and severe adverse effects, for example, urinary incontinence [10].

The assessment and management of cough can vary widely between clinicians [11] and there is variation in treatment success outcomes between clinics, ranging from 60% to 95% [12]. This variation may reflect the paucity of effective tools to investigate patients, and also of treatment options. The American College of Chest Physicians (ACCP) cough guidelines were one of the first to be published by an international society in 1998 [13] and many others have been published subsequently in an attempt to standardise practice and improve outcomes. The focus of most guidelines has been the secondary case setting, with some attention to patients with acute cough in primary care. The algorithm for most adult cough guidelines is based on investigating patients according to the anatomic diagnostic protocol [14], which evaluates patients for asthma, gastro-oesophageal reflux disease (GORD) and rhinitis before rarer causes. In paediatrics, aetiology-based management is emphasised with avoidance of an empiric approach.

There has been little focus on developing protocols for specialist cough clinics in tertiary care, although this is the setting where

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ORIGINAL REPORT

BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
The phase III BEYOND trial was undertaken to confirm in a Chinese patient population the efficacy seen with first-line bevacizumab plus platinum doublet chemotherapy in globally conducted studies.

Patients and Methods
Patients age ≥ 18 years with locally advanced, metastatic, or recurrent advanced nonsquamous non–small-cell lung cancer (NSCLC) were randomly assigned to receive carboplatin (area under the curve, 6) intravenously and paclitaxel (175 mg/m^2) intravenously (CP) on day 1 of each 3-week cycle, for ≤ six cycles, plus placebo (Pl+CP) or bevacizumab (B+CP) 15 mg/kg intravenously, on day 1 of each cycle, until progression, unacceptable toxicity, or death. The primary end point was progression-free survival (PFS); secondary end points were objective response rate, overall survival, exploratory biomarkers, safety.

Results
A total of 276 patients were randomly assigned, 138 to each arm. PFS was prolonged with B+CP versus Pl+CP (median, 9.2 *v* 6.5 months, respectively; hazard ratio [HR], 0.40; 95% CI, 0.29 to 0.54; $P < .001$). Objective response rate was improved with B+CP compared with Pl+CP (54% *v* 26%, respectively). Overall survival was also prolonged with B+CP compared with Pl+CP (median, 24.3 *v* 17.7 months, respectively; HR, 0.68; 95% CI, 0.50 to 0.93; $P = .0154$). Median PFS was 12.4 months with B+CP and 7.9 months with Pl+CP (HR, 0.27; 95% CI, 0.12 to 0.63) in *EGFR* mutation–positive tumors and 8.3 and 5.6 months, respectively (HR, 0.33; 95% CI, 0.21 to 0.53), in wild-type tumors. Safety was similar to previous studies of B+CP in NSCLC; no new safety signals were observed.

Conclusion
The addition to bevacizumab to carboplatin/paclitaxel was well tolerated and resulted in a clinically meaningful treatment benefit in Chinese patients with advanced nonsquamous NSCLC.

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INTRODUCTION

Platinum-based chemotherapy remains the standard of care for patients with unresectable, advanced, non–small-cell lung cancer (NSCLC).[1] Platinum-based chemotherapy plus third-generation agents (including gemcitabine, paclitaxel, and pemetrexed) have produced significant incremental survival benefits.[2] Existing literature supports both cisplatin and carboplatin as valid first-line treatment for advanced NSCLC.[1,3,4] In China, first-line platinum-based doublets are widely used, and gemcitabine and paclitaxel are two of the most common companion agents in clinical practice.[5]

The discovery of activating mutations of the epidermal growth factor receptor (*EGFR*) and the echinoderm microtubule-associated protein like 4–anaplastic lymphoma kinase (*EML4-ALK*) fusion has led to changing treatment for patients with NSCLC who harbor these drivers. Agents that inhibit the tyrosine kinase binding sites of these molecules have demonstrated improved progression-free survival (PFS) versus chemotherapy.[6-8]

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PARTICLE AND FIBRE TOXICOLOGY

RESEARCH Open Access

Cationic nanoparticles directly bind angiotensin-converting enzyme 2 and induce acute lung injury in mice

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Abstract

Background: Nanoparticles have become a key technology in multiple industries. However, there are growing reports of the toxicity of nanomaterials to humans. In particular, nanomaterials have been linked to lung diseases. The molecular mechanisms of nanoparticle toxicity are largely unexplored.

Methods: Acute lung injury was induced in wild-type mice and angiotensin-coverting enzyme 2 (ACE2) knockout mice by the intratracheal instillation of cationic polyamidoamine dendrimer (PAMAM) nanoparticles. For rescue experiments, losartan (15 mg/kg in PBS) was injected intraperitoneally 30 min before nanoparticle administration.

Results: Some PAMAM nanoparticles, but not anionic PAMAM nanoparticles or carbon nanotubes, triggered acute lung failure in mice. Mechanistically, cationic nanoparticles can directly bind ACE2, decrease its activity and down-regulate its expression level in lung tissue, resulting in deregulation of the renin-angiotensin system. Gene inactivation of *Ace2* can exacerbate lung injury. Importantly, the administration of losartan, which is an angiotensin II type I receptor antagonist, can ameliorate PAMAM nanoparticle-induced lung injury.

Conclusions: Our data provide molecular insight into PAMAM nanoparticle-induced lung injury and suggest potential therapeutic and screening strategies to address the safety of nanomaterials.

Keywords: Nanoparticles, Angiotensin II, Angiotensin-converting enzyme 2, Acute lung injury, Losartan

Background

Nanoparticles have become key materials in the pharmaceutical, information, and communication industries as well as in multiple other areas that require strong, light materials [1]. However, several concerns have been raised about the safety of the widespread use of nanoparticles [2,3]. Among these concerns, the potential toxicity of nanoparticles to humans is among the most distressing. Nanomaterials have been reported to be harmful at the cellular, subcellular, and protein levels, and they have been found to elicit injurious responses in various organisms [4-6]. Many of these studies have focused on lung diseases, including clinical studies of workers who developed pulmonary disease from nanoparticle exposure [7-11]. A worldwide moratorium on nanomaterials has even been called until the safety issues have been resolved [12]. Nanoparticle safety in the respiratory system is important not only for workers who have high exposure to the particles but also in pulmonary drugs where nanoparticles serve as a vehicle directly to the lung [13]. Therefore, it is of critical importance to elucidate the molecular mechanisms by which nanoparticles induce lung injury.

Polyamidoamine (PAMAM) dendrimers are a family of dendritic polymers that are based on an ethylenediamine

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Authors' contributions

YS, FG, ZZ, CGL, XXH, YZ, and CXW performed most of the experiments, with technical support provided by HLW, HLL, ZSH, KT, BS, ZYM, and KK, JMG measured the blood oxygenation. BL analyzed mice to determine the extent of the injury induced by the nanoparticles. NSZ, QHL, CW, and DSL contributed helpful ideas. CYJ conceived the project and, together with YS, FG, ZZ, JMP, designed the experiments, analyzed the data, and wrote the manuscript. All authors read and approved the final manuscript.

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Ceftaroline fosamil for community-acquired pneumonia

We have concerns related to the Article by Nan Shan Zhong and colleagues[1] assessing the non-inferiority and superiority of ceftaroline fosamil versus ceftriaxone for the management of community-acquired pneumonia in Asian patients. First, regarding the timing of assessment of clinical cure between groups, the authors define clinical cure as "resolution of all signs and symptoms of community-acquired pneumonia or improvement to such an extent that further antimicrobial treatment was unnecessary" and state that this was assessed for all patients 8–15 days after the last dose of antibiotics. However, the authors did not report any differences in assessment times between groups, which can be prone to reporting bias. As shown by El Moussaoui and colleagues,[2] many symptoms (including those of wellbeing) take up to 14 days or longer for resolution, which should be accounted for by Zhong and colleagues.

Second, on the basis of the results obtained and Zhong and colleagues' arguments, we are not convinced that ceftaroline fosamil is superior to ceftriaxone for Asian patients and we believe that the authors' overgeneralise the results outside of what was studied. Instead, we interpret the findings to be relevant to the geographical regions, rather than patient ethnic origin, and would not generalise these results to Asian patients living outside of the studied regions, including our own centre. The results of this study are not convincing enough to modify our treatment approach for Asian patients as a whole.

We also need to mention concerns with respect to Zhong and colleagues' conclusions. Ceftaroline fosamil is a new drug and this is the only large randomised controlled trial so far to show superiority over a standard treatment for community-acquired pneumonia.[1] Previous studies were only able to show non-inferiority with a similar comparator.[3,4] Although we agree with Zhong and colleagues that ceftaroline fosamil is probably effective for community-acquired pneumonia, we fear that widespread use will increase resistance when the drug has the potential to be reserved for treatment of meticillin-resistant *Staphylococcus aureus* (MRSA). Additionally, to call for use as a comparator in future trials is not supported by study findings (ceftaroline fosamil has not yet become a standard therapy for community-acquired pneumonia) and is suspect in view of the industry support declared. Our conclusions from this Article[1] are that ceftaroline fosamil is probably an effective option for community-acquired pneumonia (PORT class III and IV) but should not be recommended for widespread use until its ability to treat MRSA-related community-acquired pneumonia is known.

We declare no competing interests.

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Authors' reply

We thank Shane Pawlak and Kyle Wilby for their interest in our study, and will first address the question of our finding of superiority of ceftaroline fosamil over ceftriaxone. Pawlak and Wilby correctly state that the earlier randomised controlled trials of ceftaroline fosamil in community-acquired pneumonia, FOCUS 1 and 2,[1] used a non-inferiority design; ours is the first trial designed to also assess superiority. Across these trials, the non-inferiority (and superiority) criteria were agreed with regulatory authorities and are widely accepted. The FOCUS trials each showed a positive response trend in favour of ceftaroline fosamil, and in a pooled analysis, the treatment difference met the same superiority criteria applied in this trial.[1] We believe the superiority conclusion is thus robust and the previous results are consistent with this finding. Moreover, a meta-analysis of all three trials showed the same outcome (efficacy favouring ceftaroline fosamil and consistency across the trials). Numerical differences between the trials seemed to be affected by the level of antecedent antibiotic use; our trial had the lowest rate of such prior therapy and hence the clearest treatment difference.[2]

Space constraints prevented inclusion of timings of test-of-cure assessments; this has been analysed and we confirm there was no bias between groups. Patients were also assessed at a late follow-up visit 21–28 days after end of treatment and there were few cases of relapse in those clinically cured at the main test-of-cure assessment (ceftaroline fosamil 3%; ceftriaxone 2%), suggesting that the results at the test-of-cure visit are robust. Indeed, El Moussaou and

collegues conclude that "presence of symptoms beyond 28 days... reflect[s] age and comorbidity rather than the persistent effects of the pneumonia itself".[3]

We do not generalise the results outside of the study population; however, we consider the overall conclusions to be justified based not only on the clinical results but also on the microbiological and pharmacokinetic data outlined in the discussion, which include greater in-vitro potency against trial isolates, lower protein binding, and possibly improved lung tissue penetration for ceftaroline versus ceftriaxone.

Finally, we acknowledge that ceftaroline fosamil is not yet a standard therapy for community-acquired pneumonia; guidelines inevitably take time to catch up with clinical evidence (although some, such as the National Institute for Health and Care Excellence in the UK, have already incorporated some of the evidence about ceftaroline fosamil).[4] However, we stand by the suggestion that ceftaroline fosamil should be a comparator in future community-acquired pneumonia trials because it is the only agent to have shown superiority to an established standard of care.

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Antimicrobial stewardship and public knowledge of antibiotics

Haley Morrill and Kerry LaPlante report that several US states have announced policies to promote responsible antibiotic use among health-care providers.[1] In March 2015, in recognition of the public health threat and economic costs of antimicrobial resistance, the Obama administration made a commitment to reduce inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings by 2020, compared with 2011. However, the national plan to combat antibiotic resistance does not address the effect of patient knowledge and expectations on the overconsumption of antibiotics.

Data from the National Science Foundation's nationally representative Survey of Public Attitudes Toward and Understanding of Science and Technology show that public knowledge of antibiotics in the USA remains suboptimum.[2] Nationally, correct responses to the question "Antibiotics kill viruses as well as bacteria. Is that true or false?" increased from 30% in 1990 to 50% in 2000 but then mostly plateaued until 2012 (figure). Women were more likely to answer the question correctly (51%), compared with men (44%). Respondents without postsecondary education were less likely to answer the question correctly (37%), compared with those who completed university (70%). Hispanic people (29%) and non-Hispanic black people (35%) were also less likely than non-Hispanic white people (63%) to correctly identify that antibiotics do not kill viruses. In a parallel survey in the European Union, 46% of respondents correctly identified antibiotics as ineffective against viruses. Even fewer respondents in China and India answered the question correctly—raising troubling implications for the future of infectious disease control in emerging economies.[2,3]

These deficits in the public's knowledge of the ineffectiveness of antibiotics against viral infections might be contributing factors to the overprescribing of antibiotics. It has been well documented that the knowledge and attitudes of both the prescribing physician and the patient influence the prescribing of antibiotics.[4] However, little empirical data exist about the effect of national campaigns on public knowledge regarding antibiotics. Continued surveillance of global attitudes toward antibiotics could help policymakers design more effective campaigns to raise public awareness of the necessity of prudent antibiotic use.

Survey data suggest that there are important disparities in knowledge by race, ethnic origin, sex, and educational status—factors that point to the importance of ensuring that educational campaigns reach underserved populations. Prior studies have suggested that physicians are significantly more likely to prescribe antibiotics inappropriately to children of parents with low socioeconomic status.[5] There might also be substantial differences in expectations. For example, Latino parents were significantly more likely than non-Hispanic white parents to expect antibiotics for the common cold.[6] Targeting prescribers

呼吸疾病国家重点实验室

Chinese Consensus on Early Diagnosis of Primary Lung Cancer (2014 Version)

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The incidence and mortality of lung cancer in China have rapidly increased. Lung cancer is the leading cause of cancer death in China, possibly because of the inadequate early diagnosis of lung cancer. Reaching a consensus on early diagnostic strategies for lung cancer in China is an unmet needed. Recently, much progress has been made in lung cancer diagnosis, such as screening in high-risk populations, the application of novel imaging technologies, and the use of minimally invasive techniques for diagnosis. However, systemic reviews of disease history, risk assessment, and patients' willingness to undergo invasive diagnostic procedures also need to be considered. A diagnostic strategy for lung cancer should be proposed and developed by a multidisciplinary group. A comprehensive evaluation of patient factors and clinical findings should be completed before treatment. ***Cancer* 2015;121:3157-64**. *© 2015 American Cancer Society.*

KEYWORDS: bronchoscopy, diagnosis, lung cancer, screening.

INTRODUCTION

Primary lung cancer (hereinafter referred to as *lung cancer*) is a malignant tumor that severely threatens human health. Among all malignant tumors, lung cancer ranks first in both incidence (1,200,000 year) rates according to World Health Organization data published in 2003. Between 2000 and 2005, the incidence and mortality of lung cancer in China increased by 116,000 and 101,000 cases, respectively. The impact of the disease is climbing quickly in China , as a result of the rapidly increasing number of smokers.[1] If China does not control smoking and air pollution in a timely manner, then China's annual incidence of lung cancer will be >1,000,000 by the year 2025, and it will become first in the world for lung cancer incidence.[2] The 5-year survival rate of patients with lung cancer is only 17.8%.[1] The main reason for this is that approximately 75% of patients have advanced lung cancer at the time of diagnosis. Because inadequate early diagnosis of lung cancer may lead to a poor prognosis, improving the early diagnosis of lung cancer is an unmet needed.

The concept of early diagnosis of lung cancer refers to the correct detection and diagnosis of[3,4] lung cancer in the early stages to increase the proportion of patients diagnosed with early stage disease in the general population, reduce diagnosis time, and treat patients in a timely fashion to achieve the ultimate goal of reducing lung cancer mortality. In this consensus report, we focus on how to detect and diagnose lung cancer in the early stages.

Clinical Information Collection

Assessment of risk factors

Lung cancer is a lifestyle and environmental factor-related disease. The following risk factors are closely associated with the development of lung cancer:

Tobacco smoke. Tobacco smoking is a major modifiable risk factor in the development of lung cancer and accounts for 85% of all lung cancer-related deaths.[5] A dose-response relation exists between smoking tobacco and the risk of developing lung cancer. The cessation of tobacco smoking decreases the risk of lung cancer. However, even former smokers have a

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See editorial on pages 3055-7, this issue.

All members of the Lung Cancer Study Group of the Chinese Thoracic Society and the Chinese Alliance Against Lung Cancer Expert Group contributed equally to this consensus.

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Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/β-catenin pathway

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Keywords: *Cir-ITCH*, ESCC, Wnt/β-catenin pathway

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ABSTRACT

Circular RNAs with exonic sequences represent a special form of non-coding RNAs, discovered by analyzing a handful of transcribed genes. It has been observed that circular RNAs function as microRNA sponges. In the present study, we investigated whether the expression of circular RNAs is altered during the development of esophageal squamous cell carcinoma (ESCC). Using a TaqMan-based reverse transcriptase polymerase chain reaction assay, the relationship between *cir-ITCH* and ESCC was analyzed in a total of 684 ESCC and paired adjacent non-tumor tissue samples from eastern and southern China. We found that *cir-ITCH* expression was usually low in ESCC compared to the peritumoral tissue. The functional relevance of *cir-ITCH* was further examined by biochemical assays. As sponge of miR-7, miR-17, and miR-214, *cir-ITCH* might increase the level of *ITCH*. *ITCH* hyper expression promotes ubiquitination and degradation of phosphorylated Dvl2, thereby inhibiting the Wnt/β-catenin pathway. These results indicate that *cir-ITCH* may have an inhibitory effect on ESCC by regulating the Wnt pathway.

INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide and sixth most common cause of cancer death [1]. One of the main subtypes is esophageal squamous cell carcinoma (ESCC), which is a malignancy that arises from esophageal epithelial cells [2]. Cancer is widely regarded as a genetic disease, and ESCC is no exception, but the molecular and genetic basis of esophageal carcinogenesis remains largely unknown [3, 4].

