中山大学热带病防治研究教育部重点实验室

Key Laboratory of Tropical Disease Control (Sun Yat-Sen University), Ministry of Education

2017 年学术年报

中山大学中山医学院

广　州

2018 年 3 月

前　言

中山大学热带病防治研究教育部重点实验室于 2003 年批准立项建设（教技函[2003]57 号），于 2007 年通过验收并正式开放运行（教技函[2007]55 号），2010 年评估获得“优秀”。重点实验室发展定位为：针对在热带亚热带流行、以及在这些地区起源并流行至其他区域的感染性疾病，在开展病原致病机制及其分子遗传学、宿主免疫及其病理损伤机制等先导性研究的基础上，紧扣战略发展重点，突破分子诊断、特异性药物和防控策略中的关键理论和技术。本重点实验室围绕与热带亚热带气候环境相关疾病，结合国际前沿研究方向，经过几年建设，已构建了病原基因组学、病原蛋白质组学、贵重仪器共享以及生物安全实验设施等平台，并在重要热带病特异性药物研发与免疫细胞的再生工程，热带亚热带流行病病原的分子诊断及防控策略等方向形成了研究特色和优势，并取得重要的进展和成果。

实验室现有固定人员 72 人，其中具有博士学位人员 58 人，高级职称 48 人。通过学校“211 工程”、“985 工程”等建设支持，本重点实验室条件得到了全面改善。实验室面积达 9200 平方米，仪器设备总值 8000 多万元。已初步建成了具有国际水平的热带病防治研究中心，大大增强了我国在热带病防治研究上的国际竞争力。2017 年新增纵向科研项目 43 项，项目总经费达 5349.1 万元。2017 年实验室发表论文 150 篇，其中 SCI 收录论文 115 篇，申请国家专利 24 项，获得授权专利 22 项，获得国家医疗器械证书 16 项。人才培养方面，培养博士研究生 23 名，硕士研究生 27 名。

本集年报收录了实验室 2017 年发表的部分论文摘要，以期反映实验室的研究现状、研究进展和科研成果。

中山大学中山医学院
热带病防治研究教育部重点实验室
2018 年 3 月

目　录

2017 年实验室固定人员

序号	姓名	性别	学位	职称	专业
1	詹希美	男	博士	教授	人体寄生虫学
2	江丽芳	女	硕士	教授	病原生物学
3	余新炳	男	博士	教授	人体寄生虫学
4	何蕴韶	男	博士	教授	病原诊断技术
5	凌文华	男	博士	教授	流行病学
6	蒋玮莹	女	博士	教授	遗传学
7	吴长有	男	博士	教授	免疫学
8	袁岩	男	博士	教授	病毒学
9	席丽艳	女	博士	教授	皮肤病与性病学（真菌）
10	古洁若	女	硕士	教授	免疫学
11	张辉	男	博士	教授	病毒学
12	Dmitry Isaak Gabrilovich	男	博士	教授	免疫学
13	吕芳丽	女	博士	教授	人体寄生虫学学
14	刘焕亮	男	博士	教授	病毒学
15	吴忠道	男	博士	教授	寄生虫学学
16	曹开源	男	博士	教授	免疫学
17	高志良	男	博士	教授	免疫学
18	黄曦	男	博士	教授	免疫学
19	赖小敏	男	硕士	教授	免疫学
20	黎孟枫	男	博士	教授	病原生物学
21	李刚	男	博士	教授	病原诊断技术
22	陆家海	男	博士	教授	流行病学
23	郑小英	女	硕士	副教授	虫媒学
24	潘景轩	男	博士	教授	病原生物学

25	高国全	男	博士	教授	分子生物学
26	张晋昕	男	博士	副教授	分子生物学
27	胡旭初	男	博士	副教授	寄生虫学
28	郝元涛	男	博士	教授	流行病学
29	周家国	男	博士	教授	病原生物学
30	陶海燕	女	博士	副教授	地理模拟与疾病监控
31	周兴旺	男	博士	教授	分子寄生虫学
32	李学荣	男	博士	教授	医学微生物学
33	洪海	女	博士	副教授	免疫学
34	李隽	男	博士	教授	病原生物学
35	郭学敏	女	博士	教授	病原生物学
36	顾怀宇	男	博士	教授	微生物学
37	周毅	男	博士	副教授	免疫学
38	周洁	女	博士	教授	免疫学
39	吕志跃	男	博士	教授	寄生虫学
40	李义平	男	博士	教授	分子病毒学
41	王琴	女	博士	教授	医学微生物学
42	蔡卫斌	男	博士	教授	人体寄生虫学
43	罗海华	女	硕士	实验师	病毒学
44	吴瑜	女	硕士	副教授	分子生物学
45	徐霖	女	博士	副教授	微生物学
46	张萍	女	博士	教授	病原生物学
47	夏敏	男	博士	教授	统计学
48	柏川	男	博士	副教授	免疫学
49	罗海彬	男	博士	教授	流行病学
50	黄艳	女	博士	副教授	寄生虫学
51	付清玲	女	博士	教授	免疫学
52	袁洁	女	博士	副教授	病原生物学
53	刘超	男	博士	副教授	病毒学

54	曾谷城	男	博士	教授	免疫学
55	朱勋	男	博士	副教授	分子生物学
56	田国宝	男	博士	副教授	免疫学
57	李博	男	博士	教授	分子病毒学
58	孙希	女	博士	副教授	寄生虫学
59	杨克礼	男	博士	教授	免疫学
60	陈小舒	女	博士	教授	免疫学
61	吴敏昊	女	博士	教授	免疫学
62	蔡俊超	男	博士	副教授	病原生物学
63	潘婷	女	博士	特聘研究员	病毒学
64	袁广卿	女	中专	高级实验师	生物安全
65	胡黎平	男	博士	高级实验师	设备管理
66	吴珏珩	女	硕士	高级实验师	设备管理
67	李美玉	女	硕士	实验师	设备管理
68	陈省平	男	博士	副研究员	实验室管理
69	关苑君	女	硕士	助理实验师	实验室管理

2017 年实验室新增科研项目和获得科研经费

序号	项目编号	项目名称	负责人	立项日期	计划完成日期	任务来源	经费（万元）
1	2017A030306012	质粒介导多粘菌素耐药新机制 mcr-1 及其传播风险因素研究	田国宝	2017-05-01	2021-05-01	广东省自然科学基金	100
2	2017B030311014	LXRβ 对肿瘤中髓系抑制性细胞的调控作用及病理意义	周洁	2017-05-01	2020-05-01	广东省自然科学基金	50
3	2017A030313198	信号分子 H2S 对大肠埃希菌表型异质性的调控作用及分子机制	郭学敏	2017-05-01	2020-05-01	广东省自然科学基金	10
4	2017YFA0103504	组织干细胞体细胞突变演化和驱动基因识别研究	陈小舒	2017-07-20	2021-12-31	科技部	678
5		苯并咪唑类 Vif-A3G 蛋白复合物抑制剂的优化设计及抗其 HIV-1 活性的研究	柏川	2017-01-01	2019-12-31	广东省科技计划	30
6	2017A050501012	RNA 编辑酶 ADAR1 促寨卡病毒复制的分子机制研究	张萍	2017-08-01	2018-12-31	广东省科技计划	50
7	2017A050506017	基于岭南植物来源的抗丙型肝炎病毒天然小分子化合物的发现及体内外临床前疗效的研究	李义平	2017-12-01	2019-11-30	广东省科技计划	50
8	81772473	长链非编码 RNA LINC01996 同时维持 PTEN 的蛋白活性和稳定性从而抑制肺癌发生发展的作用与机制研究	蔡俊超	2017-08-17	2021-12-31	国家自然科学基金	57
9	81772212	肝吸虫致肝纤维化重要分子——核糖核酸酶 T2 和溶血磷脂酶的作用机制研究	余新炳	2017-08-17	2021-12-31	国家自然科学基金	55
10	81772177	以宿主蛋白 APE1 为靶点的抗 KSHV 及相关肿瘤的药物研究	袁岩	2017-08-17	2021-12-31	国家自然科学基金	56
11	81771772	浆细胞样树突状细胞产生 I 型干扰素的机制研究	杨克礼	2017-08-17	2021-12-31	国家自然科学基金	55

12	81771665	ATF3 通过 Tfh 调控 B 细胞活化的机制及在 IBD 中的病理意义	周洁	2017-08-17	2021-12-31	国家自然科学基金	56
13	81730060	关于 HIV-1 病毒储存库形成的表观遗传学机制及其清除手段的机理研究	张辉	2017-08-17	2022-12-31	国家自然科学基金	295
14	81722030	临床细菌耐药与感染	田国宝	2018-01-01	2020-12-31	国家自然科学基金	130
15	31771406	利用高通量测序技术检测在不同基因表达水平和不同环境中蛋白编码基因的点突变对适应度的影响	陈小舒	2017-08-17	2021-12-31	国家自然科学基金	60
16		中山大学科技人员面向基层、社区、中小学校，开展高校科技“三下乡”系列活动，完善科普基地建设	胡黎平	2017-03-01	2017-03-31	其他项目	25
17		毕赤酵母精准基因控制表达五步蛇毒纤溶酶 FII 对 LPS 诱导的兔弥散性血管内凝血的拮抗作用	顾怀宇	2017-03-01	2019-09-28	其他项目	10
18	201604020020	儿童遗传性智力低下与神经退行性疾病精准诊治规范的研究	蒋玮莹	2017-09-01	2021-12-31	广州市科技计划	54
19		超保守非编码 RNA uc.243 诱导卵巢癌顺铂耐药的分子机制	李隽	2018-01-01	2020-12-31	国家自然科学基金	100
20		2017 年国际免疫学研讨会-广州	周洁	2017-11-02	2018-07-31	国家自然科学基金	8
21		广东省抗病原微生物药物与免疫技术工程技术研究中心运行资助	张辉	2017-01-01	2017-12-31	高校基本业务费	10
22		2017 年千人计划入选者省财政配套科研工作经费（陈小舒）	陈小舒	2017-10-13	2020-12-31	广东省专项财政资金	50
23		2017 年特支计划科研工作经费（刘超）	刘超	2017-04-20	2022-04-20	广东省特支计划	10
24	201704030087	针对输入性病毒传染病的新药筛选平台的建立及其应用	柏川	2017-05-01	2020-04-30	广州市科技计划	100
25	2016ZT06S638	肿瘤精准化免疫治疗创	李博	2017-08-01	2022-07-31	广东省引进创	1925

		新团队				新科研团队	
26	201704020226	寨卡病毒病诊、治新策略及适宜防控新技术的应用与临床转化研究	黄曦	2017-03-01	2020-02-29	广州市科技计划	300
27	201707010452	COX-1 通过调节性 Tfh 滤泡 T 细胞 (Tfr)而参与 B 细胞活化的机制研究	周洁	2017-05-01	2020-04-01	广州市科技计划	20
28		昱普生物科技——中山大学联合创新研究中心	胡旭初	2017-09-30	2022-06-30	医学科研管理基金	500
29		2016 年第二批万人计划入选人才特殊支持经费 2	李隽	2017-01-01	2019-12-31	人才项目	50
30		2016 年第二批万人计划入选人才特殊支持经费	李隽	2017-01-01	2019-12-31	人才项目	80
31	17ykjc29	Endophilin A2 维持血压稳态的细胞和分子机制	周家国	2017-08-14	2019-08-31	高校基本业务费	100
32		利用活体动物模型实时研究代表性纳米载体对血-脑脊液屏障的生物效应	顾怀宇	2017-01-30	2021-12-30	国家自然科学基金	75
33	201710010030	广州管圆线虫虫体抗原上调 IL-13 介导的巨噬细胞 Chil3 高表达的作用机制研究	孙希	2017-01-01	2019-12-31	广州市科技计划	30
34	17ykjc02	肿瘤转移前炎性微环境形成的分子机制	李隽	2017-05-15	2018-12-31	高校基本业务费	30
35	17ykjc01	非凋亡性细胞死亡的关键调控分子的鉴定及其在登革病毒免疫病理中的作用	张萍	2017-05-15	2018-12-31	高校基本业务费	30
36	17ykzd06	LINC01996 同时维持 PTEN 的蛋白活性和稳定性从而抑制肺癌发生发展的作用与机制研究	蔡俊超	2017-05-15	2018-12-31	高校基本业务费	30
37	17ykzd05	C3H 锌指蛋白对调控免疫疾病的机制研究	杨克礼	2017-05-15	2018-12-31	高校基本业务费	30
38	17ykpy09	虫源性分子协同 IL-13 上调巨噬细胞高表达 Chil3 在嗜酸性粒细胞增多性脑炎中的作用机制研究	孙希	2017-05-15	2019-12-31	高校基本业务费	15
39	17ykpy01	环状单磷酸鸟苷-单磷酸腺苷合成酶（cGAS）	柏川	2017-05-15	2019-12-31	高校基本业务费	15

		特异性抑制剂的研究					
40	81781240015	参加 9th HOPE Meeting 会议	蔡俊超	2017-04-13	2017-09-30	国家自然科学基金	0.7
41	81601781	基于全基因组重测序发现的基因变异与晚期血吸虫病的相关性研究	李美玉	2017-01-01	2019-12-31	国家自然科学基金	2.55
42	31611530670	丙型肝炎病毒适应性突变和准种分布在体内外感染模型中的比较研究	李义平	2017-01-01	2018-12-31	国家自然科学基金	6.86
43	81641094	华支睾吸虫分泌型磷脂酶 A2 活化肝星状细胞分子机制研究	李学荣	2017-01-01	2017-12-31	国家自然科学基金	10