High-throughput RNA sequencing (RNA-Seq), an emerging method to study the RNA regulation mechanism in the whole genome, has been able to detect circular RNA [5]. Circular RNA, in general does not encode protein, but can occur in any genomic region; 85% of circular RNAs are aligned in sense orientation to known protein-coding genes, and they span 1–5 exons [6]. The existence of circular RNA was proposed for several years in early research, for example, the circular testis-determining gene, *SRY* [7]. The most well-known circular RNA is *CDR1*, coding for cerebellar degeneration-related protein 1, which has been observed in all domains of life, but overall, circular RNAs are considered extremely rare in nature [8]. Recently, circular RNAs were proposed to harbor microRNAs (miRNAs), and were found to be enriched with functional miRNA binding sites [6, 9]. Mature miRNAs always play an important regulatory role in cell growth, proliferation, differentiation, and cell death. Following database analysis of the study by Memczak et al. on circular RNA, we found that *cir-ITCH* spanned several exons of the E3 ubiquitin (Ub) protein ligase (ITCH). Moreover, both *cir-ITCH* and the 3'-untranslated region (UTR) of *ITCH* shared some

CUR-65 Score for Community-Acquired Pneumonia Predicted Mortality Better Than CURB-65 Score in Low–Mortality Rate Settings

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Abstract: *Background:* It is not clear whether low-blood pressure criterion could be removed from CURB-65 (confusion, urea >7 mmol/L, respiratory rate ≥30/min, low blood pressure and age ≥65 years) score to orchestrate an improvement in identifying patients with community-acquired pneumonia (CAP) in low–mortality rate settings. *Methods:* A retrospective cohort study of 1,230 CAP patients was performed to simplify the CURB-65 scoring system by excluding low-blood pressure variable. The simplification was validated in a prospective 2-center cohort of 1,409 adults with CAP. *Results:* The hospital mortalities were 1.3% and 3.8% in the retrospective and prospective cohorts, respectively. The mortality rates in the 2 cohorts increased directly with the increasing scores, showing significant increased odds ratios for mortality. The pattern of sensitivity, specificity, positive predictive value and Youden's index of a CUR-65 (Confusion, Urea >7 mmol/L, Respiratory rate ≥30/min and age ≥65 years) score of ≥2 for prediction of mortality was better than that of a CURB-65 score of ≥3 in the retrospective cohort. Higher values of corresponding indices were confirmed in the validation cohort. The higher accuracy of CUR-65 score for predicting mortality was illustrated by the area under the receiver operating characteristic curve of 0.937, compared with 0.915 for CURB-65 score in the retrospective cohort ($P = 0.0073$). The validation cohort confirmed a similar paradigm (0.953 versus 0.907, $P = 0.0002$). *Conclusions:* CURB-65 score could be simplified by removing low blood pressure to orchestrate an improvement in predicting mortality in CAP patients who have a low risk of death. A CUR-65 score of ≥2 might be a more valuable cutoff value for severe CAP.

Key Indexing Terms: Community-acquired pneumonia; CUR-65; CURB-65; Mortality; Prognosis. **[Am J Med Sci 2015;350(3):186–190.]**

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A key step in the management of community-acquired pneumonia (CAP) is the initial assessment of the severity of the disease. An accurate assessment helps the clinician determine the site of care, the extent of diagnostic testing and the type and intensity of antibiotic treatment. In response, the British Thoracic Society recommends the use of CURB-65 (confusion, urea >7 mmol/L, respiratory rate ≥30/min, low blood pressure and age ≥65 years) for the prognostic assessment of CAP.[1,2]

Loke's recent systematic review and meta-analysis suggest that the CURB-65 scoring system performs well at identifying patients with pneumonia who have a low risk of death (average mortality = 7.4%).[3] It was discovered that low-blood pressure criterion showed no association with mortality in a low–mortality rate setting (average mortality = 1.3%).[4] The performance of scores did vary significantly between different studies in different health-care systems. If the population of patients to whom the score is being applied is significantly different from the original derivation, it may be necessary to perform local recalibration of the score.[5]

Two cohort studies were conducted to derive and then to validate a simplified CURB-65 scoring system by removing low blood pressure to orchestrate an improvement in identifying patients with CAP in low–mortality rate settings.

METHODS

Design and Setting

A retrospective cohort study was performed of 1,245 adult CAP patients presenting to the Department of Respiratory Medicine in a Chinese affiliated tertiary hospital of a medical college from 2005 to 2009. One thousand four hundred thirty adults with a diagnosis of CAP were recruited to a prospective 2-center cohort study at the Departments of Respiratory Medicine in 2 affiliated tertiary hospitals of 2 medical colleges in China between 2010 and 2013.

The simplified CURB-65 score, terming it CUR-65 (Confusion, Urea >7 mmol/L, Respiratory rate ≥30/min and age ≥65 years) score, was derived in the retrospective sample by excluding low systolic (<90 mm Hg) or diastolic (60 mm Hg or less) blood pressure.[4,6] The simplification was tested against the prospective 2-center validation cohort.

Criteria for Enrollment

CAP was defined as an acute infection of the pulmonary parenchyma associated with an acute infiltrate on the chest radiograph with 2 or more symptoms, including fever (>38°C), rigors, sweats, new cough or change in color of respiratory secretions, chest discomfort, or dyspnea.[7] Patients who were <18 years, who had been hospitalized during the 28 days preceding the study, who had severe immunosuppression (eg, patients with neutropenia after chemotherapy or bone marrow

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Deubiquitinases (DUBs) and DUB inhibitors: a patent review

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Abstract

Introduction—Deubiquitinating-enzymes (DUBs) are key components of the ubiquitin-proteasome-system (UPS). The fundamental role of DUBs is specific removal of ubiquitin from substrates. DUBs contribute to activation/deactivation, recycling and localization of numerous regulatory-proteins, thus playing major roles in diverse cellular-processes. Altered DUB activity is associated with multitudes of pathologies including cancer. Therefore, DUBs represent novel candidates for target-directed drug development.

Areas covered—The article is a thorough review/accounting of patented compounds targeting DUBs stratifying/classifying the patented compounds based on: chemical-structures, nucleic-acid compositions, modes-of-action and targeting-sites. The review provides a brief background on the UPS and DUBs involvement. Furthermore, methods for assessing efficacy and potential pharmacological utility of DUB inhibitor (DUBi) are discussed.

Expert opinion—The FDA's approval of the 20S proteasome inhibitors: bortezomib and carfilzomib for treatment of hematological malignancies established the UPS as an anti-cancer

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Original Article

Early quantitative CT analysis of oleic acid induced acute respiratory distress syndrome in a canine model

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Abstract: Background: Although quantitative computed tomography (CT) has been used to analyze the lungs of patients with confirmed diagnoses of acute respiratory distress syndrome (ARDS), there are few reports to show the diagnosis during the early stage of ARDS. Using a canine model and quantitative CT, we aimed to develop an oleic acid (OA) induced ARDS regarding the early stage of ARDS that could improve in the early diagnosis of ARDS. Methods: Fourteen healthy beagle dogs underwent CT. Their lung tissue was manually partitioned into four compartments, i.e., non-aerated, poorly aerated, normally aerated, and hyper-aerated lung compartments. The mean CT attenuation value Hounsfield unit (HU), tissue mass (g), residual volume (ml), and percentage of lung area were automatically determined for each lung compartment and compared between groups by receiver operating characteristic curve (ROC) analyses using area under curve (AUC). The optimized cut-off point for each parameter was determined by Youden's index. Results: Regarding lung compartments during the expiratory phase, the percentage of non-aerated lung area in the ARDS group was higher vs. controls at all time points (T1 to T6). CT attenuation values for the ARDS group increased with time during both respiratory phases compared with controls. During both respiratory phases, tissue mass within the ARDS group significantly increased compared with controls at T3-T6. Conclusions: Quantitative CT analysis can detect ARDS at an early stage with high sensitivity and specificity, providing a minimum of assistance in the early diagnosis of ARDS.

Keywords: Acute respiratory distress syndrome, computed tomography, quantitative analysis, canine model, attenuation value, Hounsfield unit

Introduction

Acute respiratory distress syndrome (ADRS) is a common critical illness with a mortality rate of 40-60%. The main reason for the high mortality rate usually stems from the severity of the inciting insult leading to the ARDS the cause for high mortality. Even once the diagnosis is made, the mortality rate remains elevated at 38.5-40% [1]. Previous studies have shown that blood gas analysis (the "gold standard" for the diagnosis of ARDS) usually lags behind pulmonary pathologic changes [2]. In addition, X-ray manifestations also lag by approximately 4-24 h behind the clinical manifestations [2, 3].

In the mid 1990's, measurement of the positive end-expiratory pressure (PEEP)-induced alveolar air volume was used to determine the reduction in the computed tomography (CT) value of the non-aerated lung parenchyma at a certain level. Generally, the level was a single CT slice close to the diaphragmatic surface, and the measured CT values were between -100 and 100 HU. This approach ignored the alveolar CT attenuation characteristics in the poorly aerated areas (with CT values between -100 HU and 500 HU) [4]. Therefore, the PEEP-induced alveolar air volume was often underestimated. In addition, estimations based on CT values from a single slice can underestimate or overestimate the alveolar air volume throughout the entire lung. Therefore, a new CT method was developed using scans which included the entire lung from apex to diaphragm. When the end-expiratory lung volume was equal to the

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ORIGINAL RESEARCH

Exogenous Interleukin-17A Inhibits Eosinophil Differentiation and Alleviates Allergic Airway Inflammation

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Abstract

IL-17 is known to play important roles in immune and inflammatory disease, such as in asthma, but its functions in allergic airway inflammation are still controversial, and the molecular mechanisms mediating these functions remain unclear. Increased production of eosinophils in bone marrow and their emergence in the airway have been linked to the onset and progression of allergic asthma. In this study, we investigated the effects of exogenous IL-17 on allergic airway inflammation and explored the underlying molecular mechanisms through eosinophil generation. Exogenous IL-17 significantly attenuated the features of allergic inflammation induced by ovalbumin in mice. It inhibited eosinophil differentiation both *in vivo* and *in vitro*, accompanied by down-regulated expression of CC chemokine receptor 3, GATA binding protein 1 (GATA-1), and GATA binding protein 2 (GATA-2), as well as reduced formation of common myeloid progenitors and eosinophil progenitors, but without influencing eosinophil apoptosis. IL-17 also significantly decreased the number of eosinophils in IL-5–transgenic mice, although it notably increased the levels of IL-3, IL-5, and granulocyte/macrophage colony–stimulating factor. In addition, IL-17 had little effect on secretion of the inflammatory cytokines by eosinophils. Neutralization of endogenous IL-17 significantly augmented eosinophil recruitment in the airways. Together, these findings suggest that exogenous IL-17 protects against allergic airway inflammation, most likely through inhibition of the eosinophil differentiation in bone marrow.

Keywords: IL-17A; eosinophil; differentiation; allergic airway inflammation

Clinical Relevance

The present study represents an initial effort to demonstrate that exogenous IL-17 attenuates airway hyperresponsiveness and airway inflammation in allergic asthma, most likely through inhibition of eosinophil differentiation followed by decreased eosinophil recruitment to inflamed tissue, rather than down-regulation of the survival and cytokine secretion of eosinophils. The study also re-emphasizes the importance of targeting the inhibition of eosinophil differentiation in allergic inflammation, which may lead to new therapeutic targets for asthma.

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Expression, purification and identification of Pla a1 in a codon-optimized *Platanus* pollen allergen

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Abstract. The present study aimed to express, purify and identify the major allergen gene, Pla a1, in *Platanus* pollen. According to previous studies, the major gene sequences of the Pla a1 allergen were obtained and codon optimization and synthesis of the genome were performed using DNAStar software. Following binding of the target gene fragment and the pET-44a vector, the JM109 cells were transfected to produce positive clones. The vectors were then transformed into *Escherichia coli* Rosetta cells to induce the expression of the target protein. The exogenous protein was purified using affinity chromatography and was identified by western blot analysis. Pla a1, the major allergen protein in *Platanus* pollen, was successfully isolated and this exogenous protein was purified using affinity chromatography. The present study was the first, to the best of our knowledge, to obtain expression of the allergen recombinant protein, Pla a1, fused with a Strep-TagII via codon optimization and provided the basis for the preparation of allergens with high purity, recombinant hypoallergenic allergens and allergen nucleic acid vaccines.

Introduction

Platanus belongs to the family Platanaceae and grows in a wide distribution. Kosisky *et al* (1) investigated airborne pollen allergens between 1998 and 2007 by quantitative collection in downtown Washington, WA, USA and the results demonstrated that the major pollen types include oak, cypress, *Pinaceae*, *Morus*, Betulaceae, *Acer*, *Platanus*, *Fraxinus* and Gramineae. Tree and grass pollens accounted for 91.2 and 7% of the total pollen count, respectively. Aira *et al* (2) demonstrated that *Platanus* and *Olea* are important local sources of pollen in Iberian Peninsula, located in the northwest of Spain. Ture *et al* (3) reported that Bilecik *Pinus*, Cupressaceae, *Platanus*, *Quercus* and *Salix* are the predominant types of regional airborne pollen in Turkey and the highest concentration of airborne pollen was observed in May. In northwestern Turkey, Celenk *et al* (4) revealed that *Pinus*, *Olea*, *Platanus*, Cupressaceae, *Quercus*, Poaceae, Urticaceae and Castanea are important in the airborne spread of pollens, of which concentrations also peaked in May. The *Platanus* pollen has a higher airborne concentration and also causes widespread allergy (4). Liu *et al* (5) investigated airborne pollen in Hubei, China, in which 2,300 patients with hay fever received skin allergen testing and seasonal incidence was analyzed. In Hubei, the pollen with the highest positive allergenic rate was *Platanus* in spring and *Artemisia* and ragweed in fall. Lu *et al* (6) screened 168 patients with allergic asthma for pollen blood allergens and the result suggested that mugwort, *Platanus*, blite, *Humulus* and Gramineae were the predominant allergenic pollens in Xi'an, China. Lauer *et al* (7) found that the allergen immunoglobulin E response rate of *Platanus* pollen is between 27.3 and 63.8% in the Mediterranean region and is the major regional airborne pollen allergen. A number of surveys and clinical epidemiological data have suggested that *Platanus* pollen is an important cause of hay fever in China and western countries (8-10).

It has been revealed that in *Platanus* pollen allergen extracts, Pla A1, Pla A2 and Pla A3 are the major allergenic proteins. The Pla a1 protein is detected in the serum of 92% of patients with *Platanus*-induced hay fever, while the Pla a2 and Pla a3 response rates are 84 and 63.8%, respectively (7,11,12). Few studies investigating the expression and purification of the major allergens in *Platanus* pollen have been performed. The present study successfully expressed, purified and identified the Pla a1 protein and provided the basis for preparations of allergens with high purity, recombinant hypoallergenic allergens and allergen nucleic acid vaccines.

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Key words: *Platanus* pollen, major allergen, codon optimization, expression

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Original article

Genetically induced moderate inhibition of 20S proteasomes in cardiomyocytes facilitates heart failure in mice during systolic overload

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ABSTRACT

The in vivo function status of the ubiquitin–proteasome system (UPS) in pressure overloaded hearts remains undefined. Cardiotoxicity was observed during proteasome inhibitor chemotherapy, especially in those with preexisting cardiovascular conditions; however, proteasome inhibition (PsmI) was also suggested by some experimental studies as a potential therapeutic strategy to curtail cardiac hypertrophy. Here we used genetic approaches to probe cardiac UPS performance and determine the impact of cardiomyocyte-restricted PsmI (CR-PsmI) on cardiac responses to systolic overload. Transgenic mice expressing an inverse reporter of the UPS (GFPdgn) were subject to transverse aortic constriction (TAC) to probe myocardial UPS performance during systolic overload. Mice with or without moderate CR-PsmI were subject to TAC and temporally characterized for cardiac responses to moderate and severe systolic overload. After moderate TAC (pressure gradient: ~40 mm Hg), cardiac UPS function was upregulated during the first two weeks but turned to functional insufficiency between 6 and 12 weeks as evidenced by the dynamic changes in GFPdgn protein levels, proteasome peptidase activities, and total ubiquitin conjugates. Severe TAC (pressure gradients >60 mm Hg) led to UPS functional insufficiency within a week. Moderate TAC elicited comparable hypertrophic responses between mice with and without genetic CR-PsmI but caused cardiac malfunction in CR-PsmI mice significantly earlier than those without CR-PsmI. In mice subject to severe TAC, CR-PsmI inhibited cardiac hypertrophy but led to rapidly progressed heart failure and premature death, associated with a pronounced increase in cardiomyocyte death. It is concluded that cardiac UPS function is dynamically altered, with the initial brief upregulation of proteasome function being adaptive, and CR-PsmI facilitates cardiac malfunction during systolic overload.

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1. Introduction

The ubiquitin–proteasome system (UPS) is responsible for the degradation of most intracellular proteins for protein quantity and quality control [1]. Proteasome-mediated degradation occurs in the interior chamber of the 20S proteasome, which is composed of an axial stack of four heptameric rings: 2 outer α rings (α1–α7) and 2 inner β rings (β1–β7). The eukaryotic proteasome possesses three peptidase activities residing in 3 distinct subunits: chymotrypsin-like (β5), trypsin-like (β2), and caspase-like (β1). Clinically used proteasome inhibitors (bortezomib and carfilzomib) target the β5 subunit, thereby inhibiting the proteasome [2].

UPS dysfunction is implicated in a variety of cardiovascular diseases [1–4], including load-dependent cardiac disorders [5–7]. The pathogenic significance of impaired UPS-mediated protein degradation in cardiac hypertrophy and cardiomyopathy is underscored by the recent association of mutations in *TRIM63*, a ubiquitin ligase, with familial hypertrophic cardiomyopathy in humans [8]. Further characterization of the

Abbreviations: CHF, congestive heart failure; PsmI, proteasome inhibition; CR-PsmI, cardiomyocyte-restricted PsmI; LV, left ventricle; NTG, non-transgenic; PFI, proteasome functional insufficiency; PQC, protein quality control; TAC, transverse aortic constriction; TG, transgenic; UPS, ubiquitin–proteasome system.

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Insulin-like growth factor-1 endues monocytes with immune suppressive ability to inhibit inflammation in the intestine

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The pathogenesis of some chronic inflammation such as inflammatory bowel disease is unclear. Insulin-like growth factor-1 (IGF1) has active immune regulatory capability. This study aims to investigate into the mechanism by which IGF1 modulates the monocyte (Mo) properties to inhibit immune inflammation in the intestine. In this study, the production of IGF1 by intestinal epithelial cells was evaluated by real time RT-PCR and Western blotting. Mos were analyzed by flow cytometry. A mouse colitis model was created with trinitrobenzene sulfonic acid. The results showed that mouse IECs produced IGF1, which could be up regulated by exposure to CpG-ODN (CpG-oligodeoxynueleotides) in the culture. Culture the CpG-ODN-primed IEC cells and Mos or exposure of Mos to IGF1 in the culture induced the Mos to express IL-10. The IGF1-primed Mos showed the immune suppressive effect on inhibiting the immune inflammation in the mouse colon. In conclusion, the IGF1-primed Mos are capable of suppressing immune inflammation in the intestine.

The pathogenesis of inflammatory bowel disease (IBD) is not fully understood. It is accepted that the nature of IBD is an inflammatory disorder[1], in which the abnormality of immune response in the local tissue plays a critical role[2]. The prevalence of IBD has reached 0.1–0.5% in the world, and continued rising despite of the research about IBD has been advancing rapidly in this area in the recent years[3]. The therapeutics of IBD is unsatisfactory currently[4]. Therefore, it is urgent to bring forth new ideas to innovate novel remedies for the treatment of IBD.

Monocytes (Mos), one of the major subtypes of the white blood cells, constitute about 2%–10% of the whole leukocytes. The signature marker of Mos is CD14 or CD14 and CD16[5]. Under given micro environment, Mos differentiate into dendritic cells or macrophages, which are directly involved in multiple immune responses[6]. After activation, Mos may differentiate into several cell types, including dendritic cells, macrophages and myeloid derived suppressor cells (MDSC)[7]. The immune suppressive effect of MDSC is well recognized in tumor studies, in which MDSCs are highly immunosuppressive on effector immune cell activities[8]. To date, the underlying mechanism by which the naïve Mos differentiate into suppressive Mos has not been fully defined.

Intestinal epithelial cells (IEC) are critical components of the intestinal epithelial barrier. IECs also communicate between the external environment (the intestinal tract) and the internal environment (intestinal mucosa)[9]. The external stimulation may activate IECs and induce IECs to produce molecules to influence the immune cell functions in the sub-epithelial region[10]. IECs express a number of Toll like receptors (TLR) and can respond to the stimuli of microbes in the intestinal tract[11]. IECs produce a number of molecules, including the transforming growth factor (TGF)-β[12]. Whether IECs produce some other growth factors, such as insulin-like growth factor-1 (IGF1), has not been fully understood.

IGF1, also called somatomedin C, is a member of the IGF family. IGF is mainly produced by the liver that is regulated by the growth hormone[13]. IGF1 is one of the most potent natural activators of the AKT signaling

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ORIGINAL ARTICLE

LincRNA-uc002yug.2 involves in alternative splicing of *RUNX1* and serves as a predictor for esophageal cancer and prognosis

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Long intergenic noncoding RNAs (lincRNAs) have critical regulatory roles in cancer biology; however, the contributions of lincRNAs to esophageal squamous cell carcinoma (ESCC) have been infrequently explored. The aim of this study was to explore the contribution of lincRNAs, located at ESCC susceptibility loci identified by genome-wide association studies, to the risk and prognosis of ESCC. The associations between lincRNAs and the risk and prognosis of ESCC were analyzed in 358 diagnosed patients from eastern China, and the findings were validated in 326 additional patients from southern China. Functional relevance of lincRNAs was further examined by biochemical assays. We found that *lincRNA-uc002yug.2* was commonly overexpressed in ESCC compared with paired peritumoral tissue in eastern and southern Chinese populations. The expression levels of *lincRNA-uc002yug.2* in ESCC might be a prognostic factor for survival. Moreover, *lincRNA-uc002yug.2* promoted a combination of *RUNX1* and alternative splicing (AS) factors in the nucleus to produce more *RUNX1a*, the short isoform and inhibitor of *RUNX1*, and reduce *CEBPα* (CCAAT/enhancer-binding protein-α) gene expression, thereby promoting ESCC progression. These results indicated that *lincRNA-uc002yug.2* might involve in AS of *RUNX1/AML1* and serve as a predictor for esophageal cancer and prognosis.

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INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is the eighth most common malignancy worldwide.[1] Therapies such as esophagectomy, chemotherapy and radiotherapy are frequently used to treat ESCC; however, the long-term outcome of this cancer is still dismal, with 5-year survival rates around 30%.[2] The occurrence and development of human neoplasms, including ESCC,[3] involve a multistep process of genetic alterations. Genetic susceptibility, environmental factors and gene–environment interactions are thought to contribute to the development of ESCC.[4] Recently, genetic variants in ESCC have been explored and susceptibility loci have been identified by several genome-wide association studies (GWAS).[2,4–12]

GWAS is a powerful strategy that identifies the presence of sequence variation, which covers the entire genome, to select disease-related loci. GWAS of cancer susceptibility loci have been mainly identified in the noncoding portions of the genome, some of which may be transcribed.[13] It has been revealed that most of the human genome is transcribed, generating a sizable repertoire of long noncoding RNAs (lncRNAs) that map to intronic and intergenic regions, and $<1\%$ of these have been characterized.[14–17] Recently, a few noncoding transcripts, which have an active role in RNA processing, gene regulation and particularly in carcinogenesis, have been characterized in mammalian species.[18–21]

Although lncRNAs might involve in various human diseases, the underlying molecular mechanisms are still largely unknown. The altered expression of several lncRNAs has been reported in various human tumors.[22–25] LncRNAs might act as modular scaffolds for protein–chromatin interactions.[26] In addition, some antisense long intergenic noncoding RNAs (lincRNAs) silence genes *in cis*.[27]

Here we identified 19 lincRNAs by using bioinformatic analysis on the basis of GWAS-based ESCC reports and human lncRNAs database,[28] and UCSC, Ensembl and Refseq databases. We further explored whether these lincRNAs contributed to the risk and prognosis of ESCC in eastern and southern Chinese populations.

RESULTS

LincRNA-uc002yug.2 was highly expressed in ESCC tissue and indicated a poor prognosis

The clinical information and demographic characteristics of the 684 ESCC patients included in this study were shown in Table 1. We identified the expression of 19 candidate lincRNAs in 358 pairs of ESCC and non-tumor samples in eastern China (Suzhou), and noted that only *lincRNA-uc002yug.2* was remarkably upregulated (3.25-fold, $P<0.001$) in ESCC. Then, in 326 pairs of ESCC and adjacent tissues in southern China (Guangzhou), we found that *lincRNA-uc002yug.2* was significantly upregulated (4.28-fold, $P=0.023$) in ESCC. Pooled analysis also demonstrated that *lincRNA-uc002yug.2* levels were significantly higher (3.63-fold, $P=0.006$) in tumor tissues than in adjacent tissues (Figure 1a).

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Magnetic resonance angiography manifestations and prognostic significance in HIV-negative tuberculosis meningitis

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SUMMARY

OBJECTIVE: To evaluate the patterns, related factors and prognostic value of abnormal magnetic resonance angiography (MRA) in human immunodeficiency virus negative tuberculous meningitis.

MATERIALS AND METHODS: We performed a prospective study in patients aged >14 years. Abnormality on MRA was correlated with clinical, laboratory and magnetic resonance imaging findings. Modified Barthel index was used to assess outcome at 6 months after inclusion.

RESULTS: Of 101 patients included, MRA was abnormal in 45 (44.6%). The distribution of MRA abnormality was classified as disseminated irregular calibres of intracranial arteries with or without reduction in distant branches (29.7%, pattern 1) and localised stenosis at the base of the brain (26.7%, pattern 2). In logistic regression analysis, pattern 2 was related to stage of the disease ($P = 0.002$), basal exudates ($P = 0.03$) and infarction ($P = 0.000$), while pattern 1 was related to duration of disease ($P = 0.050$), hydrocephalus ($P = 0.032$) and age ($P = 0.002$). Pattern 1 was also correlated with infarction ($P = 0.000$), particularly infarction in the tubercular zone ($P = 0.035$) in univariate analysis. MRA abnormality was associated with paradoxical worsening ($P = 0.022$) and poor prognosis in univariate analysis ($P = 0.035$).

CONCLUSION: MRA abnormality is associated with stroke and poor outcomes. Although it indicates mild vascular injury, pattern 1 MRA abnormality is nevertheless associated with infarction and needs proper intervention.

KEY WORDS: meningitis; tuberculosis; MRA; infarction; vasculitis

TUBERCULOSIS (TB) is the second leading cause of death due to an infectious disease worldwide. China accounts for 12% of total global cases; however, China's human immunodeficiency virus (HIV) co-infection rate is low, at 0.73%.[1] Tuberculous meningitis (TBM) is the most severe form of extrapulmonary TB, with a mortality rate of approximately 25% in human immunodeficiency virus (HIV) negative adults. Approximately half of survivors suffer from long-term neurological disability. Stroke, which occurs in up to 13–57% TBM patients, is an important cause of disability.[2]

Strokes are caused by vasospasms early in the course of disease and involve proliferative intimal vascular disease later.[3] The conventional angiographic features of TBM include a triad of a hydrocephalic pattern, narrowing of arteries at the base of the brain, and narrowed or occluded branch arteries with early draining veins.[4] To date, several studies with small sample sizes (10–67 subjects) have described the cerebral vasculopathy of TBM, using traditional cerebral angiography, magnetic resonance angiography (MRA) or computed tomography angiography (CTA).[5–8] The proportion and significance of the involvement of branch arteries have not been evaluated.

We conducted a prospective study to evaluate the patterns and related factors of MRA abnormality in HIV-negative TBM patients. We also assessed the value of angiographic findings in determining the prognosis of TBM.

MATERIALS AND METHODS

Our database comprised 224 consecutive patients diagnosed with TBM between January 2007 and July 2014 admitted to the Department of Neurology at the

Footnote: TTL, XQL and LZ contributed equally to this work.

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Review Article

Mechanistic impact of outdoor air pollution on asthma and allergic diseases

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Abstract: Over the past decades, asthma and allergic diseases, such as allergic rhinitis and eczema, have become increasingly common, but the reason for this increased prevalence is still unclear. It has become apparent that genetic variation alone is not sufficient to account for the observed changes; rather, the changing environment, together with alterations in lifestyle and eating habits, are likely to have driven the increase in prevalence, and in some cases, severity of disease. This is particularly highlighted by recent awareness of, and concern about, the exposure to ubiquitous environmental pollutants, including chemicals with oxidant-generating capacities, and their impact on the human respiratory and immune systems. Indeed, several epidemiological studies have identified a variety of risk factors, including ambient pollutant gases and airborne particles, for the prevalence and the exacerbation of allergic diseases. However, the responsible pollutants remain unclear and the causal relationship has not been established. Recent studies of cellular and animal models have suggested several plausible mechanisms, with the most consistent observation being the direct effects of particle components on the generation of reactive oxygen species (ROS) and the resultant oxidative stress and inflammatory responses. This review attempts to highlight the experimental findings, with particular emphasis on several major mechanistic events initiated by exposure to particulate matters (PMs) in the exposure-disease relationship.

Keywords: Air pollution; asthma; allergic disease; particulate matter (PM); polycyclic aromatic hydrocarbon (PAH); transition metal; aryl hydrocarbon receptor (AhR)

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呼吸疾病国家重点实验室

Allergic diseases and asthma still remain a critical public health, medical and economic problem, and are, in fact, among the major causes of illness and disability for all ages, particularly in Taiwan. Unfortunately, the trend of disease incidence is still on the rise and has caused significant economic burden to the general public. Particularly, data from a recent survey of 24,999 first-grade students in Taiwan revealed an alarmingly high prevalence of physician-diagnosed asthma, allergic rhinitis, and atopic eczema, with 13.0%, 33.7% and 29.8%, respectively (1). This is, indeed, a disturbing trend, considering also the fact that allergic diseases are often a chronic condition for life. The initial assessment of Taiwan's National Health Insurance (NHI) expenditures for asthma* indicated that the annual healthcare cost is estimated to be more than 4 billion (NT$), when all outpatient visits and hospital admissions with asthma as one of the first three diagnoses were included*. In fact, the treatment and care for severe asthma represented more than half of the expenditure incurred. This significant increase in health cost is alarming, which highlights an urgent need for better understanding of the etiology and its causative mechanisms in order to improve treatment and

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Research Article

Metabolomic Study on the Preventive Effect of *Patrinia scabiosaefolia* Fisch on Multipathogen Induced Pelvic Inflammatory Disease in Rats

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Patrinia scabiosaefolia Fisch (PSF), a well-known traditional Chinese medicine (TCM), has been used as a "heat-clearing and detoxifying" agent. Th present study was to illustrate the preventive effect of PSF on pelvic infl mmatory disease (PID) in rats. The PID model was constructed by multipathogen infection of the upper genital tract with reference to the method previously reported. Urine metabolomic analysis was conducted with a GC-MS coupled with derivatization method. In this study, PID rats showed obvious infiltration of inflammatory cells and elevated expression of cytokines (IL-1β and IL-6) in upper genital tract, compared with control rats. Sixteen differentiating metabolites contributed to the alteration of metabolic profil in PID rats, including two amino acids, three fat acids, nine organic acids, and two types of sugars. The rats, infected by multipathogen and administered with PSF, showed decreased infi tration of infl mmatory cells and lowered expression of cytokines in upper genital tract, compared with PID rats. Meanwhile, PSF intervened in the PID-associated alterations in TCA cycle, sugar metabolism, amino acid metabolism, and other uncertain metabolic pathways. The e results indicate that PSF has preventive eff ct on multipathogen induced PID and holistic interventional effect on disease-associated metabolomic change.

1. Introduction

Traditional Chinese medicine (TCM), a complementary and alternative medicine, is considered to be a holistic approach that attempts to bring the body, mind, and spirit back to harmony [1]. As a part of system biology, metabolomics focuses on comprehensive determinations of all endogenous low molecular weight metabolites *in vivo*, and the change of metabolite profile can present the pathological or physiological change in holistic context from the metabolism aspect [2, 3]. Therefore, metabolomics meets the requirement of holistic characteristics of TCM, provides an opportunity to scientifically express the meaning of evidence-based Chinese medicine, and reduces the gap between TCM and modern drug discovery demand [1]. Thus, increasing studies in the field of pharmacology [4, 5], toxicology [6], and pharmacokinetics [7] of TCM have resorted to metabolomics methods.

Pelvic infl mmatory disease (PID) includes endocervicitis, endometritis, salpingitis, and peritonitis, caused by ascending infection of the upper female genital tract [8]. Thi

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Editorial

MicroRNAs: Emerging Novel Targets of Cancer Therapies

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所级实验室 国家重点实验室

MicroRNAs (miRNAs) are a large family of small noncoding RNAs (~22 nucleotide long) that negatively regulate protein-coding gene expression posttranscriptionally by interacting with messenger RNAs (mRNAs), causing either their degradation or translation inhibition. While miRNAs were first discovered as important regulators of developmental timing, subsequent studies have shown that their deregulations are critically involved in various diseases, including cancer. This is evident from the crucial roles they play in regulating a wide range of cellular processes such as cell survival, apoptosis, cell cycle progression and proliferation, cell-cell interaction, differentiation, and motility.

It has been found that miRNA expression levels are altered in all types of cancer and they play important roles in almost all aspects of cancer pathogenesis such as initiation, promotion, metastasis, and responses to drug treatment. These recognitions and other accumulating evidences clearly suggest that miRNAs can serve as novel targets for cancer therapies. Indeed, targeting abnormally-expressed miRNAs has been shown to have great potential in suppressing primary tumor growth, reducing tumor metastasis, and overcoming anticancer drug resistance. It is anticipated that miRNAs can be valuable cancer-specific targets and novel miRNA-based targeted therapies can be formulated to provide effective treatments for cancer. The purpose of this special issue is to provide readers with an overview of research findings on the roles of miRNAs in cancer development, progression, diagnosis and treatment, and how miRNA expression may be regulated. This issue will also update the readers about the challenges and possibilities of miRNAs to emerge as future cancer therapeutics.

A. L. Oom et al. first briefly review the potential value of miRNAs as cancer diagnostic markers, which is followed by the detailed discussion on the potential role of miRNAs in cancer therapy. The authors review literatures reporting the role of miRNAs in sensitizing of or mediating resistance to traditional and targeted cancer therapies. A nice summary about studies on miRNAs in combination with traditional cancer therapies is provided in a table. The authors also discuss the current studies on miRNA delivery systems. This review ends with discussion on challenges and perspectives of developing miRNAs as effective cancer therapies.

The review paper, authored by K. Otsuka and T. Ochiya, discusses the role of miRNAs in tumor development by uniquely focusing on the interplay between the classic tumor suppressor p53 and the emerging tumor regulatory miRNAs. The authors review recent findings showing both the regulation of expression of various miRNAs by p53 and the direct targeting of p53 by miRNAs. Particularly, this review summarizes up to date research findings about the critical roles of various miRNAs in regulation of cell cycle and apoptosis in the p53 pathways.