2017 年实验室发表论文

注：论文均标注重点实验室名称

序号	作者	论文题目	刊物，年，卷（期）：页码
1	Song L, Wu X, Zhang B, Liu J, Ning A, Wu Z.	A cross-sectional survey comparing a free treatment program for advanced schistosomiasis japonica to a general assistance program.	Parasitol Res. 2017 Nov;116(11):2901-2909. doi: 10.1007/s00436-017-5596-6. Epub 2017 Sep 7.
2	Yang Z, Li W, Yang Z, Pan A, Liao W, Zhou X.	A novel antigenic cathepsin B protease induces protective immunity in Trichinella-infected mice.	Vaccine. 2018 Jan 4;36(2):248-255. doi: 10.1016/j.vaccine.2017.11.048. Epub 2017 Dec 2.
3	Yin P, Zhang L, Ye F, Deng Y, Lu S, Li YP, Zhang L, Tan W.	A screen for inhibitory peptides of hepatitis C virus identifies a novel entry inhibitor targeting E1 and E2.	Sci Rep. 2017 Jun 21;7(1):3976. doi: 10.1038/s41598-017-04274-8.
4	Wu Y, Shi W, Lin J, Wang M, Chen X, Liu K, Xie Y, Luo L, Anderson BD, Lednicky JA, Gray GC, Lu J, Wang T.	Aerosolized avian influenza A (H5N6) virus isolated from a live poultry market, China.	J Infect. 2017 Jan;74(1):89-91. doi: 10.1016/j.jinf.2016.08.002. Epub 2016 Aug 9. No abstract available.
5	Lin BL, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, Liu QL, Peng L, Li JG, Mei YY, Weng WZ, Peng YW, Cao HJ, Xie JQ, Xie SB, Xiang AP, Gao ZL.	Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial.	Hepatology. 2017 Jul;66(1):209-219. doi: 10.1002/hep.29189. Epub 2017 May 27.
6	Zhong C, Xu M, Wang Y, Xu J, Yuan Y.	An APE1 inhibitor reveals critical roles of the redox function of APE1 in KSHV replication and pathogenic phenotypes.	PLoS Pathog. 2017 Apr 5;13(4):e1006289. doi: 10.1371/journal.ppat.1006289. eCollection 2017 Apr.
7	Pu J, He L, Xie H, Wu S, Li Y, Zhang P, Yang Z, Huang X.	Antiviral activity of Carbenoxolone disodium against dengue virus infection.	J Med Virol. 2017 Apr;89(4):571-581. doi: 10.1002/jmv.24571. Epub 2016 Dec 23.
8	Loo CS, Lam NS, Yu D, Su XZ, Lu F.	Artemisinin and its derivatives in treating protozoan infections beyond malaria.	Pharmacol Res. 2017 Mar;117:192-217. doi: 10.1016/j.phrs.2016.11.012. Epub 2016 Nov 17. Review.
9	Zhang ZQ, Cao WT, Shivappa N, Hebert JR, Li BL, He J, Tang XY,	Association Between Diet Inflammatory Index and Osteoporotic Hip Fracture in Elderly Chinese Population.	J Am Med Dir Assoc. 2017 Aug 1;18(8):671-677. doi: 10.1016/j.jamda.2017.02.011. Epub 2017

	Liang YY, Chen YM.		Apr 11.
10	Liu L, Guan H, Li Y, Ying Z, Wu J, Zhu X, Song L, Li J, Li M.	Astrocyte Elevated Gene 1 Interacts with Acetyltransferase p300 and c-Jun To Promote Tumor Aggressiveness.	Mol Cell Biol. 2017 Feb 15;37(5). pii: e00456-16. doi: 10.1128/MCB.00456-16. Print 2017 Mar 1.
11	Hu L, Li J, Cai H, Yao W, Xiao J, Li YP, Qiu X, Xia H, Peng T.	Avasimibe: A novel hepatitis C virus inhibitor that targets the assembly of infectious viral particles.	Antiviral Res. 2017 Dec;148:5-14. doi: 10.1016/j.antiviral.2017.10.016. Epub 2017 Oct 23.
12	Pang SY, Hsu JS, Teo KC, Li Y, Kung MHW, Cheah KSE, Chan D, Cheung KMC, Li M, Sham PC, Ho SL.	Burden of rare variants in ALS genes influences survival in familial and sporadic ALS.	Neurobiol Aging. 2017 Oct;58:238.e9-238.e15. doi: 10.1016/j.neurobiolaging.2017.06.007. Epub 2017 Jun 20.
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2017 年实验室申请与授权的发明专利

申请专利			
序号	专利名称	发明人	专利号
1	一种 APE1 抑制剂及其在制备用于治疗肿瘤和血管异常增生性疾病药物中的应用	袁岩、徐峻	201710138466.10
2	一种检测痛风易感基因 SNP 基因型的方法、引物及试剂盒	古洁若、车团结、杜予和	201710462876.10
3	一种强直性脊柱炎远程会诊共享平台及其使用方法	杜予和、陈萌萌、古洁若杨剑锋、郑达宜、马淑雯	201710465223.90
4	microRNA-4281 的新用途	张辉、张译文	201710087157.60
5	一种快速检测细菌多粘菌素耐药基因 mcr-1 的 LAMP 引物组、试剂盒及检测方法	田国宝、黄曦、钟兰兰、曾昆姣、沈聪	201710153044.10
6	种可降解药物缓释功能复合肠道支架及其制作方法	李刚、谢旭升、兰平、赵泽宇、孙慧、何小文、李翼	201710058493.80
7	一种可降解药物缓释材料及其制备方法	兰平、李刚、何小文、陈钰锋、谢旭升、韩植芬、王晓沁	201710305345.10
8	一种日本血吸虫和破伤风双价口服或滴鼻疫苗	李丽、陆家海	201710269904.80
9	一种无毒株弓形体和中药多糖佐剂组合物的用途、疫苗及制备方法	周兴旺、廖婉琴、杨兆收	201710408550.00
10	α-倒捻子素在制备用于治疗自身免疫疾病的药物中的应用	黄朝峰、何细新、柏川、陈焕鹏、周晓庆	201710357273.50
11	4N 杂环化合物的衍生物在制备用于治疗自身免疫疾病的药物中的应用	黄朝峰、何细新、柏川、陈焕鹏、周晓庆	201710356662.60
12	一种 N-取代吡唑并[3,4-d]嘧啶酮类化合物及制备方法与应用	罗海彬、吴一诺、吴旭年、黄雅丹、周倩	201710128523.80
13	一类吴茱萸碱类化合物及其制备方法与应用	罗海彬、盛春泉、赖增伟、陈健文、张天华	201710245872.80
14	一种取代吡咯色原酮类化合物及其应用	罗海彬、吴德燕、陈健文、张天华	201710124177.60
15	一种淡水鱼华支睾吸虫囊蚴感染胶体金快速检测试纸条及其制作方法	余新炳、孙恒昌、姜红烨、周心怡、唐泽丽、林志鹏、黄艳、陈庭金	201710087144.90
16	结核病微生物标志物在制备诊断结核病的试剂中的应用	曾谷城	201710317416.X
17	一种寄生虫虫卵的便携式检测装置及方法	吕志跃、邬燕琪、徐一月、吴忠道	201710529135.00

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19	基于电化学发光放大原理的寨卡病毒核酸检测方法	黄曦、廖玉辉、赵钊艳、谭青琴	201710857494.90
20	基于电化学发光级联放大原理的端粒酶活性检测方法	黄曦、廖玉辉、赵钊艳、谭青琴	201710857470.30
21	α-倒捻子素作为磷酸二酯酶 4 的抑制剂的用途	何细新、罗海彬、谭冰心、黄仪有	201710305295.70
22	磷酸二酯酶 4 抑制剂桑辛素 M 衍生物及其用途	何细新、罗海彬、区瑞莹、黄仪有	201710304852.30
23	一种快速检测嗜肺军团菌的 CPA 引物组及其检测方法	陆勇军、林韵、肖贤声、吴若红、肖晓臻、肖晓波、曾子芳、黄艳峰、张贵云	201710358715.80
24	一种 APE1 抑制剂及其在制备用于治疗肿瘤和血管异常增生性疾病药物中的应用	袁岩、徐峻	201710138466.10

授权专利

序号	专利名称	发明人	专利号
1	一种嵌合载体及其制备方法和应用	张辉、潘婷	201410275218.80
2	一种抗 HIV-1 病毒药物及其制备和应用	张辉、潘婷	201410275129.30
3	丁基羟基茴香醚对中央记忆性 T 细胞体外扩增中的应用	张辉、张译文	201510228515.1
4	比沙可啶对中央记忆性 T 细胞体外扩增中的应用	张辉、张译文	201510228510.90
5	一种小分子化合物在抗流感病毒药物中的应用	张辉、张峻崧、黄凤	201510171631.40
6	一种替考拉宁在抗埃博拉病毒中的应用	潘婷、张辉、周南	201510195344.70
7	用于乳腺癌的 piRNA	张辉、何欣、陈欣欣、张雪	201410247837.60
8	一种寄生虫虫卵的富集观察装置	邬燕琪、吕志跃、徐一月、吴忠道、刘记、胡玥、张梦颖	201621425689.30
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11	慢性乙型和丁型肝炎病毒肝细胞受体编码基因 SLC10A1 的新突变蛋白、编码基因及其应用	王一鸣、高志良、赵强、彭亮、胡彬、王俊、李奇斌、廖启军	201410586449.00

12	一种快速诊断活动性结核病的 gamma delta T 细胞表面活化分子及试剂盒	黄曦、吴永坚	201510824165.50
13	miR-455-3p 在食管鳞状细胞癌中的诊断、治疗和预后的应用	宋立兵、李隽、刘爱斌、曹丽雪、朱金容、吴阁艳、吴淑	201510119448.X
14	四环素类抗生素或其药用盐在制备抗肠病毒药物中的应用	郭学敏、曾施暖、张蔚	201510138304.90
15	RGD 三肽在制备治疗阿尔茨海默症药物中的用途	顾怀宇、凌楚雯、林睿邦、黄嘉琦、段松伟、林润轩	201410497303.90
16	4N 杂环化合物作为 Th17 细胞分化抑制剂的应用	黄朝峰、柏川、丁庆峰	201510134926.40
17	一类 N-取代吡唑并[3,4-d]嘧啶酮类化合物及其应用	罗海彬、万一千、黄漫娜、刘培庆、邵咏贤、朱新海、蔡颖红、刘雨果	201310517594.90
18	用于检测结核分枝杆菌感染的抗原刺激物、试剂盒及其应用	曾谷城、汪华	201410790793.10
19	一个受高盐和水杨酸诱导的逆转录转座子启动子及其应用	唐恬、梁山、林星钦、刘小如、区佩如、潘婷	201410834918.60
20	氨苄西林对中央记忆性 T 细胞体外扩增中的应用	张辉、张译文	201510228552.20
21	头孢尼西钠对中央记忆性 T 细胞体外扩增中的应用	张辉、张译文	201510228440.70
22	一种嵌合载体及其制备方法和应用	张辉、潘婷	201410275218.80

2017 年实验室获得国家医疗器械证书

序号	产品名称	注册号	生产单位
1	人乳头瘤病毒（16/18 型）核酸检测试剂盒（荧光 PCR 法）	国械注准 20173404230	中山大学达安基因股份有限公司
2	人乳头瘤病毒（6/11 型）核酸检测试剂盒（荧光 PCR 法）	国械注准 20173404237	中山大学达安基因股份有限公司
3	季节性流感病毒 H1 亚型核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173404233	中山大学达安基因股份有限公司
4	季节性流感病毒 H3 亚型核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173404234	中山大学达安基因股份有限公司
5	丙型肝炎病毒核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173404156	中山大学达安基因股份有限公司
6	乙型肝炎病毒核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173404069	中山大学达安基因股份有限公司
7	三体和性染色体多倍体检测试剂盒（荧光 PCR 毛细管电泳法）	国械注准 20173401067	中山大学达安基因股份有限公司
8	甲型 H1N1 流感病毒（2009）RNA 检测试剂盒（PCR-荧光探针法）	国械注准 20173400313	中山大学达安基因股份有限公司
9	EB 病毒核酸扩增(PCR)荧光定量检测试剂盒	国械注准 20173400176	中山大学达安基因股份有限公司
10	柯萨奇病毒 A16 型核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173400173	中山大学达安基因股份有限公司
11	I 群肠道沙门氏菌核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173400162	中山大学达安基因股份有限公司
12	肠道病毒通用型核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173400169	中山大学达安基因股份有限公司
13	呼吸道合胞病毒核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173400171	中山大学达安基因股份有限公司
14	肠道病毒 71 型核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173400167	中山大学达安基因股份有限公司
15	中东呼吸综合征冠状病毒核酸检测试剂盒（PCR-荧光探针法）	国械注准 20173400001	中山大学达安基因股份有限公司
16	人乳头瘤病毒（16/18 型）核酸检测试剂盒（荧光 PCR 法）	国械注准 20173404230	中山大学达安基因股份有限公司

2017 年实验室培养硕士研究生和博士研究生

1.2017 年毕业硕士研究生

序号	学生	毕业论文题目	导师
1	刘记	趋化因子 CCL8 在广州管圆线虫-宿主适应性中的作用研究	吴忠道
2	汤昕	CsESP 与肝\胆管癌细胞凋亡、迁移和侵袭过程的初步研究	余新炳
3	罗虹娇	2011-2016 年广州地区 RSV 流行病学特征及 A 和 B 亚型变异分析	曹开源
4	解辉	广州管圆线虫 far-1 基因克隆表达及小分子抑制剂筛选	吴忠道
5	罗诗琪	宿主 miRNA 通过靶向虫体 SOD 对广州管圆线虫寄生适应性影响的实验研究	吴忠道
6	李桃桃	丁酸通过促进 MDSC 的增殖和活化以缓解小鼠结肠炎的实验研究	周洁
7	陈玲铭	I 型干扰素通过维持 PD-1/PD-L1 衍生的 microRNA-31 来控制结核分枝杆菌感染	曾谷城
8	李茜	肥大细胞激活剂/抑制剂对弓形虫疫苗影响及 TLR2/TLR4 阳性肥大细胞对眼弓形虫感染作用	吕芳丽
9	冯毅	烟酰胺诱导 HeLa 细胞凋亡的机制研究、抑制 HeLa 细胞 G6PD 活性诱导凋亡的机制分析	蒋玮莹
10	徐晓晗	白纹伊蚊广州株对 ZIKV 易感性及 Wolbachia 对 ZIKV 抑制作用的研究	郑小英
11	陈胜杰	Galectin 蛋白家族和 Tim-3+/Gal-9+肥大细胞在小鼠眼弓形虫病中的作用研究	吕芳丽
12	郭前方	广东省登革病毒 1 型流行株的分子进化分析及生物学特性研究	江丽芳
13	陈菲	糖尿病状态下血小板异常活化的关键分子及机制和 PEDF 调控妊娠期糖病血小板功能的作用研究	高国全
14	王彩琴	华支睾吸虫颗粒蛋白促进肝/胆管癌细胞增殖迁移的信号通路研究	李学荣
15	张志强	抑制 G6PD 酶活性对恶性疟原虫感染增殖的影响及其机制研究	蒋玮莹