ARTICLE
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Journal of Cellular Biochemistry

MiR-210 Links Hypoxia With Cell Proliferation Regulation in Human Laryngocarcinoma Cancer

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ABSTRACT

The microRNA hsa-miR-210 (miR-210) is associated with hypoxia; however its function has not fully identified. In the present study, we aim to detect its role concerning proliferation in Laryngocarcinoma. We found that miR-210 was highly expressed in hypoxia, which inhibited proliferation by inducing cell cycle arrest in G1/G0 as well as apoptosis. We further identified that miR-210 targeted fibroblast growth factor receptor-like 1 (FGFRL1). Down regulation of FGFRL1 decreased cell proliferation by promoting proportion of cells in G1/G0 phase and decreasing in S and G2/M phases. Moreover, overexpression of FGFRL1 effectively released the miR-210-induced suppression of SCC10A cell proliferation. Expression of miR-210 repressed tumor xenograft growth in vivo as well. Together, our findings reveal a new mechanism of adaptation to hypoxia that miR-210 inhibits the proliferation via inducing cell cycle arrest and apoptosis by the targeting of FGFRL1. J. Cell. Biochem. 116: 1039–1049, 2015. © 2015 Wiley Periodicals, Inc.

KEY WORDS: MIR-210; HYPOXIA; CELL PROLIFERATION; LARYNGOCARCINOMA CANCER; FGFRL1

Human head and neck cancer is the eighth most common cancer in the US and the sixth most common one worldwide, representing 10–15% of all malignancies and causing 1–5% of all cancer-related deaths [American Cancer Society, 2012; Bădulescu et al., 2013]. Annually, there are approximately 650,000 patients diagnosed with head and neck cancers and 350,000 deaths in the world [Bădulescu et al., 2013]. Although intensive research and improvements in multimodality treatment, such as surgery, radiation, and chemotherapy, the 5-year survival still remains at 50–60% [Pulte and Brenner, 2010]. Early laryngeal cancer, one of the most common types of HNSCC, can usually be successfully treated with either radiotherapy or surgery. However, many advanced stage laryngeal carcinomas with limited treatment options are generally associated with considerable impairment to quality of life [Masuda et al., 2013]. Therefore, it is necessary to understand the underlying mechanism of tumor progression, as well as highlight the impact of genetic and molecular modifications in the early detection, the prediction of prognosis and therapeutic response to treatment of laryngeal carcinomas.

Hypoxia often occurs in tumors and tissue inflammation [Jordanovski et al., 2013]. Tumor hypoxia has been shown to be a

J. Zuo and M.Wen contributed equally to this work.
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Medicine®

OBSERVATIONAL STUDY

OPEN

Modified IDSA/ATS Minor Criteria for Severe Community-Acquired Pneumonia Best Predicted Mortality

Hai-yan Li, Qi Guo, MD, PhD, Wei-dong Song, MD, PhD, Yi-ping Zhou, Ming Li, Xiao-ke Chen, Hui Liu, Hong-lin Peng, Hai-qiong Yu, MD, PhD, Xia Chen, Nian Liu, Zhong-dong Lü, Li-hua Liang, Qing-zhou Zhao, and Mei Jiang

Abstract: It is not clear whether the IDSA/ATS minor criteria for severe community-acquired pneumonia (CAP) could be simplified or even be modified to orchestrate improvements in predicting mortality.

A retrospective cohort study of 1230 CAP patients was performed to simplify and to modify the scoring system by excluding 4 noncontributory or infrequent variables (leukopenia, hypothermia, hypotension, and thrombocytopenia) and by excluding these variables and then adding age ≥65 years, respectively. The simplification and modification were tested against a prospective 2-center validation cohort of 1409 adults with CAP.

The increasing numbers of IDSA/ATS, simplified, and modified minor criteria present in the retrospective cohort were positively associated with the mortality, showing significant increased odds ratios for mortality of 2.711, 4.095, and 3.755, respectively. The validation cohort confirmed a similar pattern. The sensitivity, specificity, positive predictive value, and Youden index of modified minor criteria for mortality prediction were the best pattern in the retrospective cohort. High values of corresponding indices were confirmed in the validation cohort. The highest accuracy of the modified version for predicting mortality in the retrospective cohort was illustrated by the highest area under the receiver operating characteristic curve of 0.925 (descending order: modified, simplified, and IDSA/ATS minor criteria). The validation cohort confirmed a similar paradigm.

The IDSA/ATS minor criteria could be simplified to 5 variables and then be modified to orchestrate improvements in predicting mortality in CAP patients. The modified version best predicted mortality. These were more suitable for clinic and emergency department.

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Abbreviations: AUC = area under the receiver operating characteristic curve, CAP = community-acquired pneumonia, CURB-65 = confusion, urea >7 mmol/L, respiratory rate ≥30 min^{-1}, low blood pressure, and age ≥65 years, ICU = intensive care unit, IDSA/ATS = Infectious Disease Society of America and the American Thoracic Society, OR = odds ratio, 95% CI = 95% confidence interval, PaO_2/FiO_2 = arterial oxygen pressure/fraction inspired oxygen, PPV = positive predictive value.

INTRODUCTION

Despite substantial advances in therapeutic options, the mortality due to community-acquired pneumonia (CAP) remains unacceptably high.[1,2] The assessment of severity is crucial in the management of CAP. The Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) 9 minor criteria for sever CAP included variables in the CURB-65 (confusion, urea >7 mmol/L, respiratory rate ≥30 min^{-1}, low blood pressure, and age ≥65 years) score except age, arterial oxygen pressure/fraction inspired oxygen (PaO_2/FiO_2) ≤250 mmHg, multilobar infiltrates, leucopenia, thrombocytopenia, and hypothermia.[1]

Liapikou et al[3] could not demonstrate an association between hypotension, thrombocytopenia and multilobar involvement, and mortality. Our study suggests that leukopenia, hypothermia, and hypotension were not associated with mortality.[4] However, Phua et al[5] and Chalmers et al[6] revealed that each minor criterion was predictive of mortality. How to deal with the discrepancies? Salih et al[7] recently reported that the criteria could be simplified by removing 3 infrequent variables (leukopenia, thrombocytopenia, and hypothermia), but could not improve the prediction of mortality and intensive care unit (ICU) admission. A recent clinical study showed that the IDSA/ATS minor criteria can improve patient management.[8] Improvement in patient management first depends on the accuracy of ICU admission prediction. Therefore, this is the correct application of the minor criteria. Our previous study

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H-YL, QG, and W-DS made substantial contributions to conception and design, were in charge of data collection, and wrote the manuscript. L-HL and Q-ZZ read the chest radiographs and computed tomographic scans. Y-PZ, ML, X-KC, HL, H-LP, H-QY, XC, NL, and Z-DL made substantial contributions to acquisition of data. MJ was in charge of statistical analysis.
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ORIGINAL PAPER

Molecular cloning and characterization of gloverin from the diamondback moth, *Plutella xylostella* L. and its interaction with bacterial membrane

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Abstract Gloverin restricted to Lepidoptera is known to be a glycine-rich and heat stable antimicrobial protein. The current research reports a 650 bp full-length cDNA encoding gloverin from *Plutella xylostella* (*Px*Glo) by reverse transcription polymerase chain reaction and rapid amplification of cDNA ends. *Px*Glo transcript was detected in both developmental stages and several tissues of 4th instar naïve larvae of *P. xylostella* with higher levels in the fat bodies. The mRNA levels of *Px*Glo increased appreciably in fat bodies after injection of *Escherichia coli* K12. The recombinant *Px*Glo expressed in S2 cells was purified by Anti-V5 M2 agarose beads which showed high activity against *E. coli* K12, while low activity against *Bacillus thuringiensis*, *Staphylococcus aureus* and *E. coli* D31. The analysis of transmission electron microscope and scan electron microscope showed *Px*Glo to cause significant morphological alteration in the *E. coli* K12 cell surface. Knockdown of *Px*Glo expression by RNAi increased the larval susceptibility towards the pathogenic bacteria i.e., *Serratia marcescens* and *B. thuringiensis*. Our results showed that *Px*Glo is an inducible antibacterial peptide which exhibits high activity mainly against *E. coli* K12, and *Px*Glo performs vital roles against the infection of pathogenic bacteria.

Keywords Gloverin · Diamondback moth · RT-PCR · Antibacterial mechanism · RNA interference

Introduction

Insect's defense system includes effective antibacterial peptides that are quickly manufactured and rapidly available subsequent to infection by microorganisms (Boman 1995; Hoffmann 1995; Gely et al. 2008). These characteristics, with the little metabolic cost for the insect and low specificity, make these peptides a very flexible constituent of the insect defense mechanism (Hultmark 2003; Hoffmann 2003). Since the isolation of cecropin from *Hyalophora cecropia* (Hultmark et al. 1980; Steiner et al. 1981), numerous antibacterial peptides have been isolated from a range of insects, and their parallel genes and mechanisms have already been stated in Lepidopterans and Dipterans (Kylsten et al. 1990; Lemaitre and Hoffmann 2007). The known antibacterial peptides have five key groups: cecropins, defensins, glycine rich peptides, proline-rich peptides and lysozymes (Boman 1995; Lemaitre and Hoffmann 2007).

The glycine rich peptides ranging from 8.0 to 30.0 kDa are effective chiefly against Gram negative bacteria (Sugiyama et al. 1995; Åsling et al. 1995; Kwon et al. 2008).

X. X. Xu and F. L. Jin have contributed equally to this work.

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Mortality among severe community-acquired pneumonia patients depends on combinations of 2007 IDSA/ATS minor criteria☆

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ABSTRACT

Objectives: The individual 2007 Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) minor criteria for severe community-acquired pneumonia (CAP) are of unequal weight in predicting mortality. It is not clear whether the combinations of predictive findings might imply diverse severities or different mortalities.

Methods: A prospective two centre cohort study was performed of 385 severe CAP patients fulfilling three or more IDSA/ATS minor criteria amongst 1430 patients.

Results: Hospital mortality rose sharply from 5.7%, 9.9%, and 16.5%, respectively, for patients with none of three predictive findings most strongly associated to mortality ($PaO_2/FiO_2 \leq 250$ mm Hg, confusion and uraemia), one of those, and two of those to 38.6% for patients with all those ($p < 0.001$). The number of three predictive findings present had a significantly increased odds ratio for mortality of 2.796 ($p < 0.001$), and had the degree of positive association with sequential organ failure assessment scores at 72 hours, incurring significantly longer hospital stay and higher costs.

Conclusions: Different combinations of 2007 IDSA/ATS minor criteria for severe CAP were associated to diverse severities and different mortalities. The combination of $PaO_2/FiO_2 \leq 250$ mm Hg, confusion and uraemia predicted more severity and higher mortality compared with others.

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1. Introduction

Community-acquired pneumonia (CAP) is a common infection. Despite substantial advances in therapeutic options, the mortality remains unacceptably high.[1,2] It was as high as 58% when severe CAP patients were admitted to the intensive care unit (ICU).[3] The Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) issued guidelines in 2007 which defined severe CAP—when one of two major criteria (the need for invasive mechanical ventilation or vasopressors) or three of nine minor criteria are fulfilled. The minor criteria included variables in the CURB-65 score except age, arterial oxygen pressure/fraction inspired oxygen (PaO_2/FiO_2) ≤ 250 mm Hg, multilobar infiltrates, leucopenia, thrombocytopenia, and hypothermia. However, whether each of the minor criteria is of equal weight is not clear.[1]

Brown et al.[4] reported the IDSA/ATS 2007 criterion of confusion was the most predictive of severe CAP. Liapikou et al.[5] found that each of the minor criteria is of unequal weight in predicting mortality (mental confusion and leucopenia had the strongest association with mortality) and could not demonstrate an association between hypotension, thrombocytopenia and

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THEMATIC ISSUE: Normal and Malignant Hematopoiesis
• REVIEW •

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Natural products against hematological malignancies and identification of their targets

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Naturally occurring molecules derived from higher plants, animals, microorganisms and minerals play an important role in the discovery and development of novel therapeutic agents. The identification of molecular targets is of interest to elucidate the mode of action of these compounds, and it may be employed to set up target-based assays and allow structure-activity relationship studies to guide medicinal chemistry efforts toward lead optimization. In recent years, plant-derived natural compounds possessing potential anti-tumor activities have been garnering much interest and efforts are underway to identify their molecular targets. Here, we attempt to summarize the discoveries of several natural compounds with activities against hematological malignancies, such as adenanthin, oridonin, gambogic acid and wogonoside, the identification of their targets, and their modes of actions.

natural products, adenanthin, hematological malignancies, target identification

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The use of bioactive small molecules, either as single molecular entities or as mixtures, for treating disease is an integral part of human medicine [1,2]. Actually, the great reservoir of natural compounds derived from higher plants, animals, microorganisms and minerals demonstrate their important role in the discovery and development of novel therapeutic drugs [3,4]. According to a detailed analysis of new medicines approved by the US Food and Drug Administration (FDA) between 1981 and 2010, about 34% of these medicines based on small molecules were natural products or direct derivatives of natural products [5]. However, while there is an enormous diversity in the number of plant species (besides animals, microorganisms and minerals) worldwide, less than 10% have been screened for biological activity, and only 15% have been phytochemically evaluated. Information concerning the mechanisms of action of bioactive natural products at a molecular level, especially the molecular target(s) of a drug candidate, is of great sig-

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Neural respiratory drive and breathlessness in COPD

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ABSTRACT The aim of this study was to test the hypothesis that neural respiratory drive, measured using diaphragm electromyogram (EMG_{di}) activity expressed as a percentage of maximum ($EMG_{di\%max}$), is closely related to breathlessness in chronic obstructive pulmonary disease. We also investigated whether neuroventilatory uncoupling contributes significantly to breathlessness intensity over an awareness of levels of neural respiratory drive alone.

EMG_{di} and ventilation were measured continuously during incremental cycle and treadmill exercise in 12 chronic obstructive pulmonary disease patients (forced expiratory volume in 1 s±SD was 38.7±14.5 % pred). EMG_{di} was expressed both as $EMG_{di\%max}$ and relative to tidal volume expressed as a percentage of predicted vital capacity to quantify neuroventilatory uncoupling.

$EMG_{di\%max}$ was closely related to Borg breathlessness in both cycle (r=0.98, p=0.0001) and treadmill exercise (r=0.94, p=0.005), this relationship being similar to that between neuroventilatory uncoupling and breathlessness (cycling r=0.94, p=0.005; treadmill r=0.91, p=0.01). The relationship between breathlessness and ventilation was poor when expansion of tidal volume became limited.

In chronic obstructive pulmonary disease the intensity of exertional breathlessness is closely related to $EMG_{di\%max}$. These data suggest that breathlessness in chronic obstructive pulmonary disease can be largely explained by an awareness of levels of neural respiratory drive, rather than the degree of neuroventilatory uncoupling. $EMG_{di\%max}$ could provide a useful physiological biomarker for breathlessness in chronic obstructive pulmonary disease.

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Exertional breathlessness in patients with severe COPD is closely related to levels of neural respiratory drive http://ow.ly/BO6MI

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Conflict of interest: None declared.

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Neural respiratory drive and symptoms that limit exercise in chronic obstructive pulmonary disease

Caroline Jolley, Yuanming Luo, Joerg Steier, Karl Sylvester, William Man, Gerrard Rafferty, Michael Polkey, John Moxham

Abstract

Background **Exercise capacity in chronic obstructive pulmonary disease (COPD) is limited by both breathlessness and leg muscle fatigue. Neural respiratory drive, measured as diaphragm electromyogram (EMGdi) activity expressed as a proportion of maximum (EMGdi%max), quantifies the mechanical load on the respiratory muscles and relates closely to breathlessness. We tested the hypothesis that end-exercise EMGdi%max would be higher in patients stopping because of breathlessness than in those limited by leg fatigue.**

Methods **EMGdi, ventilation, rate of oxygen consumption (VO_2), and ventilatory reserve (ventilation/maximum ventilatory volume ratio [VE/MVV]) were measured continuously in patients with COPD during exhaustive cycle ergometry. EMGdi was measured with a multipair oesophageal catheter passed per-nasally. Differences in physiological variables between groups of patients stopping because of breathlessness, leg fatigue, or both were assessed with one-way ANOVA.**

Findings **23 patients were included (median FEV_1 39% of predicted, IQR 30·0–56·8). End-exercise EMGdi%max was significantly higher in patients stopping exercise because of breathlessness (n=12, median EMGdi%max 75·7% [IQR 69·5–77·1]) than in those stopping because of leg fatigue (n=8, 44·1 [39·4–63·3]) or both (n=3, 74·1 [63·6–81·2]) (p=0·02). There were no significant differences between the groups in end-exercise ventilation (breathlessness 25·7 L/min [16·3–32·0] *vs* leg fatigue 31·5 [20·9–39·6] *vs* both 22·0 [17·7–35·7]), VO_2 (13·4 mL/min per kg [11·6–14·2] *vs* 12·1 [10·4–14·8] *vs* 9·4 [9·1–12·4]), or VE/MVV (80·4% [72·6–88·3] *vs* 57·8 [52·1–92·6] *vs* 63·9 [34·5–88·9]).**

Interpretation **These results suggest that patients limited by breathlessness due to ventilatory constraints can be identified as those reaching near-maximum levels of neural respiratory drive during exercise. Measurement of EMGdi%max during exercise could prove useful in identifying patients whose functional performance would be best optimised by improvment in pulmonary mechanics rather than interventions to train peripheral muscle groups.**

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Contributors

CJ, YL, GR, MP, and JM conceptualised the study. CJ, JS, YL, KP, and WM collected the data. CJ analysed and interpreted the data. All authors were involved in drafting the abstract and approved the final version.

Declaration of interests

We declare no competing interests.

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Poster 81

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呼吸疾病国家重点实验室

Ovarian cancer transformation from adenocarcinoma to undifferentiated small cell carcinoma: A case report

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Abstract. The ovaries contain cells that have the capacity for regeneration and cancer stem cells (CSC) that are capable of differentiating aberrantly from the homeostatic controls. The histology of ovarian cancer does not usually change in a patient. However, CSCs are the origin of a number of tumors. CSCs are known to exist in ovarian carcinomas and the expression of CD44, c-Kit and CD133 has been identified in such carcinomas. This study presents the case of a patient diagnosed with ovarian cancer with an abdominal mass who underwent surgery, eight cycles of gemcitabine-paclitaxel chemotherapy and irradiation. Pathological examination indicated a transformation from adenocarcinoma to undifferentiated small cell carcinoma. The expression of CD133 changed from negative to positive in ovarian carcinomas. The present case indicates that any histological changes observed in ovarian neoplasms originate from neoplastic stem cells. In addition, this case demonstrates the importance of repeatedly assessing therapy by tumor biopsy throughout the course of ovarian cancer treatment.

Introduction

It is widely accepted that the histology of ovarian cancer does not change in a patient. However, cancer stem cells (CSCs) are the origin of numerous tumors (1). Ovarian CSCs form spheroids and multicellular colonies that differentiate along epithelial, granulosa and germ cell lineages *in vivo* (2). CSCs have been shown to exist in ovarian carcinomas, and the expression of cluster of differentiation (CD)44, c-Kit and CD133 have been detected in these tumors (1). It appears that the histology of ovarian cancer would be change in the period of therapy with CSCs existing. To the best of our knowledge, no studies currently exist regarding the transformation of ovarian cancer from one histology into another. In the present study, the ovarian cancer transformed from adenocarcinoma into undifferentiated small cell carcinoma, supporting the hypothesis that CSCs can differentiate into different types of mature neoplastic cells.

Case report

A 27-year-old female presented to The Affiliated Wujing Hospital of Guangzhou Medical College (State Key Laboratory of Respiratory Disease, Guangzhou, Guangdong, China) with an abdominal mass in April 2011. Computed tomography (CT) revealed a large intraperitoneal cystic mass and ascites. The patient presented with abdominal pain, but no fever. Complete blood count, and liver and renal function test results were normal. An ascites sample obtained by abdominocentesis tested positive for adenocarcinoma. The patient underwent surgery in June 2011, and multiple pelvic nodules, a large intraperitoneal cystic mass with ovarian involvement and an abdominal peritoneal implant, measuring 1.0 cm in diameter, were found. The inguinal and retroperitoneal lymph nodes were negative for cancer cell invasion. The pathological analysis of the mass indicated moderately-differentiated adenocarcinoma (Fig. 1). The patient was diagnosed with ovarian cancer, stage IIIb T3bN0M0, according to the International Federation of Gynecology and Obstetrics staging system (1988) (3). The patient was treated with combination chemotherapy consisting of platinum and paclitaxel. This chemotherapy regimen involved the administration of placlitaxel (120 mg, i.v.) followed by platinum (120 mg) every three weeks for six cycles. The treatment outcome was evaluated as a partial response after 18 weeks. The abdominal mass recurred, and the patient underwent surgery in June 2012. The pathology of the mass indicated a poorly-differentiated adenocarcinoma in February 2012 (Fig. 2). The ovarian carcinoma cells were negative for CD133 expression. The patient was treated with two cycles of gemcitabine-paclitaxel chemotherapy. Tumor biopsy results indicated an undifferentiated small cell carcinoma and positive CD133 expression in the ovarian carcinoma cells (Figs. 3 and 4). Positron emission tomography-CT revealed evidence of extensive metastatic disease in the neck, thoracic lymph nodes and liver, nodules

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Key words: ovarian cancer, adenocarcinoma, undifferentiated small cell carcinoma

呼吸疾病国家重点实验室

Overexpression of CHD1L is positively associated with metastasis of lung adenocarcinoma and predicts patients poor survival

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Keywords: *non-small-cell lung carcinoma, CHD1L protein, metastasis, prognosis, gene amplification*

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ABSTRACT

CHD1L **(chromodomain helicase/ATPase DNA binding protein 1-like gene) has been demonstrated as an oncogene in hepatocellular carcinoma (HCC), however, the role of *CHD1L* in non-small-cell lung cancer (NSCLC) tumorigenesis hasn't been elucidated. In this study, the expression and amplification status of *CHD1L* were examined by immunohistochemistry and fluorescence *in situ* hybridization respectively in 248 surgically resected NSCLCs. The associations between CHD1L expression and clinicopathologic features and the prognostic value of CHD1L were analyzed. Overexpression and amplification of *CHD1L* was found in 42.1% and 17.7% of NSCLCs, respectively. The frequency of *CHD1L* overexpression (53.2% *vs*. 28.1%, *P* = 0.002) and amplification (25.2% *vs*. 8.2%, *P* = 0.020) in adenocarcinoma (ADC), was much higher than that in squamous cell carcinoma (SCC). CHD1L overexpression was associated closely with ascending pN status (*P* < 0.001), advanced clinical stage (*P* = 0.001) and tumor distant metastasis (*P* = 0.001) in ADCs, but not in SCCs. For the whole cohort and ADC patients, univariate survival analysis demonstrated a significant association of CHD1L overexpression with shortened survival; and in multivariate analysis, CHD1L overexpression was evaluated as a independent predictor for overall survival and distant metastasis free survival. These results suggested that overexpression of CHD1L is positively associated with tumor metastasis of lung ADC, and might serve as a novel prognostic biomarker and potential therapeutic target for lung ADC patients.**

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide [1]. Non-small-cell lung cancer (NSCLC), which accounts for almost 80% of such death, is a very heterogeneous group of malignancies [2]. Even for earlier stages patients, a significant proportion of them will suffer from local recurrence and/or distant metastasis after radical surgery [3]. However, the international staging system is still inadequate to reliably predict patients' prognosis. Since chromosomal aberrations are believed to play an important role in tumor progression [4], it will be of great value to search the specific gene alterations in NSCLC which

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Para-toluenesulfonamide induces tongue squamous cell carcinoma cell death through disturbing lysosomal stability

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Para-toluenesulfonamide (PTS) has been implicated with anticancer effects against a variety of tumors. In the present study, we investigated the inhibitory effects of PTS on tongue squamous cell carcinoma (Tca-8113) and explored the lysosomal and mitochondrial changes after PTS treatment *in vitro*. High-performance liquid chromatography showed that PTS selectively accumulated in Tca-8113 cells with a relatively low concentration in normal fibroblasts. Next, the effects of PTS on cell viability, invasion, and cell death were determined. PTS significantly inhibited Tca-8113 cells' viability and invasive ability with increased cancer cell death. Flow cytometric analysis and the lactate dehydrogenase release assay showed that PTS induced cancer cell death by activating apoptosis and necrosis simultaneously. Morphological changes, such as cellular shrinkage, nuclear condensation as well as formation of apoptotic body and secondary lysosomes, were observed, indicating that PTS might induce cell death through disturbing lysosomal stability. Lysosomal integrity assay and western blot showed that PTS increased lysosomal membrane permeabilization associated with activation of lysosomal cathepsin B. Finally, PTS was shown to inhibit ATP biosynthesis and induce the release of mitochondrial cytochrome *c*. Therefore, our findings provide a novel insight into the use of PTS in cancer therapy. *Anti-Cancer Drugs* 26:1026–1033 **Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: apoptosis, lysosome, mitochondria, para-toluenesulfonamide, tongue squamous cell carcinoma

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Introduction

Para-toluenesulfonamide (PTS) is a novel anticancer agent with good lipophilic ability. As an adjunct to chemotherapy and radiation therapy, PTS is usually delivered by an intravenous or an intratumoral injection. Recent studies suggested that PTS inhibits tumor progression by induction of tumor necrosis [1]. A phase II clinical trial showed that chemotherapy with a concurrent PTS local injection was well tolerated and had efficient clinical outcomes in patients with peripherally advanced lung cancer [2]. However, the mechanisms of anticancer effects of PTS remain elusive.

Lysosomes are highly dynamic cellular organelles that play critically important roles in endocytosis, autophagy, phagocytosis, and exocytosis [3]. Disturbance of lysosomal stability induces cancer cell death [4]. A limited release of lysosomal contents to the cytoplasm triggers apoptosis or apoptosis-like cell death, whereas generalized lysosomal rupture results in rapid cellular necrosis [5]. Released lysosomal proteases including cathepsin B and D also cause mitochondrial damage and dysfunction, which further amplifies the cell death signals [6–8]. It has been reported previously that PTS suppressed H460 lung cancer cells by necrotizing tumor in a nude mice model [1]. However, the mechanisms of PTS-induced cell death remain unknown. To determine whether PTS treatment is associated with lysosome-mediated cell death, we examined the effects of PTS on the human tongue squamous cell carcinoma Tca-8113 cell line.

Materials and methods

Cell culture and reagents

The human tongue squamous cell carcinoma Tca-8113 cell line was purchased from the China Center for Type Culture Collection (Wuhan, China). Nontumor normal mucosa tissues were obtained from patients who underwent primary surgical resection of gingival squamous cell carcinoma with informed consent at West China Hospital of Stomatology (Chengdu, China). The age range of all individuals was 35–65 years. Mucosa tissues were washed with PBS, minced, and incubated for 4 h at 37°C in 5 ml of 10% collagenase type I (Sigma-Aldrich, St Louis, Missouri, USA). Cells were spun at 225*g* for 5 min, washed with PBS, and cultured. Human gingival fibroblast (HGF) cells were incubated in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine

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Physical Biology

PAPER

Post-transcriptional regulation tends to attenuate the mRNA noise and to increase the mRNA gain

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Abstract

Post-transcriptional regulation is ubiquitous in prokaryotic and eukaryotic cells, but how it impacts gene expression remains to be fully explored. Here, we analyze a simple gene model in which we assume that mRNAs are produced in a constitutive manner but are regulated post-transcriptionally by a decapping enzyme that switches between the active state and the inactive state. We derive the analytical mRNA distribution governed by a chemical master equation, which can be well used to analyze the mechanism of how post-transcription regulation influences the mRNA expression level including the mRNA noise. We demonstrate that the mean mRNA level in the stochastic case is always higher than that in the deterministic case due to the stochastic effect of the enzyme, but the size of the increased part depends mainly on the switching rates between two enzyme states. More interesting is that we find that in contrast to transcriptional regulation, post-transcriptional regulation tends to attenuate noise in mRNA. Our results provide insight into the role of post-transcriptional regulation in controlling the transcriptional noise.

1. Introduction

Stochasticity and its role in cells and microorganisms have been a hot topic since the seventies of the last century [1, 2]. For a biochemical reaction system, probability of molecules encountering reactive species is in general very low due to the small copy numbers of these species, resulting in stochastic fluctuations in their population levels. It has been verified that the size of these fluctuations depends heavily on the network structure as well as other network properties [3–6]. While many previous works focusing on the negative effects of stochasticity [7, 8], e.g. the emergence of diverse disease states have been attributed to the elevated expression noise [8], there is increasing interest in exploring the possible functional role of molecular noise [9, 10]. It is not surprising that cells use different regulatory mechanisms to exploit gene expression noise [10]. Therefore, it is important to understand how different regulatory processes shape the dynamics and noise in gene expression.

Recent advances in the single-molecule experimental methods have made it possible to observe mRNA expression in great details, enabling discoveries of high variability in mRNA levels in a wide range of organisms such as prokaryotes, primitive eukaryotes, and higher eukaryotes [11, 12]. Previous studies have reported that transcription and translation can occur in time-localized bursts resulting in a geometrically distribution of the species molecule number [13–15]. Without relying on any external factors, this phenomenon can be captured by a stochastic two-state promoter model (denoted as TR) [16–18] (figure 1), where transcription is initiated by a two-state promoter that randomly switches between the active state and the inactive state. There have existed various mathematical tools to analyze the dynamical behaviors of gene expression models [19–22]. Continuous-deterministic approximation based on

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Quantitative assessment of single-cell whole genome amplification methods for detecting copy number variation using hippocampal neurons

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Single-cell genomic analysis has grown rapidly in recent years and finds widespread applications in various fields of biology, including cancer biology, development, immunology, pre-implantation genetic diagnosis, and neurobiology. To date, the amplification bias, amplification uniformity and reproducibility of the three major single cell whole genome amplification methods (GenomePlex WGA4, MDA and MALBAC) have not been systematically investigated using mammalian cells. In this study, we amplified genomic DNA from individual hippocampal neurons using three single-cell DNA amplification methods, and sequenced them at shallow depth. We then systematically evaluated the GC-bias, reproducibility, and copy number variations among individual neurons. Our results showed that single-cell genome sequencing results obtained from the MALBAC and WGA4 methods are highly reproducible and have a high success rate. The MALBAC displays significant biases towards high GC content. We then attempted to correct the GC bias issue by developing a bioinformatics pipeline, which allows us to call CNVs in single cell sequencing data, and chromosome level and sub-chromosomal level CNVs among individual neurons can be detected. We also proposed a metric to determine the CNV detection limits. Overall, MALBAC and WGA4 have better performance than MDA in detecting CNVs.

Interest in single-cell whole genome analysis is growing rapidly, especially for profiling rare or heterogeneous populations of cells. Single-cell whole genome sequencing has been applied to study cancer biology, cell development, neurobiology, and pre-implantation genetic diagnosis[1–4]. Single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs) are two major types of genetic polymorphism contributing to the heterogeneity of cell populations. To detect SNPs in single cells, deep sequencing at >30X coverage is usually performed. For example, Hou *et al.*[5] performed single cell exome sequencing on myeloproliferative neoplasm at 30X coverage and identifi d essential thrombocythemia-related candidate mutations. To detect CNVs, chromosome rearrangement, large-scale insertion/deletion, shallow

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RESEARCH Open Access

Quantitative evaluation of the immunodeficiency of a mouse strain by tumor engraftments

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Abstract

Background: The mouse is an organism that is widely used as a mammalian model for studying human physiology or disease, and the development of immunodeficient mice has provided a valuable tool for basic and applied human disease research. Following the development of large-scale mouse knockout programs and genome-editing tools, it has become increasingly efficient to generate genetically modified mouse strains with immunodeficiency. However, due to the lack of a standardized system for evaluating the immuno-capacity that prevents tumor progression in mice, an objective choice of the appropriate immunodeficient mouse strains to be used for tumor engrafting experiments is difficult.

Methods: In this study, we developed a tumor engraftment index (TEI) to quantify the immunodeficiency response to hematologic malignant cells and solid tumor cells of six immunodeficient mouse strains and C57BL/6 wild-type mouse (WT).

Results: Mice with a more severely impaired immune system attained a higher TEI score. We then validated that the NOD-*scid-IL2Rg–/–* (NSI) mice, which had the highest TEI score, were more suitable for xenograft and allograft experiments using multiple functional assays.

Conclusions: The TEI score was effectively able to reflect the immunodeficiency of a mouse strain.

Keywords: Immunodeficiency, Tumor, Leukemia, Xenograft, Allograft

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Background

Research on human diseases has relied on experiments using immunodeficient mouse models [1]. The derivations of nude and severe combined immunodeficiency (*scid*) mice, which are widely used for xenotransplantation, were milestones in the development of immunodeficient mice. However, although nude mice lacked T cells, they harbored B cells and natural killer (NK) cells and did not allow lasting human cell reconstitution [2]. The limitations that impeded human cell engraftment in *scid* and recombination-activating 2 deficient (*Rag2–/–*) mice included the remaining mouse T and B cells and high levels of host NK cells [3, 4]. The development of NOD.Cg-*Prkdc*^{scid} (NOD-*scid*) mice with lower levels of NK cells and additional innate immune defects allowed higher levels of human cell engraftment, but the mice were still not ideal [5]. A major breakthrough in the generation of humanized mice was the development of immunodeficient *IL2Rg–/–* mice, such as the NOD/*ShiLtSz-scid/IL2Rγ*^{null} (NSG) and NOD/*Shi*Jic-*scid/IL2Rγ*^{null} (NOG) strains. These mice withstood greatly increased engraftments of human tissues (hematopoietic stem cells (HSCs) and peripheral blood mononuclear cells (PBMCs)) than all previously developed immunodeficient humanized mouse models [6, 7]. Cancer cells and the host immune system constantly interact with one another in the tumor microenvironment [8, 9]. Clinical data have demonstrated that immunodeficient individuals are susceptible to a dramatic increase in tumor incidence. For example, the

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Additional files

Additional file 1: Figure S1. Establishment of K562-GFP and RMA-GFP cell line. A. Flow chart of establishing K562-GFP and RMA-GFP cells that that constitutively expressed green fluorescent protein (GFP). B. Representative fluorescence-activated cell sorting plots show K562-GFP and RMA-GFP cells before and after GFP+ enrichment.

Additional file 2: Figure S2. Experimental design for assessing the capabilities of leukemic (top) or solid (bottom) grafts in immunodeficient mice. Three groups of mice (five mice per group) were assayed; a high number (1×10^6, H), medium number (1×10^5, M), and low number (1×10^4, L) of grafts (K562-GFP, RMA-GFP, A549, and B16F10) were injected into NSI, *IL2Rg−/−*, NOD-*scid*, *scid*, *Rag2−/−*, nude, and WT mice.

Additional file 3: Table S1. The final TEI scores of NSI, NOD-*scid*, *scid*, nude, *Rag2−/−*, *IL2Rg−/−*, and WT mice measured by xenograft experiments.

Additional file 4: Table S2. The final TEI score of NSI, NOD-*scid, IL2Rg−/−*, *Rag2−/−*, *scid*, nude and WT mice measured by allograft experiments.

Additional file 5: Figure S3. Flow chart of the functional verification of NSI mice by establishing a BLT model. Sub-lethally irradiated NSI mice were transplanted with human fetal liver and thymus tissue from the same human donors, and engrafted with autologous CD34+ hematopoietic stem cells. BLT-NSI mice were tested with flow cytometry 12 weeks after engraftment. At 12 weeks, BLT-NSI mice were immunized with OVA twice and then the serum was analyzed for human IgG.

Additional file 6: Figure S4. Tumors dissected from NSCLC PDX mice contained the bone marrow-derived cells of the hosts. Representative plots of FACS analysis show dissociated cells from the tumors contained both human cells (HLA+) and murine cells (MHC I+) that were further subjected for analysis of murine Ly6g and CD11b expression.

Additional file 7: Figure S5. Generation and characterization of the lung cancer xenograft model using dissociated tumour cells in NSI mice. Primary tumors from NSCLC patients were digested and dissociated with trypsin and were subsequently injected into NSI mice. Representative hematoxylin and eosin-stained tissues of an adenocarcinoma (left) and corresponding early-generation xenografts (right); scale bar = 50 μm.