16	尹红玲	华支睾吸虫硫氧还蛋白过氧化物酶抗氧化损伤的作用研究	胡旭初
17	王子偲	计算机辅助药物设计筛选表皮生长因子受体短肽激动剂的研究	顾怀宇
18	钟兰兰	大肠埃希菌多粘菌素耐药机制研究	吴敏昊
19	孔洁琛	新生期接种乙肝疫苗抵消丰富环境诱导的神经发生增加和空间学习能力提高	顾怀宇
20	孔洁琛	新生期接种乙肝疫苗抵消丰富环境诱导的神经发生增加和空间学习能力提高	顾怀宇
21	郑福祥	1a 型丙型肝炎病毒在肝癌细胞系 Huh7 里的适应性研究	李义平
22	郝桃方	荧光素酶标记的过表达 ROP18 弓形虫的构建及 ROP18 与宿主 UBE2N 相互作用的验证	周兴旺
23	甘一川	不同等位基因结核多肽/HLA-DR 四聚体结合的结核患者 CD4+ TCR CDR3 区序列分析	赖小敏
24	司露露	登革病毒 prM 蛋白感染增强表位 pr4 关键氨基酸位点的筛选与鉴定	江丽芳
25	郭鹏豪	新型隐球菌感染临床特点分析、药物敏感性检测及基因分型	胡旭初
26	李成德	HBV 相关性原发性肝癌外周血 B7-H3、IL-21 和 INF-γ 表达及意义	洪海
27	蔡文莹	广州地区浅部真菌病病原谱分析及分子诊断技术研究	余新炳

2.2017 年毕业博士研究生

序号	学生	毕业论文题目	导师
1	马才启	Kallistatin/oxLDL 在胃癌淋巴结转移中的作用及机制研究	高国全
2	李宇清	KSHV 持续性感染口腔间充质干细胞并诱导肿瘤发生的循证和机制研究	袁岩
3	贺平	广东地区入侵物种尖膀胱螺与双脐螺的生物学特性及灭螺剂研究	吴忠道
4	张燕楠	转位蛋白（TSPO）配体在体内外对 T 细胞的免疫调控机制研究	吴长有
5	董慧敏	华支睾吸虫感染对乙肝患者抗病毒治疗及肝纤维化进程的影响研究	余新炳
6	刘珍	广州管圆线虫感染诱导小鼠胸腺萎缩及其机制的研究	吴忠道
7	尚梅	华支睾吸虫感染诱导细胞自噬及上皮间质转化的机制研究	李学荣
8	蒲洁莹	NLRP12 和甘珀酸钠的抗登革病毒作用及其机制	黄曦
9	唐泽丽	华支睾吸虫半胱氨酸蛋白酶保护性免疫效果研究	余新炳
10	李星	MDSC 在新生儿免疫耐受和坏死性小结肠炎发病中的保护作用及分子机制	周洁
11	林晓莹	血友病遗传学诊断体系的完善及其种植前诊断体系的建立	蒋玮莹
12	陈灿灿	Tat-like 相关药物的筛选及其对 HIV-1 潜伏感染激活的分子机理	张辉
13	邹帆	特异性敲除抑制性受体表达的新型 CAR-T 细胞在清除实体肿瘤中的应用	张辉
14	钟灿榕	以宿主蛋白 APE1 为靶点的抗 KSHV 及相关肿瘤的药物研究	袁岩
15	陈鑫	不动杆菌对碳青霉烯类抗生素的耐药机制研究	郭学敏
16	冯娟	Serpins 家族成员 KBP 调控巨噬细胞延缓糖尿病伤口愈合的相关研究和 IL-25 在巨噬细胞	高国全
17	李荣	肿瘤抑制蛋白 CK1α 通过诱导自噬抑制非小细胞肺癌细胞恶性生长的分子机制研究	黎孟枫

18	胡忆文	寨卡病毒蛋白介导的天然免疫逃逸功能和分子机制研究	黎孟枫
19	余蓓信	Bestrophin3 改善高脂饮食诱导的肝脏脂质沉积和胰岛素抵抗及其机制研究	周家国
20	贾磊	人 Th9 细胞的表型、分化及在儿童过敏性哮喘中的作用	吴长有
21	黄璐	靶向 mTOR/RSK 信号通路药物抗 γ-疱疹病毒裂解复制的研究	袁岩
22	李薇	非编码 RNA 在肿瘤转移中的生物学功能及作用机制	黎孟枫
23	黄桃生	一种新型的用于检测华法林药物敏感型基因的电化学传感器	何蕴韶

附：2017 年重点实验室发表的部分论文摘要

Parasitol Res
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ORIGINAL PAPER

A cross-sectional survey comparing a free treatment program for advanced schistosomiasis japonica to a general assistance program

Langui Song[1,2,3] · **Xiaoying Wu**[4] · **Beibei Zhang**[1,2,3] · **Jiahua Liu**[1,2,3] · **An Ning**[5] · **Zhongdao Wu**[1,2,3]

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Abstract The prevalence and intensity of schistosomiasis has dropped dramatically in China due to an effective integrated control program. However, advanced schistosomiasis is becoming a key challenge on the road to elimination. The aims of this study were to compare the disease condition between advanced cases under the general assistance program (GAP) and free treatment program (FTP) and to determine whether the FTP should be popularized to provide an objective reference for policymakers in China's advanced schistosomiasis control program. One hundred and ninety-four patients with schistosomiasis japonica who were enrolled in the GAP or FTP participated in this study. Little significant difference was observed in the potential confounders, including general characteristics, comorbidities, and lifestyle, indicating a similar effect on the pathology of liver damage caused by schistosome infection. There was no apparent difference in the incidence of common clinical symptoms. Furthermore, no significant difference was observed in the ultrasound findings, implying that the GAP and FTP groups shared a similar degree of liver lesion. With the exception of the abnormal rates of aspartate aminotransferase (AST), alkaline phosphatase (ALP), and hyaluronic acid (HA), the other serological indicators were comparable between the groups. Overall, the FTP is not a better option for controlling advanced schistosomiasis in China. It is important to reveal the precise mechanism underlying the pathogenesis of advanced schistosomiasis so that specific approaches to treating and preventing the development of advanced schistosomiasis can be developed and schistosomiasis can be eliminated in China.

Keywords *Schistosoma japonicum* · Advanced schistosomiasis · P. R. China · Free treatment program · General assistance program

Langui Song, Xiaoying Wu, Beibei Zhang, and Jiahua Liu contributed equally to this work.

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Background

Schistosomiasis japonica, caused by *Schistosoma japonicum*, was once highly prevalent in China, Indonesia, and the Philippines (Gordon et al. 2012; Yin et al. 2015), but its prevalence and intensity have dropped dramatically in China due to the effective integrated control program (Zhou et al. 2005; Zhou et al. 2010; Xu et al. 2016; Yuan et al. 2000). However, approximately 5–10% of chronic infections still progress to advanced or late-stage, schistosomiasis, the most severe form of schistosomiasis japonica, which is more serious than *S. mansoni*-related hepatosplenic schistosomiasis in America and Africa (Jia et al. 2011).

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A novel antigenic cathepsin B protease induces protective immunity in *Trichinella*-infected mice

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ABSTRACT

Trichinellosis is a foodborne disease that remains a public health hazard and an economic problem in food safety. Vaccines against the parasite can be an effective way to control this disease; however, commercial vaccines against *Trichinella* infection are not yet available. *Trichinella* cathepsin B proteins appear to be promising targets for vaccine development. Here, we reported for the first time the characterization of a novel cDNA that encodes *Trichinella spiralis* (*T. spiralis*) cathepsin B-like protease 2 gene (*TsCPB2*). The recombinant mature TsCPB2 protein was successfully expressed in *E. coli* system and purified with Ni-affinity chromatography. TsCPB2 expression was detected at all the developmental stages of *T. spiralis* and it was expressed as an excretory–secretory protein of *T. spiralis* muscle larvae. Immunization with TsCPB2 antigen induced a combination of humoral and cellular immune responses, which manifested as a mixed Th1/Th2 response, as well as remarkably elevated IgE level. Moreover, vaccination of mice with TsCPB2 that were subsequently challenged with *T. spiralis* larvae resulted in a 52.3% ($P < .001$) reduction in worm burden and a 51.2% ($P < .001$) reduction in muscle larval burden. Our results suggest that TsCPB2 induces protective immunity in *Trichinella*-infected mice and might be a novel vaccine candidate against trichinellosis.

1. Introduction

Trichinella spiralis (*T. spiralis*) is an intracellular nematode infecting humans and other animals. The entire life cycle of *T. spiralis* takes place in a single host, which involves three different developmental stages, the muscle larvae (ML), adult worm (Ad), and new born larvae (NBL). Trichinellosis, caused by *Trichinella* infection, is a cosmopolitan foodborne disease that is not only a public health hazard but also represents as an important problem in food safety and global trade in various animals and their meat [1,2]. Human trichinellosis outbreaks occur worldwide with an annual global average of 5751 cases and 5 deaths [3]. Currently, the reliable early diagnosis of trichinellosis is still lacking due to its nonspecific clinical manifestations [4]. In this case, invading *Trichinella* muscle larvae are usually established at the time of primary diagnosis, which results in ineffective drug treatment [5]. Therefore, it is of significant interest to develop effective vaccines to prevent *Trichinella* infection.

Excretory-secretory (ES) proteins released by *T. spiralis* muscle larvae have been suggested to play a critical role in modulating the host immune system, thus facilitating the establishment of *T. spiralis* parasitism and survival [6,7]. It has been reported that immunization with ES protein elicits a robust immune response and high protection against *T. spiralis* infection in mice and rats [8,9]. Gamble et al. also showed that inoculation pigs with *T. spiralis* larval ES antigens could significantly reduce the adult worm burden [10]. Thus, *T. spiralis* ES proteins offer promising targets for the development of vaccines.

Secretory cathepsin proteases, a major papain-like cysteine protease, play key roles in parasite survival, host invasion, and host immune response [11,12] and have high potential as vaccine targets [13]. Previously, we reported that treatment with a recombinant *T. spiralis* cathepsin B-like protein, TsCPB, induces a Th2 response in *Trichinella*-infected mice and ameliorates mouse intestinal ischemia/reperfusion injury via promoting a switch from M1 to M2 macrophages [14,15]. These results confirm the important function of the cathepsin protein in host immunity. Recently, a cathepsin F-like protease from *T. spiralis* was cloned and expressed, which might be involved in parasite life-cycle

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SCIENTIFIC REPORTS

OPEN

A screen for inhibitory peptides of hepatitis C virus identifies a novel entry inhibitor targeting E1 and E2

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Hepatitis C virus (HCV) entry into hepatocytes is a multistep process that represents a promising target for antiviral intervention. The viral envelope protein E1E2 plays a critical role in HCV entry. In this study, we sought to identify peptide inhibitors of HCV by screening a library of overlapping peptides covering E1E2. Screening the peptide library identified several novel anti-HCV peptides. Four peptides from glycoprotein E2 were selected for further investigation. The 50% effective dose (ED50) was approximately 5 nM for each peptide. Our data indicated that these peptides inhibited HCV entry at the post-attachment step. Moreover, these peptides blocked cell-to-cell transmission of HCVcc and had broad-spectrum antiviral effects on HCVcc. These peptides exhibited combination inhibitory effects on HCVcc infection when combined with IFN-α2b or anti-CD81 antibody. Interestingly, we observed that E2-42 associated with E1 and E2. Our results indicate that E2-42 inhibits HCV entry via E1 and E2. These findings suggest a new avenue for HCV therapeutic development.

Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver diseases, including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). Recent estimates suggest that 64–103 million people are infected with HCV worldwide[1]. No effective vaccine against HCV infection is available, and treatment with PEGylated interferon alpha (PEGIFN-α) plus ribavirin is associated with a response rate of only approximately in patients infected with the most prevalent genotype, genotype 1. Although recently developed direct-acting antivirals (DAAs), including inhibitors of HCV NS3/4 A protease (Boceprevir, Telaprevir, and Simeprevir), NS5A (Daclatasvir, Ledipasvir, and Ombitasvir), and NS5B polymerase (Sofosbuvir, Mericitabine, and Dasabuvir), have revolutionized hepatitis C treatment, several important challenges remain[2,3]. Potential adverse effects, the risks of selecting drug-resistant mutants, drug-drug interactions, and difficult-to-treat populations are important issues that limit the availability of DAAs to all HCV-infected patients[3]. More importantly, the high cost of DAAs restricts their accessibility in most parts of the world. Thus, continuous development of alternative potential inhibitors that target different steps of the HCV life cycle, including viral entry, is urgently needed.

As a member of the Flaviviridae family, HCV is an enveloped positive-sense single-strand RNA virus. The viral genome encodes structural (core, E1, E2 and p7) and non-structural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins[4]. Of these, E1 and E2 are important for HCV entry. HCV entry is a multi-step process that begins with the attachment of a viral particle to the cell surface via attachment factors, followed by a complex process involving a series of cellular entry co-receptors, including scavenger receptor class B type I (SR-BI)[5], CD81[6], claudin-1[7], occludin[8], and the receptor tyrosine kinases epidermal growth factor receptor (EGFR)[9], ephrin receptor A2[9], Niemann-Pick C1-like 1 (NPCL1)[10], and transferrin receptor 1 (TfR1)[11–14]. The viral particle enters the host cell via clathrin-mediated endocytosis, which is followed by viral genome release, translation, replication, assembly, and exit of progeny virions to complete the HCV life cycle[14].

Due to its multi-step nature, HCV entry is an attractive target for inhibiting HCV. Monoclonal antibodies and small molecules inhibiting HCV entry have been considered[12,13]. Short peptides derived from viral envelope

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NAR Breakthrough Article

A snoRNA modulates mRNA 3′ end processing and regulates the expression of a subset of mRNAs

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ABSTRACT

mRNA 3′ end processing is an essential step in gene expression. It is well established that canonical eukaryotic pre-mRNA 3′ processing is carried out within a macromolecular machinery consisting of dozens of trans-acting proteins. However, it is unknown whether RNAs play any role in this process. Unexpectedly, we found that a subset of small nucleolar RNAs (snoRNAs) are associated with the mammalian mRNA 3′ processing complex. These snoRNAs primarily interact with Fip1, a component of cleavage and polyadenylation specificity factor (CPSF). We have functionally characterized one of these snoRNAs and our results demonstrated that the U/A-rich SNORD50A inhibits mRNA 3′ processing by blocking the Fip1-poly(A) site (PAS) interaction. Consistently, SNORD50A depletion altered the Fip1–RNA interaction landscape and changed the alternative polyadenylation (APA) profiles and/or transcript levels of a subset of genes. Taken together, our data revealed a novel function for snoRNAs and provided the first evidence that non-coding RNAs may play an important role in regulating mRNA 3′ processing.

INTRODUCTION

All metazoan pre-mRNAs require extensive processing during their maturation. One essential step is 3′ end processing (1–4). Canonical mRNA 3′ processing involves an endonucleolytic cleavage within the pre-mRNA sequences and the addition of a poly(A) tail to the 3′ end of the transcript, and both steps take place within a macromolecular machinery called mRNA 3′ processing complex (5–7). There are ∼85 trans-acting proteins in the human mRNA 3′ processing complex, including the poly(A) polymerase (PAP) and four core multi-subunit complexes (CPSF, CstF, CF I and CF II), as well as other peripheral factors that associate with other biological processes (7). Despite much progress in deciphering the protein–protein and RNA–protein interaction within the mRNA 3′ processing complex (8–12), it remains poorly understood how a specific poly(A) site (PAS) is selected when multiple PASes are present in the pre-mRNAs and how PAS selection can be regulated in a tissue- or developmental stage-specific manner. These questions are important as alternative polyadenylation (APA) is increasingly recognized as a critical mechanism for post-transcriptional gene regulation (13–18), and APA regulation impacts a variety of physiological processes including stem cell differentiation and cancer development (19–20). Although a number of protein factors have been shown to

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LETTERS TO THE EDITOR

Aerosolized avian influenza A (H5N6) virus isolated from a live poultry market, China

Dear Editor,

Recent articles in this Journal have referred to avian influenza H5N6 infections in China[1—3] and examination of the Global Initiative on Sharing All Influenza Data (GISAID) database, one observes that more than 90 percent of China's recent laboratory-confirmed human infections with avian H7N9 or H5N6 influenza A viruses have been associated with exposure to live poultry or live poultry markets (LPMs). While cross-species poultry-to-person avian influenza transmission has been well documented[4,5] and avian influenza virus (AIV) can be transmitted between mammals, few studies have evaluated aerosolization of AIV within LPMs.[6] Numerous successful studies described to collect airborne microbes with bioaerosol sampling in different environments.[7] Influenza A (H1N1, H1N2 and H3N2 subtypes) virus infectious aerosols were detected in the air samples and that these aerosols could be exhausted from pig barns and be transported downwind.[8] To survive on the risk presence of airborne AIV in LPMs and provide potential clue in circulation of AIV, we conducted bioaerosol surveillance for AIV among LPMs located in Zhongshan, Guangdong, China.

During January 13, 2015 to April 20, 2016, weekly bioaerosol surveillance for AIV was conducted in 3 of Zhongshan's LPMs. The sampling technique was as previously described.[9] Air samples were collected using SKC Biosamplers (SKC Inc., Eighty Four, PA; catalog number 225-9595) attached to SKC BioLite Pumps (SKC Inc., Eighty Four, PA; catalog number 228-9610). The collection medium consisted of 15 ml of phosphate buffered saline (PBS) with 0.5% (w/v) bovine serum albumin fraction V powder (Sigma—Aldrich, St. Louis, MO), and an adjusted collection flow rate which is suitable for maintaining viability of captured viruses of 8 L/min for 30 min was used. Biosamplers were placed at a collection height of 0.8 m above the ground and 0.2 m away from the poultry cages which were randomly selected in the LPMs. Collected samples were hand-carried on ice to the Zhongshan Center for Disease Control and Prevention viral laboratory where they were concentrated using Amicon Ultra-15 Centrifugal Filter Units (EMD Millipore, Billerica, MA) at 2500 g for 15 min. Total nucleic acid was extracted using the QIAxtractor (Qiagen, Inc., Venlo, The Netherlands) and then tested for influenza A virus RNA (vRNA) using a real-time reverse transcription polymerase chain reaction (rRT-PCR).[9]

Positive samples were inoculated into embryonated chicken eggs, and the allantoic fluid harvested after incubation of the inoculated eggs for 2 days. The harvested allantoic fluid was then retested with rRT-PCR. Whole genome sequencing of the harvested virus was accomplished using a MiSeq (Illumina Inc., USA).

Genomic sequences (GenBank accession numbers, KX223685 through KX223692) were assembled and analyzed by CLC Genomics workbench (CLC Bio). Deduced amino acid sequences alignment and dendrogram analysis of the full-length genomic sequences with homologs were carried out by using the software of MEGA software (version 6). Phylogenetic trees were constructed using the maximum likelihood method with 1000 bootstrap tests.

Of the 243 air samples collected, 19 (7.8%) were initially positive for influenza A vRNA. One sample collected February 29, 2016 was positive by rRT-PCR post-inoculation in embryonated chicken eggs, and identified as an influenza A (H5N6) virus by whole-genome sequencing. This identified strain was designated A/Environment/Zhongshan/ZS01/2016(H5N6) (abbreviated as ZS01 in this manuscript).

Phylogenetic analysis of the hemagglutinin (HA) gene revealed that the virus isolate belonged to clade 2.3.4.4. (Fig. 1A). The HA protein of strain ZS01 has multiple basic amino acids at the HA cleavage site (PLRERRRKR/GLF), which is characteristic of highly pathogenic AIV. Furthermore, no mutations that encode Q222L or G224S (H5 numbering system) were found within the HA gene, suggesting that the virus had an avian-like (a2, 3-SA) receptor binding preference. However, several mammalian-adaptive mutations and species associated signature positions were found within HA (I151T, S123P, T156A) (Supplementary Table 1). The HA and NA genes of ZS01 exhibited high identities in coding sequence with A/chicken/Zhejiang/727155/2014 (H5N6) (98.83% and 97.03% respectively) and with A/chicken/Shenzhen/1061/2013(H5N6) (98.36%, 98.48% respectively) (Fig. 1A, B). HA and NA genes also demonstrated high identities with human H5N6 isolates (Supplementary Table 2). PB1, NP, PA, MP, NS genes of ZS01 were located in the H5 clade, Eurasian lineage (Supplementary Fig. 1A—F), consistent with China's human H5N6 isolates.[1,3]

The neuraminidase (NA) gene shared high identities with those of Guangdong poultry H6N6 strains (Supplementary Table 2). The PB2 gene of ZS01 shared 99.2% identity with

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Allogeneic Bone Marrow–Derived Mesenchymal Stromal Cells for Hepatitis B Virus–Related Acute-on-Chronic Liver Failure: A Randomized Controlled Trial

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Mortality from hepatitis B virus (HBV)–related acute-on-chronic liver failure (ACLF) is high due to limited treatment options. Preclinical and clinical investigations have proved that treatment with mesenchymal stromal cells (MSCs) is beneficial for recovery from liver injury. We hypothesized that the outcome of HBV-related ACLF would be improved by MSC treatment. From 2010 to 2013, 110 patients with HBV-related ACLF were enrolled in this open-label, nonblinded randomized controlled study. The control group (n = 54) was treated with standard medical therapy (SMT) only. The experimental group (n = 56) was infused weekly for 4 weeks with 1.0 to 10 × 10^5 cells/kg allogeneic bone marrow–derived MSCs and then followed for 24 weeks. The cumulated survival rate of the MSC group was 73.2% (95% confidence interval 61.6%-84.8%) versus 55.6% (95% confidence interval 42.3%-68.9%) for the SMT group (P = 0.03). There were no infusion-related side effects, but fever was more frequent in MSC compared to SMT patients during weeks 5-24 of follow-up. No carcinoma occurred in any trial patient in either group. Compared with the control group, allogeneic bone marrow–derived MSC treatment markedly improved clinical laboratory measurements, including serum total bilirubin and Model for End-Stage Liver Disease scores. The incidence of severe infection in the MSC group was much lower than that in the SMT group (16.1% versus 33.3%, P = 0.04). Mortality from multiple organ failure and severe infection was higher in the SMT group than in the MSC group (37.0% versus 17.9%, P = 0.02). *Conclusion:* Peripheral infusion of allogeneic bone marrow–derived MSCs is safe and convenient for patients with HBV-related ACLF and significantly increases the 24-week survival rate by improving liver function and decreasing the incidence of severe infections. (HEPATOLOGY 2017;66:209-219).

Acute-on-chronic liver failure (ACLF) occurs in patients with previously diagnosed or undiagnosed chronic liver disease and is characterized by acute hepatic insults such as jaundice and coagulopathy and complicated within 4 weeks by ascites and/or encephalopathy.[1] In Asia, ACLF is mainly caused by hepatitis B[2]; mortality is as high as 63%-72.3%.[3,4] Antiviral treatment can improve outcomes,

Abbreviations: ACLF, acute-on-chronic liver failure; ALB, albumin; ALT, alanine aminotransferase; BM-MSC, bone marrow-derived MSC; CD, cluster of differentiation; HBV, hepatitis B virus; HRS, hepatorenal syndrome; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; MSC, mesenchymal stromal cell; SMT, standard medical therapy; TBil, total bilirubin.

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RESEARCH ARTICLE

An APE1 inhibitor reveals critical roles of the redox function of APE1 in KSHV replication and pathogenic phenotypes

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Abstract

APE1 is a multifunctional protein with a DNA base excision repair function in its C-terminal domain and a redox activity in its N-terminal domain. The redox function of APE1 converts certain transcription factors from inactive oxidized to active reduced forms. Given that among the APE1-regulated transcription factors many are critical for KSHV replication and pathogenesis, we investigated whether inhibition of APE1 redox function blocks KSHV replication and Kaposi's sarcoma (KS) phenotypes. With an shRNA-mediated silencing approach and a known APE-1 redox inhibitor, we demonstrated that APE1 redox function is indeed required for KSHV replication as well as KSHV-induced angiogenesis, validating APE1 as a therapeutic target for KSHV-associated diseases. A ligand-based virtual screening yielded a small molecular compound, C10, which is proven to bind to APE1. C10 exhibits low cytotoxicity but efficiently inhibits KSHV lytic replication (EC_{50} of 0.16 μM and selective index of 165) and KSHV-mediated pathogenic phenotypes including cytokine production, angiogenesis and cell invasion, demonstrating its potential to become an effective drug for treatment of KS.

Author summary

As a major AIDS-associated malignancy, Kaposi's sarcoma (KS) is caused by Kaposi's sarcoma-associated herpesvirus (KSHV). Currently there is no definitive cure for KS. In this study, we identified a cellular protein, namely APE1, as an effective therapeutic target for blocking KSHV replication and inhibiting the development of KS phenotypes. We showed that the redox function of APE1 is absolutely required for KSHV replication, virally induced cytokine secretion and angiogenesis. Blockade of APE1 expression or inhibition of APE1 redox activity led to inhibition of KSHV replication and reduction of cytokine release and angiogenesis. Furthermore, we identified a novel small molecular compound,

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Short technical report

An efficient cumate-inducible system for procyclic and bloodstream form *Trypanosoma brucei*

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ABSTRACT

In *Trypanosoma brucei*, the tetracycline-inducible system enables tightly-regulated, highly-efficient expression of recombinant proteins or double-stranded RNA in both procyclic and bloodstream form cells, providing useful molecular genetic tools to study gene functions. An alternative, vanillic acid-inducible system is recently described for procyclic *T. brucei*, providing ~18-fold increase in GFP reporter expression upon induction (Sunter JD. Mol. Biochem. Parasitol. 2016, 207:45–48). Here we describe a cumate-inducible system that allows efficient, tunable gene expression showing > 300-fold increase in GFP expression upon induction. The cumate-inducible system can be used alone or together with the tetracycline-inducible system, in both procyclic and bloodstream form *T. brucei*. Efficient cumate-inducible expression is also achieved in *T. brucei*-infected mice.

Trypanosoma brucei is a protozoan parasite causing African sleeping sickness in humans and nagana in domestic animals [1]. In addtion to its medical importance, *T. brucei* has served as a useful model organism to study antigenic variation [2], organelle biogenesis [3,4], stress responses [5,6], flagellum and cytoskeleton organisation [7,8] and other cellular processes [9]. Many advanced, reverse genetic tools such as RNA interference (RNAi)-mediated knockdown [10] and homologous recombination-mediated gene replacement or knockout [11,12] are available, allowing gene functions to be studied.

A tightly-regulated tetracycline-inducible system has been widely used for inducible protein expression and inducible-RNAi in *T. brucei* functional genomics research [11]. In order to control the activity of different genes simultaneously and independantly, new inducible systems that are compatible with the tetracycline based system are needed. Recently, a vanillic acid inducible expression system is developed in procyclic *T. brucei* [13]. Upon induction with vanillic acid, ~18-fold increase in GFP expression was observed. This is lower compared to the ~250-fold increase observed in the tetracycline-inducible system, preventing assays that require high level expression. In this study, we established a highly-efficient cumate-inducible (cumate-ON) system that exhibited > 300-fold increase in GFP expression upon induction, in both procyclic and bloodstream form trypanosomes.

Cumate, also known as 4-isopropylbenzoic acid or cumic acid, is a 164.2 Da compound catabolized in some bacterial species [14,15]. The cumate switch system has been successfully used for inducible expression in mammalian [16] and bacterial cells [17]. At up to 50 μg/ml, cumate did not have observable effects on cell morphology or cell growth, for both procyclic and bloodstream form cells in culture (Fig. S1).

A cumate repressor (CymR) gene with codons optimized for expression in *T. brucei* was fused to an N-terminal nuclear targeting sequence (Fig. S2). The recombinant gene was then inserted into the pSmOx vector [18] between the T7 RNA polymerase (RNAP) and tetracycline repressor (TetR), to create a pSmOxNus (Single Marker Oxford, NUS modified) vector (Fig. 1A). The pSmOxNus vector was then digested with Hind III, and stably transfected into bloodstream form Lister 427 cells or freshly differentiated procyclic AnTat1.1 cells by integration into the α/β tubulin intergenic sequences. The resultant stable cell lines were named DIb427 (bloodstream form) and DIpAnT (procyclic form), respectively, for dual inducibility by tetracycline and cumate.

Abbreviations: TetO, tetracyclin operator; CuO, cumate operator; TetR, tetracyclin repressor; CymR, cumate repressor; RNAP, RNA polymerase

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ORIGINAL PAPER

Angiostrongylus cantonensis: An optimized cultivation of this parasitic nematode under laboratory conditions

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Abstract *Angiostrongylus cantonensis* (*A. cantonensis*), a parasitic nematode, is the important neurotropic pathogen which causes human angiostrongyliasis. It has a complex life-cycle and severe parasite-host interaction in contrast to free-living nematode. Establishment of a well-suited life-cycle and in vitro cultivation of *A. cantonensis* in the laboratory will be one of the key techniques to elucidate the mechanism of parasite-host interaction. However, the low survival and growth rate of worms is still to be the problem. We optimized the known life-cycle of *A. cantonensis* in the laboratory, showing that small in size, easy to breed, and high compatibility of *Biomphalaria straminea* precede the common snails as an intermediate host of *A. cantonensis*. Furthermore, the egg hatching rate in Ham's F-12 medium reached approximately 80% using the eggs of mature female adult worms. We also demonstrated that the survival of larvae could be sustained for more than 30 days by in vitro cultivation of L1 larvae in DMEM with mixed antibiotics (100 units/mL of penicillin G potassium, 50 μg/mL of streptomycin sulfate, and 0.5 μg/mL of amphotericin B) and L3, L4, and L5 larvae in Waymouth's medium with 20% fetal calf serum and mixed antibiotics. Infective L1 and L3 larvae kept high infective rate to the snail and rat after cultivation in these media, respectively. It will provide the basis for studying on genetic manipulations for functional genes, new drug screening, and the mechanism of parasite-host interaction of parasitic nematodes.