Abbreviations

TEI: Tumor engraftment index; WT: C57BL/6 wild type; *Scid*: Severe combined immunodeficiency; *Rag2−/−*: Recombination-activating 2 deficient; NOD-*scid*: NOD.Cg-*Prkdc*^{scid}; *IL2Rg−/−*: B6.129S4-*IL2Rg*^{tm1Wjl}/J; NK: Natural killer; NSG: NOD/*ShiLtSz-scid/IL2Rγ*^{null}; NOG: NOD/*ShiJic-scid/IL2Rγ*^{null}; NSI: NOD-*scid-IL2Rg−/−*; PBMCs: Peripheral blood mononuclear cells; HSCs: Hematopoietic stem cells; ZFN: Zinc-finger nuclease; TALEN: Transcription activator-like effector nuclease; CRISPR: Clustered regularly interspaced short palindromic repeats; Cas: CRISPR associated; BLT: Bone marrow/liver/thymus; B-ALL: B cell acute lymphoblastic leukemia; PDX: Patient-derived xenograft; WT: Wild type; BM: Bone marrow; SP: Spleen; PB: Peripheral blood; OVA: Ovalbumin; NSCLC: Non-small cell lung cancer.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PL, DP, and WY conceived the study and designed the experiments. WY and SL performed most of the transplantation experiments using cell lines. YX and WY performed the lung cancer PDX experiments. ZJ performed the B-ALL single-cell transplantation experiments. YL, GL, BX, HY, LX, and YL provided and prepared B-ALL samples. BJ, MZ, HY, ZL, and SC provided and prepared cord blood samples. ZH, JL, FF, and ZW provided and prepared lung cancer patient samples. DW, LZ, and PL contributed the discussion part of the manuscript. YY provided vital new reagents and revised the manuscript. WY, YX, PL, and DP discussed and wrote the manuscript. All authors read and approved the final manuscript.

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Rapamycin inhibition of eosinophil differentiation attenuates allergic airway inflammation in mice

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RELATIONSHIP BETWEEN PPARGC1A GENE POLYMORPHISMS WITH THE INCREASED RISK OF CORONARY ARTERY DISEASE AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS IN IRAN

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Abstract

Background. Type 2 diabetes (T2D) increases the risk of coronary artery disease (CAD) in patients with type 2 diabetes compared with nondiabetic subjects. Several genetic variants are considered as risk factors for CAD, including those implicated in dyslipidaemia and oxidative stress. The PPARGC1A gene is considered as a key regulator of pathophysiological processes contributing to CAD.

Aim. We investigated whether the Gly482Ser polymorphism (rs8192678) increased susceptibility to CAD in Iranian population and whether it was associated with clinical and metabolic parameters.

Patients and methods. A total of 290 subjects including 149 CAD patients with a history of diabetes and 149 controls were included in our study. The Gly482Ser polymorphism was genotyped using ARMS-PCR method. Based on the type of variables, by the use of SPSS software (Statistical Package for Social Sciences Inc., Chicago, IL, USA) statistical analyses were performed.

Results. We found a significant difference in the Gly482Ser substitution between the case and control subjects in Iranian population. However, no significant association was observed between Gly482Ser genotypes and physiologic variables.

Conclusion. This gene polymorphism PPARGC1A Gly482Ser may be a potential marker for increased risk of CAD in diabetic patients in clinical treatment and diagnosis in the Iranian population.

Key words: Coronary artery disease, PPARGC1A gene, CAD susceptibility.

INTRODUCTION

One of the cardiovascular complications of diabetes mellitus is coronary artery disease (CAD) (1). Type 2 diabetes increases the risk of CAD at least by two- to three fold in patients with type 2 diabetes compared with nondiabetic subjects (2). In addition to environmental factors, such as lifestyle, obesity, sedentary life and smoking, several genetic variants are considered as risk factors for CAD, including those implicated in dyslipidaemia and oxidative stress (1, 3, 4). Peroxisome proliferator-activated receptor (PPAR) is a key transcription factor in adipocyte differentiation (5). Peroxisome proliferator-activated receptor-G coactivator-1 alpha (PPARGC1A) is a transcriptional co-activator of PPAR (6, 7). The PPARGC1A gene encoding for PGC-1α is a strong biological candidate for cardiovascular and metabolic disease. It is also considered as a key regulator of pathophysiological processes contributing to CAD (8, 9). PGC-1 interaction with PPAR-α regulates mitochondrial fatty acid oxidation enzyme gene expression in the heart, brown adipose tissue and liver (10). PGC-1α has also been considered to up-regulate glucose transporter 4 and, as a result, increase glucose uptake in the muscle (11). In addition, PGC-1α is implicated in hepatic gluconeogenesis by increasing gene transcription of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (12). The well established role of PGC-1 as a critical regulator for adaptive cellular energy metabolism, vascular stasis, oxidative stress and adipogenesis has prompted many scientists investigation on associations between

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Article

Residue Asn277 Affects the Stability and Substrate Specificity of the SMG1 Lipase from *Malassezia globosa*

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Abstract: Thermostability and substrate specificity are important characteristics of enzymes for industrial application, which can be improved by protein engineering. SMG1 lipase from *Malassezia globosa* is a mono- and diacylglycerol lipase (MDL) that shows activity toward mono- and diacylglycerols, but no activity toward triacylglycerols. SMG1 lipase is considered a potential biocatalyst applied in oil/fat modification and its crystal structure revealed that an interesting residue-Asn277 may contribute to stabilize loop 273–278 and the $3_{10}4$ helix which are important to enzyme characterization. In this study, to explore its role in affecting the stability and catalytic activity, mutagenesis of N277 with Asp (D), Val (V), Leu (L) and Phe (F) was conducted. Circular dichroism (CD) spectral analysis and half-life measurement showed that the N277D mutant has better thermostability. The melting temperature and half-life of the N277D mutant were 56.6 °C and 187 min, respectively, while that was 54.6 °C and 121 min for SMG1 wild type (WT). Biochemical characterization of SMG1 mutants were carried out to test whether catalytic properties

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Resveratrol induces cell apoptosis in adipocytes via AMPK activation

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ABSTRACT

Resveratrol is identified as polyphenolic compound with anti-inflammatory, antioxidant, anti-insulin resistance characteristics. Moreover, resveratrol exerts pro-apoptotic effects in varieties of cancer cell lines. However, effects and mechanisms of resveratrol on the regulation of adipocytes apoptosis remain largely unknown. In this study, we found that resveratrol treatment could induce cell apoptosis in murine 3T3-L1 adipocytes. Furthermore, resveratrol activated the mitochondrial apoptotic signaling pathway with the decrease in the mitochondrial membrane potential (MMP), and the activation of caspase 3. Mechanistically, we found that phosphorylation level of AMP-activated protein kinase α (AMPKα) was elevated, accompany with reduced level of phosphorylation of protein kinase B (AKT) when cells were exposed to resveratrol. By using small interfering RNAs of AMPKα and specific inhibitor for p-AKT, it was shown that activation of AMPKα could inhibit downstream of p-AKT, consequently activating mitochondrion-mediated apoptotic pathway. Additionally, we observed similar pro-apoptotic effects of Res on mouse primary adipocytes. Our findings clarified the apoptotic effects and underlying mechanisms of resveratrol in adipocytes, suggesting its potential therapeutic application in the treatment or prevention of obesity and related metabolic symptoms.

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1. Introduction

Obesity is considered a major risk factor for metabolic diseases, such as type 2 diabetes, liver steatosis, hyperlipidemia, atherosclerosis, etc. Excess energy intake, and (or) lacking of physical activity, leading to excess triacylglycerols stored in adipocytes, eventually impair energy homeostasis [1]. The fat mass is determined by the size of fat cells and/or the number of adipocytes. Therefore, the strategy to reduce fat mass may involve the direct loss of lipids (through lipolysis), the inhibition of adipogenesis or the apoptosis of adipocytes. Among these, the reduction of adipocyte number, for example, via induction of cell apoptosis, becomes attractive and receives widespread attention as a promising way to attenuate obesity.

Resveratrol (Res) is one of the phytochemicals which is enriched in grapes, peanuts, wine, and other food sources [2]. Res exerts biological functions as a cancer chemopreventive and chemotherapeutic agent and has anti-inflammatory, antioxidant, and neuroprotective properties [3]. The anti-proliferative and apoptosis-inducing effects of Res cause cell cycle arrest and apoptosis in different cancer cell lines [4]. In addition, Res was found to improve dyslipidemia, hyperinsulinemia and hypertension in animal models [5–7]. Despite the beneficial effects of Res on maintenance of energy homeostasis, Res directly affects lipid synthesis in fat cells by regulating adipogenesis and cell apoptosis [8,9]. In the previous research, we found out Res could inhibit cell differentiation in 3T3-L1 adipocytes via activation of AMPK [10]. Moreover, we reported that Res could induce cell apoptosis in 3T3-L1 pre-adipocytes in SIRT1-dependent manner [11], suggesting the important role of Res involved in determination of fat cell fates. Up to date, it was reported that Res could induce cell apoptosis in 3T3-L1 adipocytes [8,9], however, the underlying mechanisms remain unclear.

AMPK is a serine/threonine protein kinase, which is activated by cellular stress when ATP is depleted. AMPK is also implicated in cancer development and is considered as a potential anti-tumor target molecule [12]. Interestingly, in the previous study, we showed Res could stimulate cell apoptosis in pre-adipocytes by activation of SIRT1, which consequently inhibited AKT activation and further decreased the expression of survivin, meanwhile,

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Simian Immunodeficiency Virus Infection Evades Vaccine-Elicited Antibody Responses to V2 Region

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Objectives: An effective AIDS vaccine should elicit protective antibody responses against HIV/simian immunodeficiency virus (SIV) infection. We recently reported that mucosal priming with a replicating modified vaccinia Tiantan virus (MVTTgpe)-based vaccine regimen induces durable protection against pathogenic SIV_{mac239} infection in rhesus monkeys. Here, we aim to conduct a comprehensive analysis on antigenic determinants recognized by specific antibody responses generated by vaccination and SIV_{mac239} infection.

Methods: A novel yeast surface displayed antigen library of entire SIV_{mac239} envelope (Env) glycoprotein was established and validated to map the major antigenic determinants (MAD) in monkey sera elicited by vaccination and infection. MAD-directed antibody responses were further analyzed for correlation of protection.

Results and Conclusions: The yeast surface displayed library allows the mapping of SIV-specific linear and conformational MAD. The MVTTgpe-based regimen induces antibodies targeting mainly to 6 antigenic domains covering the entire gp160. Critically, this regimen induced a uniquely predominant antibody response against a distinct MAD in variable region 2 (V2) as compared with the Ad5gpe-based vaccine and SIV_{mac239} infection. This MAD was associated with a higher titer of anti-V2 antibody responses, which was inversely correlated with peak and set-point viral loads. Unexpectedly, the pathogenic SIV_{mac239} challenge evaded the vaccine-elicited anti-V2 antibody response. Instead of recalling B-cell memory responses to the V2 MAD, viral infection directed anti-V1V2 antibodies primarily to V1 region. Moreover, the anti-V1V2 antibody responses diminished significantly in infected macaques after they enter the stage of simian AIDS. Our findings have critical implications to AIDS vaccine efforts with focus on V2 region.

Key Words: SIV, V2, yeast surface display, major antigenic determinant, MVTT

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INTRODUCTION

An ideal HIV/AIDS vaccine should elicit high levels of protective antibody and cytotoxic T lymphocyte to neutralize viral infection and to eliminate virus infected cells, respectively. Because of the extensive genetic diversity of HIV and its devious immune evasion strategies, such a vaccine has yet to be discovered. To change this situation, in-depth analysis of vaccine-elicited immune responses is particularly important. To this end, the first evidence of efficacy for AIDS vaccine candidate in the RV144 trial has demonstrated a modest level of 31.2% against HIV risk,[1] which is related to the binding IgG antibodies targeting V1V2 region of gp120, rather than to bNAbs.[2,3] Therefore, it is of great interest to investigate the antigen–antibody interaction to reveal the major antigenic determinants (MAD) of vaccine-elicited antibody responses in protection.

Significant progresses have been made in understanding the role of antibody responses against simian immunodeficiency virus (SIV) infection in rhesus macaques. Similar to HIV infection, the protective role of antibodies has been demonstrated by passive immunization experiments using plasma[4–6] or purified immunoglobulin derived from SIV-infected long-term nonprogressor macaques.[7] Recently, a mimic study of RV144 in rhesus macaques indicated that the level of V1V2-binding antibodies was inversely correlated with SIV risk.[8] It, therefore, becomes necessary to investigate the role of V1V2-directed antibodies in other vaccine-elicited protection studies.

We recently reported that mucosal priming with a replicating modified vaccinia Tiantan virus (MVTTgpe)

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J.G. and T.Z. contributed equally to this study. Conceived and designed the experiments: J.G., T.Z., and Z.C. YSD assay development: L.Z., J.G., T.Z., and Z.C. Performed the experiments: J.G., T.Z., X.W., L.C., and J.T. Shared research materials: C.S., L.F., L.C., and L.Z. Analyzed the data: J.G., T.Z., X.W., L.Z., and Z.C. Wrote the article: J.G., L.Z., and Z.C. All authors read and approved the final article.

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Original Article

Structure of product-bound SMG1 lipase: active site gating implications

Shaohua Guo, Jinxin Xu, Ioannis V. Pavlidis, Dongming Lan, Uwe T. Bornscheuer, Jinsong Liu, Yonghua Wang

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Abstract

Monoacylglycerol and diacylglycerol lipases are industrially interesting enzymes, due to the health benefits that arise from the consumption of diglycerides compared to the traditional triglyceride oils. Most lipases possess an α-helix (lid) directly over the catalytic pocket which regulates the activity of the enzyme. Generally, lipases exist in active and inactive conformations, depending on the positioning of this lid subdomain. However, lipase SMG1, a monoacylglycerol and diacylglycerol specific lipase, has an atypical activation mechanism. In the present study we were able to prove by crystallography, in silico analysis and activity tests that only two positions, residues 102 and 278, are responsible for a gating mechanism that regulates the active and inactive states of the lipase, and that no significant structural changes take place during activation except for oxyanion hole formation. The elucidation of the gating

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Electronic Supplementary Information

Surface-enhanced Resonance Raman Scattering (SERRS) Simulate PCR for Sensitive DNA Detection†

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呼吸疾病国家重点实验室

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ORIGINAL ARTICLE

Tc17 cells are associated with cigarette smoke-induced lung inflammation and emphysema

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ABSTRACT

Background and objective: **Some types of T lymphocytes, especially cytotoxic T-cells (Tc1) and T-helper (Th17) cells, play a pivotal role in cigarette smoke-induced lung diseases. However, whether Tc17 cells are involved remains largely unknown. We investigated Tc17 involvement using a cigarette smoke-exposure model.**

Methods: **Groups of mice were exposed to cigarette smoke or filtered air. At weeks 2, 8, 12 and 24, mice were sacrificed to observe histological changes by HE stain and/or immunohistochemical staining. The frequency of T cell subsets in the lung and spleen were detected by flow cytometry. In addition, the expression levels of T cell-related factors were measured by real-time polymerase chain reaction or enzyme-linked immunosorbent assay.**

Results: **Cigarette smoke caused substantial inflammatory cell infiltration and led to emphysema. Cigarette smoke exposure promoted the expression of interferon-gamma (IFN)-γ and interleukin (IL)-17A at the messenger ribonucleic acid and protein levels. In addition to Tc1 and Th17 cells, pulmonary and splenic Tc17 cells increased, which was accompanied by the upregulation of cytokines IL-6, transforming growth factor beta (TGF)-β) and transcriptional factors Stat3 and RAR-related orphan receptor gamma. Compared with untreated mice, γH2AX-positive cells were more frequently observed in mice exposed to cigarette smoke.**

Conclusions: **Long-term cigarette smoke exposure induced Tc17 cell expansion both locally and distally, which was associated with emphysema and deoxyribonucleic acid damage. As an important source of IL-17A, this T cell subset may be a potential target for chronic obstructive pulmonary disease therapy.**

Key words: cigarette smoke, DNA damage, emphysema, inflammation, Tc17.

SUMMARY AT A GLANCE

Cigarette smoke exposure led to persistent inflammation and emphysematous change in a mouse model. Cigarette smoke induced the expansion of Tc17, a novel type of interleukin (IL)-17A-producing cells, locally and distally, which was associated with deoxyribonucleic acid (DNA) damage.