Keywords *Angiostrongylus cantonensis* · In vitro cultivation · Egg · Larvae · Life-cycle

Abbreviations

A. cantonensis	*Angiostrongylus cantonensis*
A. costaricensis	*Angiostrongylus costaricensis*
A. fulica	*Achatina fulica*
C. elegans	*Caenorhabditis elegans*
C. hamulosa	*Cheilospirura hamulosa*

Introduction

Parasitic nematodes include vector-borne parasites and soil-transmitted helminths (World Health Organization 2015; Zhang 2013). Over two billion humans have been infected by approximately 60 medically important parasitic nematodes (Pullan et al. 2014) leading to severe clinical manifestations that include blindness, persistent inflammation and pain, tissue damage, physical disfigurement, childhood stunting, anemia, malnutrition, fatigue, and chronic morbidity (Bethony et al. 2006; Taylor et al. 2010; Yu et al. 2010). However, the progress on the studies of parasite-host interactions still develops slowly.

One of the key reasons is the lacking of high-efficient cultivation conditions for parasitic nematodes in the laboratory. The hermaphroditic free-living nematode *Caenorhabditis*

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Antiviral Activity of Carbenoxolone Disodium Against Dengue Virus Infection

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As one of the most important mosquito-borne viral diseases, dengue infection is now becoming a global concern due to its rapid spread and rise in incidence. Currently, there is no approved vaccine or effective antiviral drug for dengue virus (DENV) infection. Glycyrrhetinic acid (GNa) and its related derivatives have been reported to inhibit a broad spectrum of viruses. However, it is unknown whether Carbenoxolone disodium (CBX), one of the GNa derivatives, affects DENV infection. Here, we found that the production of infectious DENV particles was significantly decreased by CBX treatment in DENV-permissive cells, while the viral RNA and viral protein synthesis were not affected. Moreover, results from time-of-addition study showed that the inhibitory effect of CBX on DENV was exhibited by targeting the virus itself, not the host cells. Directly incubating DENV with CBX resulted in a remarkable reduction of virus titer and virus infectivity. Furthermore, DENV RNA from progeny virions in the supernatants was significantly decreased by CBX treatment in a dose-dependent manner. Taken together, these data indicate that the antiviral activity of CBX against DENV may be mainly due to a virucidal effect exerted by the compound itself. Our work, for the first time, demonstrates that CBX has antiviral activity against DENV infection, providing useful information for development of potential therapeutic interventions against dengue. ***J. Med. Virol. 89:571–581, 2017***.

KEY WORDS: dengue virus; carbenoxolone; antiviral compound; virucidal effect

INTRODUCTION

Dengue virus (DENV), a member of the genus Flavivirus in the family Flaviviridae, causes one of the most widespread mosquito-borne diseases in human. There are four serotypes of dengue virus, types 1 (DENV-1) to 4 (DENV-4), which have similar clinical manifestations and epidemiology in tropical and subtropical regions of the world [Wang et al., 2000].

Abbreviations: DENV, dengue virus; CBX, Carbenoxolone disodium; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; GNa, glycyrrhetinic acid; GRa, glycyrrhizic acid; HIV, human immunodeficiency virus; VSV, vesicular stomatitis virus; HSV, herpes simplex virus; MOI, multiplicity of infection; CPE, cytopathic effects; PBMC, peripheral blood mononuclear cells

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Conflicts of interest: none.

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Review

Artemisinin and its derivatives in treating protozoan infections beyond malaria

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ABSTRACT

Parasitic protozoan diseases continue to rank among the world's greatest global health problems, which are also common among poor populations. Currently available drugs for treatment present drawbacks, urging the need for more effective, safer, and cheaper drugs. Artemisinin (ART) and its derivatives are some of the most important classes of antimalarial agents originally derived from *Artemisia annua* L. However, besides the outstanding antimalarial and antischistosomal activities, ART and its derivatives also possess activities against other parasitic protozoa. In this paper we review the activities of ART and its derivatives against protozoan parasites in vitro and in vivo, including *Leishmania* spp., *Trypanosoma* spp., *Toxoplasma gondii*, *Neospora caninum*, *Eimeria tenella*, *Acanthamoeba castellanii*, *Naegleria fowleri*, *Cryptosporidium parvum*, *Giardia lamblia*, and *Babesia* spp. We conclude that ART and its derivatives may be good alternatives for treating other non-malarial protozoan infections in developing countries, although more studies are necessary before they can be applied clinically.

Contents

Abbreviations: ART, artemisinin; b.i.d., two times per day; CH_2CL_2, dichloromethane; CI, cell index; DART, dehydroartemisinin; Deoxy-ATS, deoxygenated artesunate; Deoxy-DHA, deoxydihydroartemisinin; DHA, dihydroartemisinin; DMSO, dimethyl sulphoxide; HFF, human foreskin fibroblast; IC_{50}, concentration that causes 50% inhibition of growth; IC_{90}, concentration that causes 90% inhibition of growth; i.g., intragastric administration; i.m., intramuscular injection; i.p., intraperitoneal injection; iTRAQ, isobaric tags for relative and absolute quantitation; i.v., intravenous injection; Luc value, luciferase value; MeOH, methanol; NO, nitric oxide; PCV, packed cell volume; PGDH, phosphoglycerate dehydrogenase; p.i., post-infection; PI staining, propidium iodide staining; p.o., oral administration; PSAT, phosphoserine aminotransferase; q.d., one time per day; q.i.d., four times per day; RBC, red blood cell; s.c., subcutaneous injection; SEM, scanning electron micrograph; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; SI, selectivity index; TD_{50}, median cytotoxic dose; TI, therapeutic index; TEM, transmission electron micrograph; t.i.d., three times per day; t.p., topical administration.

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RESEARCH ARTICLE

Astrocyte Elevated Gene 1 Interacts with Acetyltransferase p300 and c-Jun To Promote Tumor Aggressiveness

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ABSTRACT Astrocyte elevated gene 1 (AEG-1) is an oncoprotein that strongly promotes the development and progression of cancers. However, the detailed underlying mechanisms through which AEG-1 enhances tumor development and progression remain to be determined. In this study, we identified c-Jun and p300 to be novel interacting partners of AEG-1 in gliomas. AEG-1 promoted c-Jun transcriptional activity by interacting with the c-Jun/p300 complex and inducing c-Jun acetylation. Furthermore, the AEG-1/c-Jun/p300 complex was found to bind the promoter of c-Jun downstream targeted genes, consequently establishing an acetylated chromatin state that favors transcriptional activation. Importantly, AEG-1/p300-mediated c-Jun acetylation resulted in the development of a more aggressive malignant phenotype in gliomas through a drastic increase in glioma cell proliferation and angiogenesis *in vitro* and *in vivo*. Consistently, the AEG-1 expression levels in clinical glioma specimens correlated with the status of c-Jun activation. Taken together, our results suggest that AEG-1 mediates a novel epigenetic mechanism that enhances c-Jun transcriptional activity to induce glioma progression and that AEG-1 might be a novel, potential target for the treatment of gliomas.

KEYWORDS E1A binding protein p300 (p300), acetylation, astrocyte elevated gene 1 (AEG-1), c-Jun transcription factor, glioma

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Glioma is the most common and aggressive type of central nervous system tumor (1). Despite intensive research and clinical efforts, the prognosis for patients with this tumor type remains poor, largely attributable to its highly invasive and fast proliferating phenotype. The median life expectancy of patients with a grade IV glioma, known as a glioblastoma multiforme (GBM), is less than 1 year (2). Therefore, the definition of appropriate targets against which effective strategies to treat glioma may be developed represents a major goal in glioma research. A better comprehension of the molecular mechanisms mediating glioma progression is crucial to developing an efficacious therapeutic strategy that prevents the infiltration, invasion, and proliferation of glioma cells.

The product of the gene astrocyte elevated gene 1 (*AEG-1*), also known as the metadherin (*MTDH*) or *LYRIC* gene, was initially identified to be a novel protein whose expression is induced by human immunodeficiency virus type 1 (HIV-1) or by tumor necrosis factor alpha (TNF-α) in primary human fetal astrocytes (3–6). AEG-1 is a multifunctional protein that interacts with diverse partners in different types of cancers and promotes the development of essentially all hallmarks of cancer (7–12). Previous

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BASIC RESEARCH PAPER

ATP-driven and AMPK-independent autophagy in an early branching eukaryotic parasite

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ABSTRACT

Autophagy is a catabolic cellular process required to maintain protein synthesis, energy production and other essential activities in starved cells. While the exact nutrient sensor(s) is yet to be identified, deprivation of amino acids, glucose, growth factor and other nutrients can serve as metabolic stimuli to initiate autophagy in higher eukaryotes. In the early-branching unicellular parasite *Trypanosoma brucei*, which can proliferate as procyclic form (PCF) in the tsetse fly or as bloodstream form (BSF) in animal hosts, autophagy is robustly triggered by amino acid deficiency but not by glucose depletion. Taking advantage of the clearly defined adenosine triphosphate (ATP) production pathways in *T. brucei*, we have shown that autophagic activity depends on the levels of cellular ATP production, using either glucose or proline as a carbon source. While autophagosome formation positively correlates with cellular ATP levels; perturbation of ATP production by removing carbon sources or genetic silencing of enzymes involved in ATP generation pathways, also inhibited autophagy. This obligate energy dependence and the lack of glucose starvation-induced autophagy in *T. brucei* may reflect an adaptation to its specialized, parasitic life style.

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Introduction

Autophagy is a conserved cellular process during which unnecessary or dysfunctional proteins or organelles are engulfed by autophagosomes and targeted for bulk degradation in lysosomes. This 'self-eating' pathway can support cell survival under starvation or other stress conditions by maintaining the cell energy level, recycling the amino acids for essential new protein synthesis, and eliminating harmful cellular materials.[1]

Autophagy can be triggered by a multitude of stress conditions. Among them, low cellular energy charge or deprivation of essential nutrients, including glucose and amino acids have been extensively studied.[2] The AMP-activated protein kinase (AMPK) senses low energy levels (high AMP:ATP ratio) in cells, that usually occur upon glucose depletion, and acts as a checkpoint for cell growth, autophagy and metabolism coordination.[3] However, the exact role of glucose in autophagy is still controversial (reviewed in[4]). On the other hand, limitations of nonessential amino acids trigger autophagy by at least 2 distinct mechanisms. First, accumulation of uncharged tRNA species upon amino acid starvation activates EIF2AK4/Gcn2 (eukaryotic translation initiation factor 2 α kinase 4), thus blocking protein synthesis and inducing autophagy.[5] Second, depletion of lysosomal amino acids can lead to inactivation of MTORC1 by dissociating the complex from lysosomal surface.[6-8] Amino acid deprivation has also been reported in mammalian and nonmammalian models to affect intracellular levels of acetyl-CoA (AcCoA) and α-ketoglutarate and thus trigger autophagy.[7,9,10] While autophagy is required to maintain ATP production in starved cells,[11] ATP is also required for at least several autophagy steps.[12] However, cellular ATP levels under amino acid starvation have been rarely investigated. Increased,[7] unchanged[13,14] and decreased[15-17] cellular ATP have all been reported in various organisms, making it difficult to extrapolate the correlation between ATP production and amino acid starvation-induced autophagy.

Despite it being a highly conserved eukaryotic pathway, most of the autophagy studies have focused on mammalian cells and yeast. Much less is known about autophagy in the early-branching protozoan parasites, which include many important human and animal pathogens. Studies of autophagy in these unicellular parasites however, may provide insights to the diverse functions and the evolution of the autophagic process.[18] Until now, approximately 40 AuTophaGy-related (*ATG*) genes have been identified in yeast or mammalian cells. Among them, only half have been found in the protozoan parasites. While the Atg8–PE conjugation system is highly conserved, proteins involved in other autophagy steps lack conservation or have not been detected in the parasite genomes, suggesting the presence of a divergent autophagic pathway.[19] The core autophagy events, from double-membrane autophagosome formation to the final degradation in lysosomes is conserved,[20]

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Avasimibe: A novel hepatitis C virus inhibitor that targets the assembly of infectious viral particles

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ABSTRACT

Direct-acting antivirals (DAAs), which target hepatitis C virus (HCV) proteins, have exhibited impressive efficacy in the management of chronic hepatitis C. However, the concerns regarding high costs, drug resistance mutations and subsequent unexpected side effects still call for the development of host-targeting agents (HTAs) that target host factors involved in the viral life cycle and exhibit pan-genotypic antiviral activity. Given the close relationship between lipid metabolism and the HCV life cycle, we investigated the anti-HCV activity of a series of lipid-lowering drugs that have been approved by government administrations or proven safety in clinical trials. Our results showed that avasimibe, an inhibitor of acyl coenzyme A:cholesterol acyltransferase (ACAT), exhibited marked pan-genotypic inhibitory activity and superior inhibition against HCV when combined with DAAs. Moreover, avasimibe significantly impaired the assembly of infectious HCV virions. Mechanistic studies demonstrated that avasimibe induced downregulation of microsomal triglyceride transfer protein expression, resulting in reduced apolipoprotein E and apolipoprotein B secretion. Therefore, the pan-genotypic antiviral activity and clinically proven safety endow avasimibe exceptional potential as a candidate for combination therapy with DAAs. In addition, the discovery of the antiviral properties of ACAT inhibitors also suggests that inhibiting the synthesis of cholesteryl esters might be an additional target for the therapeutic intervention for chronic HCV infection.

1. Introduction

Hepatitis C virus (HCV), an enveloped positive-sense RNA virus, belongs to the *Hepacivirus* genus of the *Flaviviridae* family (Scheel and Rice, 2013). More than 180 million individuals worldwide are infected with HCV; approximately 75%–85% of them develop chronic infection, of which, 10%–20% develop progressive liver injury, fibrosis, cirrhosis or hepatocellular carcinoma over a period of 20–30 years (Chen and Morgan, 2006; Thrift et al., 2017). Currently, there is no effective prophylactic or therapeutic vaccine against HCV. In the past, the combination of ribavirin plus interferon (IFN)-α was the standard anti-HCV therapy, but its disappointing efficacy and severe side effects compelled researcher to identify other advanced antiviral agents (Carter et al., 2017). Recently, revolutionary direct-acting antivirals (DAAs) have demonstrated amazing efficacy in the management of chronic hepatitis C infection, making it a curable disease in the majority of treated patients (Li and De Clercq, 2017). However, the extremely high cost of DAAs reduces their accessibility to patients even in high-

Abbreviations: DAAs, direct-acting antivirals; HCV, hepatitis C virus; HTAs, host-targeting agents; ACAT, acyl coenzyme A:cholesterol acyltransferase; IFN, interferon; MTTP, microsomal triglyceride transfer protein; ApoE, apolipoprotein E; ApoB, apolipoprotein B; siRNAs, small interfering RNAs; DENV, dengue virus; HCVpp, HCV pseudoparticles; SGR, subgenomic replicon; VLDL, very-low-density lipoprotein

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Avian Influenza A (H7N9) viruses isolated from patients with mild and fatal infection differ in pathogenicity and induction of cytokines

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ABSTRACT

Since 2013, a novel Influenza A (H7N9) virus strain has continued to circulate within poultry and causing human disease. Influenza A (H7N9) virus results in two types of infection: mild and severe. The different results of clinical findings may be related with host susceptibility and characteristics of the virus itself. In order to investigate potential pathogenesis of Influenza A (H7N9) virus, we performed pathogenecity and cytokines analysis of two isolates, A/Guangdong/6/2013 H7N9 virus (GD-6) from a patient with a mild infection, and A/Guangdong/7/2013 H7N9 virus (GD-7) from a patient with a fatal infection. We found that GD-7 replicated to higher levels than GD-6 in human peripheral blood mononuclear cells (PBMCs), lung tissues, and mice. Furthermore, GD-7 infection resulted in more severe lung damage in mice lung tissues than GD-6 infection. GD-7 elicited higher levels of interleukin-6 (IL-6) and tumor necrosis factor-α(TNF-α) than GD-6 did. In conclusion, GD-7 was more pathogenic and induced higher levels of proinflammatory cytokines than GD-6 did.

1. Introduction

In February 2013, a novel avian influenza H7N9 virus (A-H7N9) emerged in Shanghai and was found to infect humans [24]. Subsequently, new H7N9 cases were discovered in Anhui, Zhejiang, Jiangxi, Guangdong, and other Chinese provinces. As of 15 June 2017, a total of 1533 laboratory-confirmed cases of human infection with avian influenza A(H7N9) viruses, with 134 cases reported in the spring of 2013, 306 in 2013–14, 219 in 2014–15, 114 in 2015–16, and 760 in 2016–17, including at least 592 deaths, have been reported to WHO [1]. There were three waves of A-H7N9 infections during this period. From March to May 2013, the pandemic was mainly concentrated in the eastern region of China, with 133 human cases including 45 deaths reported [2]. From October 2013 to May 2014, the pandemic spread to south China and Zhejiang province, where 266 cases were reported [3]. From October 2014 to March 2015, cases were mainly concentrated in the southern region of China, with 118 cases leading to 37 deaths reported [4] (see Table 1).

Human infections with other H7 influenza viruses (H7N2, H7N3, and H7N7) have previously been reported in the Netherlands, USA, Canada, and UK and resulted in conjunctivitis with mild upper respiratory symptoms. Notably, current clinical findings have determined that A-H7N9 results in two types of infection: mild and severe. Mild infections have been presented typically in children and are characterized by flu-like symptoms such as fever, cough, and pharyngeal congestion [5]. On the other hand, severe infections have been typically reported in older adults with rapid illness development that appears as severe pneumonia and rapid development for ARDS, septic shock, and multiple organ failure that leads to death [2]. The different results of clinical findings may be related with host susceptibility and characteristics of the virus itself [6]. Infections with highly pathogenic avian influenza virus such as H5N1 can result in the excessive release of proinflammatory cytokines and chemokines that lead to dysregulation of the host immune response. This “cytokine storm” causes damage to the lung

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Burden of rare variants in ALS genes influences survival in familial and sporadic ALS

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ABSTRACT

Genetic variants are implicated in the development of amyotrophic lateral sclerosis (ALS), but it is unclear whether the burden of rare variants in ALS genes has an effect on survival. We performed whole genome sequencing on 8 familial ALS (FALS) patients with *superoxide dismutase 1 (SOD1)* mutation and whole exome sequencing on 46 sporadic ALS (SALS) patients living in Hong Kong and found that 67% had at least 1 rare variant in the exons of 40 ALS genes; 22% had 2 or more. Patients with 2 or more rare variants had lower probability of survival than patients with 0 or 1 variant ($p = 0.001$). After adjusting for other factors, each additional rare variant increased the risk of respiratory failure or death by 60% ($p = 0.0098$). The presence of the rare variant was associated with the risk of ALS (Odds ratio 1.91, 95% confidence interval 1.03–3.61, $p = 0.03$), and ALS patients had higher rare variant burden than controls (MB, $p = 0.004$). Our findings support an oligogenic basis with the burden of rare variants affecting the development and survival of ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of motor neurons, progressive paralysis, and death. The world-wide incidence of ALS is 0.3–7.0 per 100,000 per year (Cronin et al., 2007) and in Hong Kong, the incidence of ALS was estimated to be 0.6 per 100,000 per year (Fong et al., 2005). Five to 10% of cases are familial. There are more than 20 known causative genes, with more showing association with risk of disease (Leblond et al., 2014). Mutations in *superoxide dismutase 1 (SOD1)* and *chromosome 9 open reading frame 72 (C9ORF72)*, the 2 most common causes of familial ALS (FALS) in populations of European ancestry, account for about half of familial cases collectively (Finsterer and Burgunder, 2014). Mutations in ALS genes are also found in 10% of patients with sporadic ALS (SALS) (Renton et al., 2014). While twin studies from European populations showed ALS heritability to be around 61% in sporadic cases (Al-Chalabi et al., 2010), genome-wide association analyses showed that common single nucleotide polymorphisms (SNPs) contribute to 8.5%–12% of SALS's heritability (Fogh et al., 2014; van Rheenen et al., 2016). The difference in these heritability estimates, or "missing heritability," suggests that there is a notable genetic role in ALS that remains to be elucidated.

There is considerable variability in ALS phenotype: age and site of onset, relative degree of upper and lower motor neuron involvement, and rate of progression (Swinnen and Robberecht,

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PLOS | NEGLECTED TROPICAL DISEASES

SYMPOSIUM

Case report: A rare case of urinary myiasis induced by the fourth instar larvae of *Telmatoscopus albipunctatus*

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Abstract

Telmatoscopus albipunctatus, a cosmopolitan fly, is widely distributed throughout moist environments. It is one of the most medically important insects (especially in urban environments) that may potentially cause myiasis. Urinary myiasis and other sites of infestation, including the intestine, nasal passages, lung, and derma, have been reported. This is the first case report of a Chinese middlescent woman infected with *T. albipunctatus* in Guangzhou, China. In the present report, a 50-year-old woman came to The Third Affiliated Hospital of Southern Medical University, Guangzhou, China, because larvae were found when urinating in the morning; this had occurred every two days within the past two months. She complained of frequent micturition and urgency. Urine tests indicated that all indexes were normal except for slight urinary tract infection. Subsequently, the larvae were sent to the diagnostic section for parasitic infection in the Department of Parasitology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China. The stereoscopic microscope and transmission electron microscope were used for morphological observation. On this basis, the cytochrome oxidase subunit 1 (*COX1*) gene was specifically amplified by PCR. Sequence analysis of the PCR product and phylogenetic analysis were used to identify the species. Morphological analysis combined with molecular biology methods indicated that the insect was the fourth instar larvae of *T. albipunctatus*. Our results show that this was a case of a 50-year-old woman infected with *T. albipunctatus* larvae in her urinary tract, and the findings suggest that clinicians should be vigilant for this infection.

Introduction

Psychodidae is a cosmopolitan fly that is tiny and hairy. It belongs to the family Nematoceran and is a medically important insect, especially in urban areas. Most of the adults are distributed throughout houses, stinking ditches, or septic tanks, and the larvae are bred in moist

CCT6A suppresses SMAD2 and promotes prometastatic TGF-β signaling

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Paradoxically, during early tumor development in many cancer types, TGF-β acts as a tumor suppressor, whereas in the advanced stages of these cancers, increased TGF-β expression is linked to high metastasis and poor prognosis. These findings suggest that unidentified mechanisms may function to rewire TGF-β signaling toward its prometastatic role in cancer cells. Our current study using non–small-cell lung carcinoma (NSCLC) cell lines, animal models, and clinical specimens demonstrates that suppression of SMAD2, with SMAD3 function intact, switches TGF-β–induced transcriptional responses to a prometastatic state. Importantly, we identified chaperonin containing TCP1 subunit 6A (CCT6A) as an inhibitor and direct binding protein of SMAD2 and found that CCT6A suppresses SMAD2 function in NSCLC cells and promotes metastasis. Furthermore, selective inhibition of SMAD3 or CCT6A efficiently suppresses TGF-β–mediated metastasis. Our findings provide a mechanism that directs TGF-β signaling toward its prometastatic arm and may contribute to the development of therapeutic strategies targeting TGF-β for NSCLC.

Introduction

Non–small-cell lung carcinoma (NSCLC) is among the most commonly diagnosed cancers worldwide (1, 2). The prognosis of NSCLC remains poor, and the overall 5-year relative survival rate, including all stages and subtypes, is less than 20% (1, 3). Like nearly all cancer types, metastasis represents the main cause of death in patients with NSCLC. Biologically, tumor metastasis is a multistep, complex process that is typically driven by aberrant activation or suppression of one or more signal transduction pathways (4). Notably, among the pathways frequently dysregulated in cancer metastasis, TGF-β signaling has been widely demonstrated as one of the most commonly activated and essential pathways for the metastasis of various cancer types (5, 6). Indeed, activation of TGF-β signaling is closely related to NSCLC progression and metastasis (7–9), whereas the mechanisms that activate and sustain prometastatic TGF-β signaling remain incompletely understood.

Activation of the TGF-β signaling cascade is typically initiated by binding of a TGF-β ligand with the TGF-β type II serine/threonine receptor (TGFBR2), followed by phosphorylation and oligomerization of TGFBR1/2, which causes phosphorylation of the cytoplasmic effectors SMAD2 and SMAD3. Phosphorylated SMAD2 or SMAD3 subsequently forms a heteromeric complex with SMAD4 and is transported to the nucleus, where it binds with other DNA-binding transcription factors and consequently regulates the transcription of TGF-β target genes (5, 6, 10, 11).

It has been noted that the biological and clinical outcomes of TGF-β signaling in cancer are far more complex than was previously understood, and these effects may be more cancer type and biological context dependent than expected. Alterations of pathway component proteins, binding partners of SMADs, and microenvironmental factors may lead to variable cellular responses to TGF-β stimulation (6, 12). For example, in benign epithelia and early tumor initiation, TGF-β inhibits epithelial growth and plays a tumor-suppressive role; in contrast, in advanced tumors, dysregulated TGF-β signaling promotes tumor progression and metastasis by enhancing the epithelial-mesenchymal transition (EMT) and cancer cell colonization in distant organs (6, 12–16). Moreover, additional studies have demonstrated that in several types of cancer, the tumor-suppressive arm of TGF-β signaling may be terminated (17–23). Notably, this complexity of TGF-β signaling has complicated the initially expected feasibility of targeting this pathway as an effective antimetastatic strategy. Both preclinically and clinically, the development of TGFBR inhibitors or ligand traps has not been successful (24, 25). Thus, while TGF-β is a central promoter of metastasis and may therefore represent a potentially promising antimetastatic target, a better understanding of the molecular mechanism that directs TGF-β signaling to promote metastasis will facilitate the development of effective TGF-β–targeting antimetastasis approaches.

In the context of distinguishing the antiproliferative and prometastatic arms of TGF-β signaling, it is particularly noteworthy that SMAD2 and SMAD3 comprise 2 major TGF-β receptor–

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Parasites & Vectors

RESEARCH Open Access

Clonorchis sinensis granulin: identification, immunolocalization, and function in promoting the metastasis of cholangiocarcinoma and hepatocellular carcinoma

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Abstract

Background: Long-term infections by *Clonorchis sinensis* are associated with cholangitis, cholecystitis, liver fibrosis, cirrhosis, and even liver cancer. Molecules from the worm play vital roles in disease progress. In the present study, we identified and explored molecular characterization of *C. sinensis* granulin (*Cs*GRN), a growth factor-like protein from *C. sinensis* excretory/secretory products (*Cs*ESPs).

Methods: The encoding sequence and conserved domains of *Cs*GRN were identified and analysed by bioinformatics tools. Recombinant *Cs*GRN (r*Cs*GRN) protein was expressed in *Escherichia coli* BL21 (DE3). The localisation of *Cs*GRN in adult worms and *Balb/c* mice infected with *C. sinensis* was investigated by immunofluorescence and immunohistochemistry, respectively. Stable *Cs*GRN-overexpressed cell lines of hepatoma cells (PLC-GRN cells) and cholangiocarcinoma cells (RBE-GRN cells) were constructed by transfection of eukaryotic expression plasmid of pEGFP-C1-*Cs*GRN. The effects on cell migration and invasion of *Cs*GRN were assessed through the wound-healing assay and transwell assay. The levels of matrix metalloproteinase 2 and 9 (MMP2 and MMP9) in PLC-GRN or RBE-GRN cells were detected by real-time PCR (qRT-PCR). The levels of E-cadherin, vimentin, N-cadherin, zona occludens proteins (ZO-1), β-catenin, phosphorylated ERK (p-ERK) and phosphorylated AKT (p-AKT) were analysed by Western blotting.