Abbreviations: BALF, bronchoalveolar lavage fluid; COPD, chronic obstructive pulmonary disease; DNA, deoxyribonucleic acid; IFN-γ, interferon-gamma; IL, interleukin; mRNA, messenger ribonucleic acid; PE, phycoerythrin; SEM, standard error of the mean; Tc cell, cytotoxic T cell; Th cell, helper T cell.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common airway disease that is characterized by inflammatory cell infiltration, a not fully reversible airflow limitation, mucus overproduction and airway remodeling.[1] More than 200 million people suffer from this disease worldwide, and it is estimated that COPD will become the third leading cause of death by 2030.[2]

Cigarette smoke is considered the most important risk factor for COPD; however, the mechanisms of pathogenesis are still not fully elucidated. It is widely accepted that dysregulation of the local immune response plays a pivotal role in COPD pathogenesis.[3] Innate immunity is first initiated once airway is exposed to cigarette smoke, while adaptive immunity gradually develops after continuous stimulation by various antigens.[4,5]

Adaptive immunity involves both CD4+ and CD8+ T cells.[6] According to the specific profile of cytokine secretion, both CD4+ T cells and CD8+ T cells can be further divided into several subtypes. Among these T-cell subpopulations, cytotoxic T (Tc)1 (CD8+ interferon-gamma (IFN-γ)+) and T-helper (Th)17 (CD4+IL-17A+) cells are two subsets that are commonly considered to be involved in COPD pathogenesis. Th17 or Tc1 cells

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tert-Butylhydroquinone mobilizes intracellular-bound zinc to stabilize Nrf2 through inhibiting phosphatase activity

Yunfang Chen,[1] Sheng Wang,[3] Xin Fu,[1] Wenqu Zhou,[1] Wei Hong,[1] Dongting Zou,[1] Xichong Li,[1] Jinbao Liu,[2] Pixin Ran,[3] and Bing Li[1]

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Chen Y, Wang S, Fu X, Zhou W, Hong W, Zou D, Li X, Liu J, Ran P, Li B. *tert*-Butylhydroquinone mobilizes intracellular-bound zinc to stabilize Nrf2 through inhibiting phosphatase activity. *Am J Physiol Cell Physiol* 309: C148–C158, 2015. First published May 20, 2015; doi:10.1152/ajpcell.00031.2015.—The nuclear factor erythroid 2-related factor 2 (Nrf2) is required to combat increases in oxidative stress. The chemical compound *tert*-butylhydroquinone (tBHQ) can downregulate Kelch-like ECH-associated protein 1 (Keap1), a repressor of Nrf2, thus maintaining the stability of Nrf2. tBHQ can also increase intracellular "free" zinc in human bronchial epithelial (16HBE) cells. We aim to investigate whether the intracellular free zinc change plays a role in Nrf2 activation. tBHQ exposure dose-dependently increases intracellular free zinc concentrations within 30 min in 16HBE cells by mobilizing intracellular zinc pools. Active Nrf2 and the antioxidant enzyme heme oxygenase-1 (HO-1) increase at 3 h after tBHQ treatment. Chelating intracellular free zinc with tetrakis-(2-pyridylmethyl)ethylenediamine (TPEN) during tBHQ exposure partially abrogates the tBHQ-induced activation of Nrf2 and HO-1 expression, while Keap1 is further decreased. These results indicate that tBHQ-induced stability of Nrf2 is associated with the intracellular free zinc level. Because the activated Nrf2 is phosphorylated, the serine/threonine protein phosphatase activity, which is known to be inhibited by zinc, is assayed. The results showed that tBHQ treatment can suppress cellular protein phosphatase-2A (PP2A) and protein phosphatase-2C (PP2C) activity, which can be abrogated by adding TPEN. This finding is verified in a cell-free protein extract experiment by supplying zinc or by chelating zinc with TPEN. These results provide a novel mechanistic insight into Nrf2 activation in antioxidant enzyme induction involving zinc signaling. The increase of intracellular free zinc may be one mechanism for Nrf2 activation. The inhibition of PP2A and PP2C activity may be involved in Nrf2 phosphorylation modulation.

nuclear factor erythroid 2-related factor 2; heme oxygenase-1

OXIDATION/ANTIOXIDATION IMBALANCE plays an important cellular role and has been implicated in the pathogenesis of many diseases (12, 48). A number of cellular enzymes are induced by oxidative stress, including antioxidant proteins and phase II detoxifying enzymes (31, 34). Heme oxygenase-1 (HO-1) is one such enzyme responding to these stresses and is ubiquitously expressed and catalytically active. The importance of HO-1 expression in mediating antioxidant and anti-inflammatory effects has been well characterized both in vitro and in vivo (13, 33, 71). Patients with HO-1 deficiency are more vulnerable to oxidative stress (1, 51).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor responsible for inducing antioxidative enzyme expression (63, 72). Under basal conditions, a negative regulator named Kelch-like ECH-associated protein 1 (Keap1) tightly regulates the activity of Nrf2. Keap1 binds to Nrf2, promoting its ubiquitylation by the Cul3-Rbx1 ubiquitin ligase (1) holoenzyme and targeting Nrf2 for ubiquitination and proteasome degradation (16, 73). Keap1 contains many cysteine residues that act as redox sensors. Once exposed to oxidative stress, the cysteines in Keap1 are modified and cause profound conformational changes in Keap1, leading to a loss of the ability to bind Nrf2 (36, 37, 58). Nrf2 then translocates to the nucleus and binds to antioxidant response element (ARE), which has been identified in the promoter regions of most upstream antioxidant genes. Nrf2 activation has been shown to protect cells against carcinogens and oxidative stress by up-regulating the expression of many genes involved in antioxidative reactions, such as HO-1, glutamate cysteine ligase catalytic subunit (GCLC), and NAD(P)H quinone oxidoreductase 1 (23, 35, 45). Nrf2 phosphorylation plays an important role in controlling Nrf2 activity and stability. The phosphorylation of Nrf2 at serine-40 promotes its dissociation from Keap1 to prevent degradation, allowing "free" Nrf2 to translocate to the nucleus (26, 57). The activation of protein kinase C (PKC) (57) and casein kinase 2 (4) is clearly necessary for Nrf2 phosphorylation. These findings demonstrated that the phosphorylation of Nrf2 is an integral component of Nrf2 nuclear localization and transcriptive activation of Nrf2 (4, 27). The inhibition of certain protein phosphatases is primarily responsible for the persistent activation of Nrf2 (49, 66).

tert-Butylhydroquione (tBHQ) is a typical compound that stimulates the nuclear translocation of Nrf2 (28, 38). It is clear that tBHQ can activate Nrf2 in different ways, such as triggering the degradation of Keap1 to result in Nrf2 accumulation (25), increasing the phosphorylation of Nrf2 (4), and stabilizing Nrf2 ubiquitination (55), which dissociates Nrf2 from Keap1 to prevent degradation. However, the mechanisms underlying these activities are largely unknown.

The cytoplasmic increase in zinc involved in combating oxidative stress has been extensively studied in recent years. Oxidative stress alters many metabolic and signaling pathways by affecting the protein redox state and indirectly triggering the

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The 3 facets of regulation of herpes simplex virus gene expression: a critical inquiry

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Abstract

On entry into the body herpes simplex viruses (HSV) replicate in a series of steps that involves derepression of viral DNA activated by VP16, a virion protein, and sequential transcription of viral genes in a cascade fashion. HSV also enters into neurons in which viral DNA maintained as heterochromatin and with few exceptions viral gene expression is silenced. A third face of the interaction of HSV with its host cells takes place at the moment when the silenced viral genome in neurons is abruptly derepressed. The available data do no reveal evidence that HSV encodes different regulatory programs for each facet of its interaction with its host cells. Rather the data point to significant gaps in our knowledge of the mechanisms by which each facet is initiated and the roles of the infected cells at each facet of the interaction of viral gene products with the host cell.

Keywords

Replication; Latency; Reactivation

Introduction

If herpes simplex viruses (HSV) could unveil their moto, it would read “Multiply, Persist and Disseminate”. Indeed for more than a century it has been recognized that HSV infect people by direct contact between tissues of individuals with a herpetic lesion and those of a healthy individual. In the course of multiplication at the portal of entry the virus infects nerve endings and is transported to a dorsal root or sensory neuron where it remains quasi-silent or, in the traditional terminology, latent. In some individuals the virus remains latent for a life time. In others it periodically replicates and is transported anterograde to a site at or near the portal of entry into the body where it replicates and is transmissible by contact

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ICC COLUMN: The Voice of the Patient

The fight against chronic respiratory diseases in the elderly: the European Innovation Partnership on Active and Healthy Aging and beyond

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呼吸疾病国家重点实验室

Introduction

The International COPD Coalition (ICC) believes that COPD and other respiratory diseases that strike the elderly will become an increasing problem worldwide as the elderly become a higher proportion of the overall populations. Because the European Union has anticipated this problem and is taking many proactive steps to deal effectively with the health care needs of the elderly, we wanted to provide more detailed information about their efforts in this ICC Column in *JTD*.

Active and Healthy Aging (AHA)

Chronic respiratory diseases affect all age groups but particularly old-age patients (1). Functioning and physical health declines with advancing age and co-morbidity (2). Aging increases the likelihood of non-communicable diseases (NCDs) and co-morbidities, thereby increasing their adverse effects on health and well-being. As the general population ages, the number of patients with NCDs grows more rapidly. There are gender differences (3) that must be kept in mind, and the magnitude of the effect of NCDs on aging is greater in developing countries where budgets are fixed and limited (4). Although most NCDs are clinically evident in adults, asthma and allergic rhinitis often occur in children, persist throughout life, and should be tackled early (5), but often they are not and must be dealt with in the elderly. Most chronic respiratory diseases express age-dependent phenotypes, and in elderly adults it is often difficult to differentiate between asthma and COPD. Moreover, CRDs are intertwined with co-morbid NCDs and treatments are complex, in particular when inhalers are required.

AHA is a major societal challenge common to all European countries, but also to other populations. The elderly often experience socioeconomic inequalities, and aging is an under-appreciated cause of poverty that also hinders economic development, particular involving underserved populations and women (6). AHA should be promoted prior to old age if it is to be successful as old age arrives. Promoting AHA offers many benefits for countries worldwide in providing innovative responses to this challenge.

Let us describe the European approach to healthy aging. European Innovation Partnerships (EIP) are working to decrease societal problems in facilitating healthy aging through research and innovation. They address weaknesses in the EU research and innovation (e.g., under-investment, fragmentation, and duplication), which complicate the discovery or exploitation of knowledge and may ultimately prevent the entry of innovations in healthy aging into national market places (7).

European Innovation Partnership on Active and Healthy Aging

The pilot EIP on AHA pursues a triple benefit for Europe:

- Enabling EU citizens to lead healthy, active and independent lives while aging;

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The p.Ser267Phe Variant in *SLC10A1* Is Associated With Resistance to Chronic Hepatitis B

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In the past 50 years there have been considerable efforts to identify the cellular receptor of hepatitis B virus (HBV). Recently, *in vitro* evidence from several groups has shown that the sodium–taurocholate cotransporting polypeptide (NTCP, which is encoded by *SLC10A1* and transports bile acids into hepatic cells in enterohepatic recirculation) is a strong candidate. In particular, *in vitro* the p.Ser267Phe variation of *SLC10A1* results in loss of HBV receptor function. We tested the role of NTCP as a receptor for HBV in chronic hepatitis B patients using a genetic association study. We selected *SLC10A1* variants from 189 exomes. We used Sanger sequencing to follow up the association of the various *SLC10A1* variants in a Han Chinese cohort of 1899 chronic hepatitis B patients and 1828 healthy controls. We further investigated the potential impact of the p.Ser267Phe variant on NTCP function using structural analysis. The p.Ser267Phe variant was associated with healthy status ($P = 5.7 \times 10^{-23}$, odds ratio = 0.36) irrespective of hepatitis B virus surface antibody status ($P = 6.2 \times 10^{-21}$ and 1.5×10^{-10}, respectively, when the cases were compared with hepatitis B virus surface antibody–positive and –negative controls). The variation was also associated with a lower incidence of acute-on-chronic liver failure ($P = 0.007$). The estimated heritability explained by this single variation was ~3.2%. The population prevented fraction was around 13.0% among the southern Chinese. Our structural modeling showed that the p.Ser267Phe variant might interfere with ligand binding, thereby preventing HBV from cellular entry. *Conclusion:* The p.Ser267Phe NTCP variant is significantly associated with resistance to chronic hepatitis B and a lower incidence of acute-on-chronic liver failure. Our results support that NTCP is a cellular receptor for HBV in human infection. (HEPATOLOGY 2015;61:1251-1260)

Chronic hepatitis B (CHB) affects approximately 240 million people worldwide and is responsible for about 780,000 deaths annually (http://www.who.int/mediacentre/factsheets/fs204/en/). Clinically, CHB holds the most significant medical consequences among hepatitis B virus (HBV)–infected individuals. Acute-on-chronic liver failure (ACLF) is the most urgent and lethal condition related to CHB.

Abbreviations: ACLF, acute-on-chronic liver failure; AIM, ancestry-informative marker; ASBT, apical sodium-dependent bile acid transporter; CHB, chronic hepatitis B; HBV, hepatitis B virus; HBsAb, hepatitis B virus surface antibody; HBsAg, hepatitis B virus surface antigen; HDV, hepatitis D virus; NTCP, sodium–taurocholate cotransporting polypeptide..

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ORIGINAL ARTICLE

The p53-induced *lincRNA-p21* derails somatic cell reprogramming by sustaining H3K9me3 and CpG methylation at pluripotency gene promoters

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Recent studies have boosted our understanding of long noncoding RNAs (lncRNAs) in numerous biological processes, but few have examined their roles in somatic cell reprogramming. Through expression profiling and functional screening, we have identified that the large intergenic noncoding RNA p21 (*lincRNA-p21*) impairs reprogramming. Notably, *lincRNA-p21* is induced by p53 but does not promote apoptosis or cell senescence in reprogramming. Instead, *lincRNA-p21* associates with the H3K9 methyltransferase SETDB1 and the maintenance DNA methyltransferase DNMT1, which is facilitated by the RNA-binding protein HNRNPK. Consequently, *lincRNA-p21* prevents reprogramming by sustaining H3K9me3 and/or CpG methylation at pluripotency gene promoters. Our results provide insight into the role of lncRNAs in reprogramming and establish a novel link between p53 and heterochromatin regulation.

***Keywords*:** somatic cell reprogramming; long noncoding RNAs; p53; *lincRNA-p21*; heterochromatin; H3K9 methylation; DNA methylation

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Introduction

Induced pluripotent stem cells (iPSCs) have major implications for regenerative medicine, *in vitro* disease modeling and toxicology screening [1]. Yet, to fulfill

REVIEW ARTICLE

The rural–urban enigma of allergy: What can we learn from studies around the world?

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Keywords
allergy; environment; exposure; farm effect; microbial; rural; urban

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Abstract

Childhood asthma and related allergic conditions have become the most common chronic disorders in the Western world. Many studies from around the world have demonstrated an increasing trend of asthma prevalence over the last few decades (Lancet, 368, 2004, 733). A few recent reports also suggested that childhood asthma prevalence may be showing a plateau or even a decline in few developed countries. Given the rapid changes in the prevalence over a short period of time, environmental factors are the more likely candidates explaining such trend. One of the most consistent epidemiological findings was that subjects living in the rural areas had lower prevalence of allergies when compared to those from urban areas (Clin Exp Allergy 30, 2000, 187; Pediatr Pulmonol 44, 2009, 793). Clear understanding of the mechanisms of how the environmental determinants in the rural environment may affect the early immune system resulting in lower risk of allergies and asthma will facilitate the development of future primary preventive strategies. In this study, we review recent data from around the world and explore the epidemiology and mechanistic studies that may explain the rural–urban difference of allergies.

呼吸疾病国家重点实验室

Asthma epidemic worldwide

In the past four decades, there have been many epidemiological studies showing a rapidly increasing prevalence of asthma (1). Although some of the increase might have been due to an increased recognition of the disease, data from the International Study of Asthma and Allergies in Childhood (ISAAC) have shown very high prevalence of childhood asthma in many western countries (2). Using ISAAC methodologies to evaluate the secular trend of asthma prevalence, researchers have shown dramatic increase of asthma in children from the United Kingdom and Australia (3, 4). In the period from 1982 to 1992, the prevalence of wheezing within the past 12 months in schoolchildren aged 8–10 yrs had increased by 1.5- to 2.6-fold in two towns from New South Wales, Australia (3). In another study using the same ISAAC methodology to study asthma prevalence in adolescents from Guangzhou, China, children were studied three times from 1994 to 2009, the prevalence rates of asthma ever and current wheeze have increased from 3.9% and 3.4% in 1994 to 6.9% and 6.1% in 2009 (5).

The comparative studies of prevalence of asthma and allergies between former East and West Germany have been very informative (6). The environment and living conditions in former East and West Germany were very different. Despite a much higher level of environmental pollution in the East, the prevalence rates of wheeze, doctor diagnosed asthma and bronchial hyper-reactivity were much higher in West Germany. The difference in the prevalence was most likely due to differences in environmental exposure early in life. After unification, rapid westernization occurred in former East Germany associated with rapid increase in the prevalence of atopic sensitization and symptoms of hay fever in children from the Eastern Germany. Early life exposure factors are likely to be the important determinates for the subsequent development of allergies.

ISAAC has been developed to assess the prevalence of childhood asthma, allergic rhinitis, and atopic eczema for international comparison in a standardized way (7). The results from this international collaboration showed dramatic global variations of asthma prevalence. The prevalence rates of

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The Serum Profile of Hypercytokinemia Factors Identified in H7N9-Infected Patients can Predict Fatal Outcomes

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The novel avian origin influenza A (H7N9) virus has caused severe diseases in humans in eastern China since the spring of 2013. Fatal outcomes of H7N9 infections are often attributed to the severe pneumonia and acute respiratory distress syndrome (ARDS). There is urgent need to discover biomarkers predicting the progression of disease and fatal outcome of potentially lethal flu infections, based on sound statistical analysis. We discovered that 34 of the 48 cytokines and chemokines examined in this study were significantly elevated in the plasma samples from patients infected with H7N9. We report for the first time that the levels of MIF, SCF, MCP-1, HGF, and SCGF-β are highly positively linked to disease severity and the profile of mediators MIF, SCF, MCP-1, HGF, SCGF-β, IP-10, IL-18, and IFN-γ is an independent outcome predictor.

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The Sleep Apnea cardioVascular Endpoints (SAVE) Trial: Rationale, Ethics, Design, and Progress

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The Sleep Apnea cardioVascular Endpoints (SAVE) study is an ongoing investigator-initiated and conducted, international, multicenter, open, blinded endpoint, randomized controlled trial that was designed to determine whether treatment of obstructive sleep apnea (OSA) with continuous positive airways pressure (CPAP) can reduce the risk of serious cardiovascular (CV) events in patients with established CV disease (clinical trial registration NCT00738179). The results of this study will have important implications for the provision of health care to patients with sleep apnea around the world. The SAVE study has brought together respiratory, sleep, CV and stroke clinicians-scientists in an interdisciplinary collaboration with industry and government sponsorship to conduct an ambitious clinical trial. Following its launch in Australia and China in late 2008, the recruitment network expanded across 89 sites that included New Zealand, India, Spain, USA, and Brazil for a total of 2,717 patients randomized by December 2013. These patients are being followed until December 2015 so that the average length of follow-up of the cohort will be over 4 y. This article describes the rationale for the SAVE study, considerations given to the design including how various cultural and ethical challenges were addressed, and progress in establishing and maintaining the recruitment network, patient follow-up, and adherence to CPAP and procedures. The assumptions underlying the original trial sample size calculation and why this was revised downward in 2012 are also discussed.