Results: *Cs*GRN, including the conserved GRN domains, was confirmed to be a member of the granulin family. *Cs*GRN was identified as an ingredient of *Cs*ESPs. *Cs*GRN was localised in the tegument and testes of the adult worm. Furthermore, it appeared in the cytoplasm of hepatocytes and biliary epithelium cells from infected *Balb/c* mouse. The enhancement of cell migration and invasion of PLC-GRN and RBE-GRN cells were observed. In addition, *Cs*GRN upregulated the levels of vimentin, N-cadherin, β-catenin, MMP2 and MMP9, while it downregulated the level of ZO-1 in PLC-GRN/RBE-GRN cells. In total proteins of liver tissue from r*Cs*GRN immunised *Balb/c* mice, vimentin level decreased, while E-cadherin level increased when compared with the control groups. Meanwhile, the levels of p-ERK reached a peak at 4 weeks post immunisation and the level of p-AKT did at 2 weeks after immunisation.
(Continued on next page)

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Parasites & Vectors

RESEARCH Open Access

Clonorchis sinensis lysophospholipase A upregulates IL-25 expression in macrophages as a potential pathway to liver fibrosis

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Abstract

Background: Liver fibrosis is an excessive wound-healing reaction that requires the participation of inflammatory cells and hepatic stellate cells (HSCs). The pathogenesis of liver fibrosis caused by viruses and alcohol has been well characterized, but the molecular mechanisms underlying liver fibrosis induced by the liver fluke *Clonorchis sinensis* are poorly understood. Lysophospholipase A (LysoPLA), which deacylates lysophospholipids, plays a critical role in mediating the virulence and pathogenesis of parasites and fungi; however, the roles of *C. sinensis* lysophospholipase A (*Cs*LysoPLA) in *C. sinensis*-induced liver fibrosis remain unknown.

Methods: A mouse macrophage cell line (RAW264.7) was cultured and treated with *Cs*LysoPLA. IL-25 and members of its associated signaling pathway were detected by performing quantitative real-time PCR, Western blotting and immunofluorescent staining. A human hepatic stellate cell line (LX-2) was cultured and exposed to IL-25. LX-2 cell activation markers were examined *via* quantitative real-time PCR, Western blotting and immunofluorescent staining. Migration was analyzed in transwell plates.

Results: Treating RAW264.7 cells with *Cs*LysoPLA significantly induced IL-25 expression. Elevated PKA, B-Raf, and ERK1/2 mRNA levels and phosphorylated B-Raf and ERK1/2 were detected in *Cs*LysoPLA-stimulated RAW264.7 cells. The PKA inhibitor H-89 weakened B-Raf and ERK1/2 phosphorylation whereas the AKT activator SC79 attenuated ERK1/2 phosphorylation in RAW264.7 cells. Both H-89 and SC79 inhibited *Cs*LysoPLA-induced IL-25 upregulation. In addition, stimulation of LX-2 cells with IL-25 upregulated the expression of mesenchymal cell markers, including α-smooth muscle actin (α-SMA) and collagen type I (Collagen-I), and promoted cell migration.

Conclusions: *Cs*LysoPLA activates HSCs by upregulating IL-25 in macrophages through the PKA-dependent B-Raf/ERK1/2 pathway and potentially promotes hepatic fibrosis during *C. sinensis* infection.

Keywords: *Cs*LysoPLA, Liver fibrosis, IL-25

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ORIGINAL PAPER

Comparative analysis of immune effects in mice model: *Clonorchis sinensis* cysteine protease generated from recombinant *Escherichia coli* and *Bacillus subtilis* spores

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Abstract Clonorchiasis remains a nonnegligible public health problem in endemic areas. Cysteine protease of *Clonorchis sinensis* (*Cs*CP) plays indispensable roles in the parasitic physiology and pathology, and has been exploited as a promising drug and vaccine candidate. In recent years, development of spore-based vaccines against multiple pathogens has attracted many investigators' interest. In previous studies, the recombinant *Escherichia coli* (BL21) and *Bacillus subtilis* spores expressing *Cs*CP have been successfully constructed, respectively. In this study, the immune effects of *Cs*CP protein purified from recombinant BL21 (r*Cs*CP) and *B. subtilis* spores presenting *Cs*CP (*B.s-Cs*CP) in Balb/c mice model were conducted with comparative analysis. Levels of specific IgG, IgG1 and IgG2a were significantly increased in sera from both r*Cs*CP and *B.s-Cs*CP intraperitoneally immunized mice. Additionally, recombinant spores expressing abundant fusion *Cs*CP (0.03125 pg/spore) could strongly enhance the immunogenicity of *Cs*CP with significantly higher levels of IgG and isotypes. Compared with r*Cs*CP alone, intraperitoneal administration of mice with spores expressing *Cs*CP achieved a better effect of fighting against *C. sinensis* infection by slowing down the process of fibrosis. Our results demonstrated that a combination of Th1/Th2 immune responses could be elicited by r*Cs*CP, while spores displaying *Cs*CP prominently induced Th1-biased specific immune responses, and the complex cytokine network maybe mediates protective immune responses against *C. sinensis*. This work further confirmed that the usage of *B. subtilis* spores displaying *Cs*CP is an effective way to against *C. sinensis*.

Keywords *Clonorchis sinensis* · *Bacillus subtilis* spores · Cysteine protease · *Escherichia coli* · Immune effects

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Introduction

Clonorchiasis, induced by *Clonorchis sinensis* (*C. sinensis*), is a fish-borne zoonotic disease and one of the most neglected tropical diseases (Lun et al. 2005; Petney et al. 2013). Currently, over 15 million people are infected with *C. sinensis*, and nearly 1.5–2 million people show symptoms or complications (Hong and Fang 2012; Qian et al. 2013). Clonorchiasis has brought a severe disease burden to the endemic areas of several Asian countries, especially China (Fürst et al. 2012). Now, more than 140 years have passed since the discovery of *C. sinensis*, we have a deep understanding of the lifecycle and epidemiological features of this liver fluke. Moreover, developments regarding the omics of *C. sinensis* and the pathogenesis of clonorchiasis have brought diversified perspectives for study of new antiparasitic agents, appropriate diagnostic and vaccine targets (Qian et al. 2016; Tang et al. 2016a).

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ORIGINAL ARTICLE – CANCER RESEARCH

Comprehensive gene and microRNA expression profiling reveals a role for miRNAs in the oncogenic roles of SphK1 in papillary thyroid cancer

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Abstract
Purpose The oncogenic roles of sphingosine kinase 1 (SphK1) in various cancers, including thyroid cancer, have been well demonstrated. However, the microRNAs (miRNAs) associated with the oncogenic roles of SphK1 remain largely unknown.
Methods Global gene and miRNA expression in TPC1-Vector and TPC1-SphK1 cells was analyzed using digital gene expression (DGE) analysis and small RNA-seq, respectively. miRNA–mRNA interactions were explored by microT-CDS, and the predicted networks were visualized using CytoScape®. Cell invasion and migration were assessed by performing Transwell invasion and wound-healing assays. Luciferase reporter and immunoblot assays were used to evaluate the targeting of fibronectin 1 (FN1) by miR-144-3p.
Results In this study, we found that overexpression of SphK1 differentially regulates the expression of 46 miRNAs and 506 mRNAs in papillary thyroid cancer (PTC) TPC1 cells. Combining bioinformatics predictions of mRNA targets with DGE data on mRNA expression allowed us to identify the mRNA targets of deregulated miRNAs. The direct interaction between miR-144-3p and FN1, which mediates the pro-invasive role of SphK1 in PTC cells, was experimentally validated.
Conclusions Our results demonstrated that SphK1 overexpression drives a regulatory network governing miRNA and mRNA expression in PTC cells. We also demonstrated the roles played by miR-144-3p and FN1 in mediating the oncogenic function of SphK1, which enhanced the understanding of the etiology of PTC.

Keywords SphK1 · Papillary thyroid cancer · Invasion · miR-144-3p · FN1

Introduction

Thyroid cancer is the most common endocrine malignancy and is one of the most rapidly growing cancer diagnoses in the world (Jemal et al. 2011). Follicular epithelial cell-derived thyroid cancer is classified into the following three main histological types: papillary thyroid cancer (PTC), follicular thyroid cancer (FTC) and anaplastic thyroid cancer (ATC). PTC is the most common type of thyroid cancer, as the disease accounts for 85–90% of cases (Siegel et al. 2015). In general, most patients with PTC have a favorable prognosis. However, some patients develop extrathyroidal invasion and lymph node metastases, which leads to a poor prognosis. Therefore, a clear understanding of the molecular mechanisms involved in the development and progression of PTC remains necessary for developing new therapeutic targets.

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AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Coproduction of MCR-1 and NDM-1 by Colistin-Resistant *Escherichia coli* Isolated from a Healthy Individual

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KEYWORDS *Escherichia coli*, *mcr-1*, bla_{NDM-1}

The first transferable plasmid-mediated colistin resistance gene, *mcr-1* was reported in *Escherichia coli* isolates from food animals, food, and patients in China and now has been reported worldwide (1). Furthermore, cocarriage of *mcr-1* and bla_{NDM} has been reported in *E. coli* and other members of the family *Enterobacteriaceae* from a chicken meat sample; patients with peritonitis, urinary tract infections, and rectal cancer; and a Muscovy duck, all in China. Most recently, *E. coli* carrying *mcr-1* and bla_{NDM-5} was isolated from a patient with a urinary tract infection in the United States (2–7). Here, we report asymptomatic carriage of *E. coli* harboring both *mcr-1* and bla_{NDM-1} in an otherwise healthy individual.

A total of 151 nonduplicate, serial fecal specimens were collected from 98 inpatients and 53 healthy individuals at Guangdong General Hospital in Guangzhou, China, during the first week of January 2016 for the purpose of detecting extended-spectrum β-lactamase-producing *Enterobacteriaceae*. Each sample was screened on a Columbia blood agar plate without any antibiotics and then subcultured on MacConkey agar with 2 μg/ml cefotaxime. Colonies selected from the MacConkey agar were identified to the species level by the API 20E system (bioMérieux, Marcy l'Etoile, France) and 16S rRNA gene sequencing (8). As a result, 73 nonduplicate *E. coli* isolates were collected from 58 inpatients and 15 healthy individuals. Of these isolates, 17 were found to harbor *mcr-1* by PCR assay and sequencing performed as previously described (1, 8). Of the 17 *mcr-1*-carrying *E. coli* isolates, 2 were from clinical cultures of inpatients, 12 were from rectal surveillance cultures of inpatients, and 3 (*E. coli* GB049, GB090, and GB135) were from healthy individuals who provided rectal cultures with stool specimens after consent during outpatient visits for their annual physical examinations. Since carriage of *mcr-1* by healthy individuals is of particular epidemiologic interest, we analyzed these three strains further.

E. coli GB049 was recovered from a 23-year-old male, *E. coli* GB090 was from a 68-year-old female, and *E. coli* GB135 was from a 56-year-old female. These healthy individuals were all nonvegetarian, living in the city >10 km from commercial animal farms, drinking the municipal water, had received a secondary or tertiary education, had a mid to high socioeconomic status, and had traveled overseas. The individual with *E. coli* GB049 traveled in India for 5 days in September 2015; and the other two individuals with *E. coli* GB090 and GB135 traveled to the United States for 9 and 15 days, respectively, in December 2015. In addition, the individual with *E. coli* GB090 had taken oral amoxicillin for several days for her respiratory symptoms 3 months earlier.

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AUTHOR CORRECTION

Correction for Yang et al., "Cross Talk between Histone Deacetylase 4 and STAT6 in the Transcriptional Regulation of Arginase 1 during Mouse Dendritic Cell Differentiation"

Quan Yang,[a] Jianyang Wei,[a] Limei Zhong,[a] Maohua Shi,[a] Pan Zhou,[a] Shengkai Zuo,[c] Kang Wu,[a] Mingjiang Zhu,[c] Xi Huang,[a,b] Ying Yu,[c] Hui Zhang,[a,b] Huiyong Yin,[c] Jie Zhou[a,b]

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Volume 35, no. 1, p. 63–75, 2015, https://doi.org/10.1128/MCB.00805-14. Page 68, Fig. 4E: The HDAC5 and HDAC6 panels are very similar and may have been inadvertently duplicated. The corrected panels (top and bottom, respectively) should appear as shown below. This change does not alter the results or conclusions of the study.

Citation Yang Q, Wei J, Zhong L, Shi M, Zhou P, Zuo S, Wu K, Zhu M, Huang X, Yu Y, Zhang H, Yin H, Zhou J. 2017. Correction for Yang et al., "Cross talk between histone deacetylase 4 and STAT6 in the transcriptional regulation of arginase 1 during mouse dendritic cell differentiation." Mol Cell Biol 37:e00289-17. https://doi.org/10.1128/MCB.00289-17.

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Corrigendum

Corrigendum to "Niclosamide inhibits lytic replication of Epstein-Barr virus by disrupting mTOR activation" [(Antivir. Res.) 138 (2017) 68–78]

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The authors regret that that in the published article there was an error in "S6K" image in Fig 6A. The corrected one is appearing below. This correction does not affect any scientific conclusion of this article.

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ORIGINAL ARTICLE

Cryo-EM structures of the 80S ribosomes from human parasites *Trichomonas vaginalis* and *Toxoplasma gondii*

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As an indispensable molecular machine universal in all living organisms, the ribosome has been selected by evolution to be the natural target of many antibiotics and small-molecule inhibitors. High-resolution structures of pathogen ribosomes are crucial for understanding the general and unique aspects of translation control in disease-causing microbes. With cryo-electron microscopy technique, we have determined structures of the cytosolic ribosomes from two human parasites, *Trichomonas vaginalis* and *Toxoplasma gondii*, at resolution of 3.2-3.4 Å. Although the ribosomal proteins from both pathogens are typical members of eukaryotic families, with a co-evolution pattern between certain species-specific insertions/extensions and neighboring ribosomal RNA (rRNA) expansion segments, the sizes of their rRNAs are sharply different. Very interestingly, rRNAs of *T. vaginalis* are in size comparable to prokaryotic counterparts, with nearly all the eukaryote-specific rRNA expansion segments missing. These structures facilitate the dissection of evolution path for ribosomal proteins and RNAs, and may aid in design of novel translation inhibitors.

***Keywords*:** cryo-electron microscopy; ribosome; translation; *Trichomonas vaginalis*; *Toxoplasma gondii*; RNA
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Introduction

The ribosome is responsible for protein biosynthesis in all living organisms, and also plays diverse roles in regulating various cellular activities [1-4]. Nearly half of the naturally occurring antibiotics target prokaryotic 70S ribosomes to inhibit protein translation [5]. Eukaryotic ribosomes are also targets of many small-molecule inhibitors [6]. Given the essentiality of the ribosome and the abnormal activity of translation in many types of cancers, the ribosome-related processes have been emerging as targets for novel cancer drug development [7]. Over the past decades, an increasing number of high-resolution structures of the ribosomes from different species have been obtained (i.e., see [8-22]). Many of these structures are in complex with small-molecule inhibitors (i.e., see [5, 6, 11, 23-26]). With these structures, diverse mechanisms of small molecule-based inhibition have been elucidated in atomic details. Therefore, high-resolution structures of specific ribosomes, especially those from human pathogens are urgently needed not only for the elaboration of their unique translation regulation components but also for the structure-based drug design to overcome the increasing health threat from drug-resistant pathogens.