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BACKGROUND AND RATIONALE FOR THE SAVE STUDY

Obstructive sleep apnea (OSA), which is characterized by repeated episodes of complete or partial upper airway obstruction during sleep leading to transient hypoxemia, arousal from sleep, tachycardia, and a surge in systemic and pulmonary arterial blood pressure (BP), was first widely recognized as a clinical disorder in the 1970s. OSA, defined as more than 15 apneas and hypopneas per hour of sleep, was shown in early studies to affect approximately 7% of adults in the general population[1] and 30–60% of patients with known cardiovascular (CV) disease.[2–4] However, as rates of obesity rise worldwide, recent studies suggest that approximately 10–15% of adults may suffer from moderate-severe OSA.[5,6]

In a landmark Australian study by Sullivan and colleagues in 1981, nasal continuous positive airway pressure (CPAP) was shown to be a highly effective treatment for patients with OSA[7] by improving levels of daytime alertness and well-being through alleviating upper airway obstruction and returning sleep quality and blood oxygen levels to normal. The major goal of OSA treatment has been to relieve patients of debilitating daytime sleepiness and socially disruptive snoring, and for patients who initially accept CPAP therapy, long-term adherence is 70–80%.[8] However, there has been increasing evidence of a causal relationship between OSA and CV disease through several potential pathways of physiological disturbance during sleep.[9] Animals exposed to intermittent hypoxia similar to those experienced by patients with OSA have shown sustained elevations in BP, central nervous system damage, and abnormalities of glucose and lipid metabolism.[10–13] Clinical and community-based studies have shown OSA to be independently associated with hypertension, glucose dysregulation, and ischemic and cerebrovascular disease.[14–18] Short-term CPAP treatment of OSA has been shown to result in small reductions in systemic[19,20] and pulmonary artery blood pressure,[21,22] and improvements in some other biomarkers of CV risk,[23] but not all such intervention studies had been positive.[24] A large longitudinal but nonrandomized study completed prior to the launch of SAVE suggested that CPAP therapy might substantially reduce the risk of CV events.[16]

Since the launch of the study in 2008, several large longitudinal studies have reported independent associations between

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Three decomposition products of valepotriates from *Valeriana jatamansi* and their cytotoxic activity

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Three new decomposition products of valepotriates, valtrals A–C (**1**–**3**), and two known products, baldrinal and homobaldrinal, are formed during the isolation procedure of the ethanol extract of the whole plants of *Valeriana jatamansi*. Their structures were determined by spectroscopic methods including IR, MS, 1D, and 2D NMR experiments. Compounds **1**–**3** showed selective cytotoxicity against metastatic prostate cancer (PC-3M) and colon cancer (HCT-8) cell lines.

Keywords: *Valeriana jatamansi*; valepotriates; valtrals A–C; cytotoxicity

1. Introduction

Valepotriates are a family of iridoid ester extracted from the genus *Valeriana* and have showed anxiolytic, sedative, cytotoxic, and antitumor activities [1–4]. Our recent investigation of *Valeriana jatamansi* (syn. *Valeriana wallichii* DC.) led to the isolation of a series of valepotriates with cytotoxic activity against human cancer cell lines and the molecular mechanism of IVHD-valtrate, one of the most active valepotriates has been studied *in vitro* and *in vivo* on the inhibition of the growth of A2780 and OVCAR3 xenograft tumors [5–10]. Furthermore, a structure–activity relationship of cytotoxicity of the valepotriates against metastatic prostate cancer (PC-3M) cells has also been discussed [11].

Some valepotriates, such as valtrate and acevaltrate, are very unstable and they could be easily decomposed during the isolation procedure [12]. The most important of these decomposition products are baldrinal, homobaldrinal, and isovaltral, which are formed from valtrate and acevaltrate, respectively, during the elution process on columns using silica gel and alumina as stationary phase [13]. Our ongoing effort to search for valepotriates from this medicinal plant has also resulted in the isolation of three new decomposition products of valepotriates, valtrals A–C (**1**–**3**) (Figure 1), together with baldrinal and homobaldrinal during the elution process. We report herein the isolation, structure elucidation, and cytotoxic activities of valtrals A–C (**1**–**3**). In addition, HPLC–ESI-MS and a simulated isolation procedure on silica gel were performed to verify the decomposition products from valepotriates.

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Trek1 contributes to maintaining nasal epithelial barrier integrity

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Abstract

Epithelial barrier integrity is critical to maintain the homeostasis in the body. The regulatory mechanism of the epithelial barrier function has not been fully understood. This study aims to elucidate the role of the TWIK-related potassium channel-1 (Trek1) in the regulation of the epithelial

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Trek1 contributes to maintaining nasal epithelial barrier integrity

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Epithelial barrier integrity is critical to maintain the homeostasis in the body. The regulatory mechanism of the epithelial barrier function has not been fully understood. This study aims to elucidate the role of the TWIK-related potassium channel-1 (Trek1) in the regulation of the epithelial barrier function of the nasal mucosa. In this study, the levels of Trek1 were assessed by real time RT-PCR and Western blotting. The epithelial barrier function of the rat nasal epithelia was evaluated by the Ussing chamber system. The results showed that Trek1 was detected in the human and rat nasal epithelia, which were significantly lower in patients and rats with allergic rhinitis than that in healthy controls. Exposure to the signature T helper 2 cytokine, interleukin (IL)-4, markedly suppressed the expression of Trek1 in the nasal mucosa via up regulating the expression of the histone deacetylase (HDAC)1. The IL-4-induced rat nasal epithelial barrier dysfunction could be blocked by HDAC1 inhibitor (Trichostatin A), or sodium butyrate, or administration of *Clostridium Butyricum*. We conclude that Trek1 is critical to maintain the nasal epithelial barrier function.

The physical components of the epithelial barrier consist of the epithelial cell bodies and the tight junctions. Only water and small molecules can pass through the epithelial barrier to enter the deep tissue under healthy conditions. The epithelial barrier may be disrupted in unusual circumstances; such as psychological stress[1,2], allergic responses[3], inflammation[4] and infections[5]. The mechanisms of epithelial barrier dysfunction have been investigated extensively. However, the regulatory factors of the epithelial barrier integrity have not been fully elucidated yet.

The hyperpermeability is one of the major features of the epithelial barrier dysfunction, in which macromolecular antigens or noxious substances may pass through the barrier to reach the subepithelial region to contact immune cells to initiate unwanted immune responses. It is suggested that extrinsic molecules may pass through the epithelial barrier via the paracellular pathway or the intracellular pathway[6]. In the former case, the paracellular space may be enlarged by losing tight junction associated proteins[2,7], or increasing in the expression of some tight junction associating proteins, such as claudin 2[8]. In the latter case, the endocytic molecules are not properly decomposed in the epithelial cells, such as deficiency of ubiquitin A20[9], resulting in the macromolecular proteins or peptides with functional antigenicity to be transported across the epithelial barrier to reach the subepithelial region. The mechanism of the epithelial barrier dysfunction has not been fully understood yet.

Histone deacetylases (HDAC) are a group of enzymes that remove an acetyl group from lysine amino acid on a histone, which allows the DNA to be wrapped by the histone to prevent the gene transcription. HDAC activities are involved in multiple cell activities, including inflammation[10], cancer cell growth[11] and allergic disorders[12]. HDAC1 can bind to the Fas promoter in T cells, and butyrate inhibits the HDAC1 activity to induce Fas promoter hyperacetylation and Fas upregulation in T cells[13]. Epithelial barrier dysfunction is associated with the pathogenesis of allergic diseases and inflammation; whether HDAC regulates the epithelial barrier function is to be investigated.

The TWIK-related potassium channel-1 (Trek1) is the K2P channel (Two Pore Domain Potassium Channels), an important member of the family. Earlier studies of the expression and function of TREK 1 are more concentrated in neural systems[14,15], recent studies showed that TREK 1 expression in endothelial cells mediated vasodilation and local regulation[16].

Although its original function is for potassium ion transportation, recent reports have revealed that Trek1 plays a critical role in the maintenance of the endothelial barrier integrity in the brain blood barrier[15] and HDAC1 can

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Thrombospondin-1 (TSP1)-producing B Cells Restore Antigen (Ag)-specific Immune Tolerance in an Allergic Environment*

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Background: The generation of tolerogenic dendritic cells (TolDCs) in an allergic environment is refractory.
Results: Administration of IL-13 antagonists increases TolDCs in an allergic environment.
Conclusion: Blocking IL-13 in an allergic environment facilitates the generation of TolDCs.
Significance: Using IL-13 antagonists has the potential to enhance the therapeutic effect of the allergic diseases.

Restoration of the antigen (Ag)-specific immune tolerance in an allergic environment is refractory. B cells are involved in immune regulation. Whether B cells facilitate the generation of Ag-specific immune tolerance in an allergic environment requires further investigation. This paper aims to elucidate the mechanism by which B cells restore the Ag-specific immune tolerance in an allergic environment. In this study, a B cell-deficient mouse model was created by injecting an anti-CD20 antibody. The frequency of tolerogenic dendritic cell (TolDC) was assessed by flow cytometry. The levels of cytokines were determined by enzyme-linked immunosorbent assay. The expression of thrombospondin-1 (TSP1) was assessed by quantitative real-time RT-PCR, Western blotting, and methylation-specific PCR. The results showed that B cells were required in the generation of the TGF-β-producing TolDCs in mice. B cell-derived TSP1 converted the latent TGF-β to the active TGF-β in DCs, which generated TGF-β-producing TolDCs. Exposure to IL-13 inhibited the expression of TSP1 in B cells by enhancing the TSP1 gene DNA methylation. Treating food allergy mice with Ag-specific immunotherapy and IL-13 antagonists restored the generation of TolDCs and enhanced the effect of specific immunotherapy. In conclusion, B cells play a critical role in the restoration of specific immune tolerance in an allergic environment. Blocking IL-13 in an allergic environment facilitated the generation of TolDCs and enhanced the therapeutic effect of immunotherapy.

The underlying mechanism of immune tolerance is proposed to be that the exposure to specific antigens (Ags)[4] induces the generation of tolerogenic dendritic cells (TolDCs) and regulatory T cells (Tregs) (1). This has been supported by a large number of animal model studies, which indicate that exposure to Ags at small doses for several times or exposure to one large dose of Ags can induce TolDCs and Tregs in the body (2). However, the generation of TolDCs is quite refractory in subjects with allergic disorders; the mechanism remains to be further elucidated.

TolDCs are categorized into several subtypes based on their expression of high levels of interleukin (IL)-10, transforming growth factor (TGF)-β, or indolamine-2,3-dioxygenase, etc. (3). Various subtypes of TolDCs play important roles in the induction and maintenance of immune tolerance in the body (3). One of the mediators by which TolDCs induce Tregs is TGF-β (4). TGF-β regulates multiple cell functions, including differentiation, migration, and proliferation, inhibiting the functions of inflammatory cells and promoting the function of Tregs (5). TGF-β induces expression of Foxp3 in T cells to facilitate the generation of Tregs (6, 7). It is accepted that a subtype of TolDCs can produce TGF-β to generate Tregs; however, after synthesis, TGF-β exists as a precursor, the latent TGF-β (LTGFβ), in the cells. LTGFβ has a latency-associated peptide (LAP) attaching to the TGF-β molecular complex. It is necessary to remove the LAP from the complex to convert the LTGFβ to TGF-β; how the conversion is carried out in DCs has not yet been well defined.

Thrombospondin 1 (TSP1) is a protein that in humans is encoded by the *THBS1* gene (8). TSP1 has multiple functions, such as in platelet aggregation, angiogenesis, and tumorigenesis (9). Previous reports suggest a pathway to generate Tregs from human $CD4^+$ $CD25^-$ T cells in response to inflammation, in

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[4] The abbreviations used are: Ag, antigen; TolDC, tolerogenic dendritic cell; Treg, regulatory T cell; LTGFβ, latent TGF-β; LAP, latency-associated peptide; TSP1, thrombospondin-1; DC, dentritic cell; MACS, magnetic cell sorting; OVA, ovalbumin; FA, food allergy; Ab, antibody; SIT and MSIT, Ag-specific immunotherapy and modified Ag-specific immunotherapy, respectively; BC, B cell; IL-13R, IL-13 receptor.

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RESEARCH ARTICLE

Tumor suppressor miR-145 reverses drug resistance by directly targeting DNA damage-related gene RAD18 in colorectal cancer

Rui-Lei Liu · Ye Dong · Yan-Zhen Deng · Wen-Jun Wang · Wei-Dong Li

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Abstract Colorectal cancer (CRC) is one of the most common cancers worldwide. Although chemotherapy is used as a palliative treatment, ultimately, nearly all patients develop drug resistance. Therefore, the cell-inherent DNA repair pathway must reverse the DNA-damaging effect of cytotoxic drugs that mediates therapeutic resistance to chemotherapy. RAD18, a DNA damage-activated E3 ubiquitin ligase, is known to play a critical role in DNA damage repair in cancer cells. Here, we show that RAD18 is highly expressed in human 5-fluorouracil (5-FU)-resistant cancer cells after 5-FU treatment. In addition, RAD18 increases in CRC cells could induce DNA damage repair, suggesting that RAD18 might be a possible target for overcoming drug resistance. Moreover, the expression of tumor suppressor microRNA-145 (miR-145) was negatively correlated with RAD18 expression in CRC tissues of 140 patients. Using luciferase reporters carrying the 3′-untranslated region of RAD18 combined with Western blotting, we identified RAD18 as a direct target of miR-145. Also of interest, suppression of RAD18 by miR-145 enhanced DNA damage in CRC cells after 5-FU treatment. Finally, the 5-FU-resistant cancer cells could be selectively ablated by treatment with miR-145. Taken together, these results suggest that miR-145 can act as an RAD18 inhibitor and contribute as an important factor in reversing drug resistance after chemotherapy.

Keywords miR-145 · Colorectal cancer · DNA damage · Drug resistance · RAD18

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide. The overall incidence of CRC is 5 % in the general population, and the 5-year survival rate ranges from 40 to 60 % [1]. In 2008, CRC was the third most common cancer for both genders, with an estimated 148,810 new cases and 49,960 deaths in the USA [2]. 5-Fluorouracil (5-FU)-based chemotherapy regimens remain the standard treatment for CRC. However, response rates to 5-FU therapy are between 10 and 20 % [3]. Combining 5-FU with the DNA-damaging agent oxaliplatin has significantly improved response rates for advanced colorectal cancer to 40–50 %; however, 5-year overall survival remains less than 5 % [4]. These studies indicate that DNA damage response is involved in chemotherapy resistance in CRC.

Loss of a DNA repair pathway may be compensated for by the function of another DNA damage response (DDR) pathway, which may be upregulated and contribute toward resistance to chemotherapy and radiotherapy [5]. The RAD18 gene belongs to the RAD6 epistasis group and was originally isolated on the basis of increased sensitivity to ultraviolet rays, ionizing radiation and a variety of other DNA-damaging agents [6, 7]. RAD18 is highly conserved and contains a RING finger domain at its N-terminus and a middle zinc finger domain followed by an SAP domain. As a key factor in the PRR pathway, RAD18 forms a tight E2–E3 complex with RAD6 in yeast or HHR6A/HHR6B in humans to promote

Rui-Lei Liu and Ye Dong contributed equally to this work.

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Tumor-specific Th2 responses inhibit growth of CT26 colon-cancer cells in mice via converting intratumor regulatory T cells to Th9 cells

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The abnormality of immune regulation plays a critical role in the pathogenesis of cancer; the underlying mechanism has not been fully understood yet. This study aims to investigate the role of cancer specific T helper (Th)2 response in the inhibition of colon cancer (Cca) cell growth. The results showed that with Cca cell (CT26 cell) extracts as an antigen, the Cca-extract specific Th2 response was induced in the Cca-bearing mice. The Cca mass size was significantly reduced, or radically disappeared (5 out of 10; or 50%); the survival rate was markedly improved in mice immunized with Cca-extract, but not in those immunized with another tumor cell (U87 cell) extracts or to bovine serum albumin. The immunization with Cca-extract also induced Cca cell apoptosis and converted the intra-Cca Tregs to T helper (Th) 9 cells. In conclusion, Cca-specific Th2 responses inhibit Cca growth in a mouse model via inducing Cca cell apoptosis and converting intra-Cca Tregs to Th9 cells.

Under physiological environment, the sporadic cancer cells in the body can be recognized and eliminated by the immune surveillance[1]. The cytotoxic $CD8^+$ T cells are the major cell population to kill cancer cells[2]. Other immune cells, including natural killer cells[3], $CD4^+$ T cells[4] and macrophages[5] also inhibit cancer cells. However, in specific circumstances, the cancer killer cells may be dysfunctional; such as the intratumor infiltrating regulatory T cells (Treg) are capable of suppressing most effector T cell activities to impair the anti-tumor mechanism in the body. Tumor cells may thus escape from the immune surveillance. On the other hand, a number of publications have shown evidence to inhibit Tregs does suppress tumor growth[6,7]. However, it has not established such an anti-tumor remedy in tumor clinic.

Published data indicate that the proinflammatory $CD4^+$ T cells can inhibit cancer cells via releasing anti-tumor cytokines[8,9]. The combination of proinflammatory $CD4^+$ T cell therapy and chemotherapy may reciprocally reinforce the anti-tumor therapy, but has not been fully explored yet. The proinflammatory $CD4^+$ T cells include T helper (Th)1 cells, Th2 cells and Th17 cells; and a fraction of Th9 cells was also characterized[10,11]. Among the Th cells, it is controversial about the role of Th17 cells in tumor growth[12,13]. The anti-tumor role of Th1, Th2 and Th9 cells has been well recognized[14–16]. Thus,

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