Trichomonas vaginalis, a hydrogenosome-contain-

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RESEARCH ARTICLE

*Cs*severin inhibits apoptosis through mitochondria-mediated pathways triggered by Ca^{2+} dyshomeostasis in hepatocarcinoma PLC cells

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Abstract

Background

Numerous experimental and epidemiological studies have demonstrated a link between *Clonorchis sinensis* (*C. sinensis*) infestation and cholangiocarcinoma (CCA) as well as hepatocellular carcinoma (HCC). The underlying molecular mechanism involved in the malignancy of CCA and HCC has not yet been addressed. *Cs*severin, a component of the excretory/secretory products of C. *sinensis* (*Cs*ESPs), was confirmed to cause obvious apoptotic inhibition in the human HCC cell line PLC. However, the antiapoptotic mechanism is unclear. In the present study, we investigated the cellular features of the antiapoptotic mechanism upon transfection of the *Cs*severin gene.

Methods

In the present study, we evaluated the effects of *Cs*severin gene overexpression on the apoptosis of PLC cells using an Annexin PE/7-AAD assay. Western blotting was applied to quantify the activation of caspase-3 and caspase-9, the mitochondrial translocation of Bax and the release of Cyt c upon *Cs*severin overexpression in PLC cells. Laser scanning confocal microscopy was used to analyze the changes of intracellular calcium. Fluorescence assay and immunofluorescence assays were performed to observe the changes of the mitochondrial permeability transition pore (MPTP).

Results

The overexpression of *Cs*severin in PLC cells showed apoptosis resistance after the induction of apoptosis. Additionally, the activation of caspase-3 and caspase-9 was specifically

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Deficiency of pigment epithelium-derived factor in nasopharyngeal carcinoma cells triggers the epithelial–mesenchymal transition and metastasis

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Distant metastasis is the primary cause of nasopharyngeal carcinoma (NPC) treatment failure while epithelial–mesenchymal transition (EMT) is the critical process of NPC invasion and metastasis. However, tumor-suppressor genes involved in the EMT and metastasis of NPC have not been explored clearly compared with the oncogenes. In the present study, the expression of pigment epithelium-derived factor (PEDF), a potent endogenous antitumor factor, was diminished in human NPC tissues and associated with clinicopathological and EMT features. The knockdown of PEDF induced EMT in lower metastatic NPC cell lines and overexpression of PEDF restored epithelial phenotype in higher metastatic NPC cell lines with typical EMT. The inhibition of PEDF mediated NPC cell spontaneous metastasis *in vivo*. LRP6/GSK3β/β-catenin signal pathway rather than AKT/GSK3β pathway was involved in the effects of PEDF on EMT. The expression of PEDF was directly downregulated by elevated miR-320c in NPC. In conclusion, our findings indicate for the first time that PEDF functions as tumor-suppressor gene in the occurrence of EMT and metastasis in NPC. PEDF could serve as a promising candidate for NPC diagnosis, prognosis and treatment.
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Nasopharyngeal carcinoma (NPC) is prevalent in southern China and South-East Asia, with an annual incidence rate of about 25–30 per 100 000 people, wheras it is rare in the Western world (1 per 100 000).[1] Although NPC is sensitive to radiotherapy and chemotherapy, the overall 5-year survival rate of NPC patients is around 80%, 20–30% patients develop distant metastasis or loco-regional recurrence eventually leading to death.[2] Therefore, understanding the mechanism of NPC metastasis and identification of effective anti-nasopharyngeal carcinoma metastasis drugs have been emerging as a promising direction for the treatment of NPC.

Recent studies have shown that epithelial–mesenchymal transition (EMT) is closely related to tumor metastasis. EMT occurs in embryogenesis, fibrosis and invasion of the tumor. They have many common characteristics, such as the loss of the connection between epithelial cells and epithelial cell phenotypic markers, increases mesenchymal markers and endows cell migration ability.[3] EMT is closely related to the invasion and metastasis of NPC as well, inhibition of NPC cell's EMT could significantly suppress the metastasis of NPC.[4–7]

The canonical Wnt/β-catenin pathway is involved in various biological processes, including embryonic development, stem cell maintenance and tumorigenesis. When Wnt/β-catenin pathway was activated, the core protein β-catenin translocates into cell nucleus and directly involve in gene transcription and cell adhesion.[8] Zeng *et al.*[9] and co-workers observed Wnt pathway was abnormally activated in NPC using nasopharyngeal tissue array. It has been reported that activation of Wnt/β-catenin pathway by oncogenes could promote EMT and metastasis in NPC.[10–12] However, tumor-suppressor genes involved in the EMT and metastasis of NPC have not been identified.

Pigment epithelium-derived factor (PEDF) is a potent and versatile endogenous inhibitor of angiogenesis.[13] Previous studies demonstrated that PEDF is a favorable prognostic indicator in colorectal, pancreatic, lung and breast cancer.[14–17] There is a complex mechanism underlying the antitumor effects of PEDF, which includes inhibition of angiogenesis and tumor cell migration, induction of apoptosis and pro-tumor differentiation in certain tumor cell types.[18] However, it is still unclear the exact role of endogenous PEDF in EMT occurrence and NPC metastasis. Previously, we have reported that PEDF could bind

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Design, synthesis, and biological evaluation of novel 7-deazapurine nucleoside derivatives as potential anti-dengue virus agents

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ABSTRACT

Dengue fever, caused by four distinct serotypes of dengue virus (DENV-1 to -4), has become the fastest spreading human infectious disease in recent years. Despite extensive efforts, there is no specific antiviral treatment approved for dengue until now. Nucleoside inhibitors represent an actively pursued area to develop small-molecule anti-dengue virus agents. In this study, we designed and synthesized a series of 7-deazapurine nucleoside derivatives and evaluated their anti-DENV activity. Our design strategy and structure activity relationship studies revealed **6e** as the most potent inhibitor (EC_{50} = 2.081 ± 1.102 μM) of DENV replication. **6e** suppressed RNA levels and DENV E protein expression, without causing any apparent cytotoxicity in A549 and HepG2 cells (CC_{50} = 150.06 ± 11.42 μM, SI = 72.11 in A549 cells, and CC_{50} = 146.47 ± 11.05 μM and SI = 63.7 in HepG2 cells). In addition, **6e** showed similar inhibition potency against four serotypes of DENV, suggesting that it restrains some evolutionarily conserved targets essential for DENV replication. We conceive that **6e** may serve as a promising lead compound for anti-DENV drug development.

1. Introduction

Dengue fever, an acute systemic infection caused by dengue virus (DENV), has become one of the most burdensome and fastest spreading human infectious diseases (Shepard et al., 2016). DENV comprises four distinct serotypes (DENV-1 to -4), and represents the most prevalent mosquito-borne viral pathogen in humans. The global public health impact of dengue has rapidly increased in recent years, affecting over 2.5 billion people worldwide with an estimated annual epidemics of 390 million human infections, of which, 96 million manifest clinically (Bhatt et al., 2013). Over the past 50 years, the global incidence of dengue has grown dramatically and DENV is now endemic in more than 100 tropical and subtropical countries of the world. The year 2015 was particularly marked with worst dengue outbreaks worldwide, as compared to the previous year 2014. Sharp increases in dengue occurrence rates were reported in countries like Philippines (169, 000 cases), Malaysia (111, 000 cases), Brazil (1.5 million cases), and India (15, 000 cases only in Delhi), and many other countries continued to record cases until 2016 (WHO, 2016). Different factors, including unplanned rapid urbanization, climate changes and migration, have created a perfect storm for dengue expansion (Gubler, 2002; Simmons et al., 2012). According to World Health Organization (WHO) reports of 2015–2016, about half of the world's population is now at risk of dengue infection (WHO, 2016).

Therapeutically, there is no specific antiviral treatment approved for tackling rapidly increasing dengue outbreaks, except a recently introduced (in late 2015) first dengue vaccine Dengvaxia® by Sanofi Pasteur (Vannice et al., 2016; World Health, 2017). Dengvaxia has been registered now for use in individuals 9–45 years living in endemic countries. There are also some other vaccine candidates (based on subunit, DNA and purified inactivated virus platforms) at earlier stages of clinical development (For some recent reviews, see references (Martin and Hermida, 2016; Rothman and Ennis, 2016; Vannice et al., 2016; Wilder-Smith and Yoon, 2016)), which indicates that significant

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ORIGINAL PAPER

Diagnosis of *Strongyloides stercoralis* by morphological characteristics combine with molecular biological methods

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Abstract Strongyloidiasis is one of the neglected tropical diseases caused by infection with the nematode *Strongyloides* genus and distributed worldwide. Strongyloidiasis can be fatal in immunosuppressed patients induced hyperinfection or disseminated strongyloidiasis. Unfortunately, until now, due to the unspecific clinical symptom in infected individuals and the low sensitivity diagnosis of strongyloidiasis, many patients were misdiagnosed every year. Furthermore, the larvae of the *Strongyloides stercoralis* (*S. stercoralis*) is similar to other nematodes such as hookworm, *Trichostrongylus* increased the difficulty of diagnosis. In this case, the patient is a 63-year-old male person, who had a nearly 30 years medical history of asthma and emphysema, and 4–5-year medical history of diabetes. The sputum examination found some parasite larvae, then we identify the larvae using clinical observation and morphological characteristics combine with examined cytochrome oxidase subunit 1 (COX1) and 18S rRNA genes by PCR, sequence analysis and finally classified by phylogenetic analysis, the larvae were diagnosed as *S. stercoralis*. Our results showed that diagnosis with strongyloidiasis by morphological characteristics combine with molecular biological methods can improve the sensitive of diagnosis and provide a final diagnosis for the disease in the clinics.

Keywords Strongyloidiasis · *Strongyloides stercoralis* · COX1 · 18S rRNA · Morphological characteristics · Molecular biological methods

Introduction

Strongyloidiasis, one of the neglected tropical diseases but widespread parasitic disease, is caused by infection with the nematode *Strongyloides stercoralis* and to a lesser extent by the zoonotic species *Strongyloides fuelleborni* (Beknazarova et al. 2016; Rodpai et al. 2016). S. *stercoralis* is common recognized parasite spread in tropical and subtropical areas, where heat and humidity favor the growth of helminths in general. According to conservative estimates, over 370 million people spread the world were infected (Bisoffi et al. 2013). *S. stercoralis* is a soil-transmitted helminth (STH); it has some peculiarities character which different from the other STHs. *S. stercoralis* has the ability to develop two distinct reproductive cycles: one asexual cycle inside the human host allowing autoinfection and the other involving sexual reproduction into the soil (Duvignaud et al. 2016). *S. stercoralis* infect human by filariform larvae through intact skin penetration; the larvae can either penetrate the intestinal mucosa and remain in the human organism (Ericsson et al. 2001).

S. stercoralis infection can cause gastrointestinal symptoms, skin problems and dermatitis or respiratory symptoms, including abdominal pain, diarrhea, nausea, vomiting, pruritus, dermatitis, cough, asthma, and dyspnea (Hochberg et al. 2001; Mascarello et al. 2011). Strongyloidiasis can be fatal in a few days or weeks in immunosuppressed patients hyperinfection or disseminated strongyloidiasis (Requena-

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Diagnostic accuracy of a selected signature gene set that discriminates active pulmonary tuberculosis and other pulmonary diseases

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Summary *Objective:* We validated the accuracy of host selected signature gene set using unstimulated whole blood (WB), and peripheral blood mononuclear cells (PBMC) in the diagnosis of tuberculosis (TB).
Methods: The unstimulated WB and PBMC from 1417 individuals with active pulmonary TB patients, other lung diseases and healthy participants were analyzed using real time polymerase chain reaction (RT-PCR).
Results: The WB cohort test demonstrates that the combination of *GBP5* and *KLF2* can differentiate active TB versus HC with sensitivity and specificity of 77.8% and 87.1%, respectively; but most importantly active TB versus OD with sensitivity and specificity of 96.1% and 85.2%, respectively. Again during treatment course, the TB score of *GBP5* and *KLF2*, analytes secretion and clinical parameters were found to be associated in disease progression. In the PBMC cohort test, we found that the only and best discriminatory combination was *GBP5*, *DUSP3* and *KLF2* in

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Parasites & Vectors

RESEARCH Open Access

Distribution and current infection status of *Biomphalaria straminea* in Hong Kong

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Abstract

Background: Schistosomiasis, also generally known as snail fever, is a parasitic disease caused by trematode flatworms of the genus *Schistosoma*. In Hong Kong and mainland China, the freshwater snail *Biomphalaria straminea* has been introduced and has the potential to transmit intestinal schistosomiasis caused by *S. mansoni*, a parasite of man which has a wide distribution in Africa and parts of the New World, especially Brazil. The first identification of *B. straminea* in Hong Kong dates back to the 1970s, and its geographical distribution, phylogenetic relationships, and infection status have not been updated for more than 30 years. Thus, this study aims to reveal the distribution and current infection status of *B. straminea* in contemporary Hong Kong.

Methods: Snails were collected from different parts of Hong Kong from July 2016 to January 2017. Both anatomical and molecular methods were applied to identify *B. straminea*. Cytochrome *c* oxidase subunit 1 (*cox*1), internal transcribed spacer 1 (ITS1), 5.8S rDNA, internal transcribed spacer 2 (ITS2), and 16S ribosomal DNA (rDNA) were sequenced from individual snails and analyzed. To detect the presence of *S. mansoni*, both biopsy and PCR analyses were carried out.

Results: Using both anatomical and molecular analyses, this study demonstrated the existence of black- and red-coloured shell *B. straminea* in different districts in the New Territories in Hong Kong, including places close to the mainland China border. None of the *B. straminea* ($n = 87$) investigated were found to be infected with *S. mansoni* when tested by biopsy and PCR. The Hong Kong *B. straminea* are genetically indistinguishable, based on the chosen molecular markers (*cox*1, ITS1-5.8S-ITS2, and 16S rDNA), and are similar to those obtained in mainland China and South America.

Conclusion: *Biomphalaria straminea* is now well established in freshwater habitats in Hong Kong. No evidence of infection with *S. mansoni* has been found. Surveillance should be continued to monitor and better understand this schistosomiasis intermediate host in mainland China and Hong Kong.

Keywords: Schistosomiasis, *Schistosoma mansoni*, *Biomphalaria straminea*, Hong Kong, China

Background

With an estimate of almost 240 million people infected worldwide, schistosomiasis is considered by the World Health Organization as the second most prevalent parasitic disease after malaria. This disease remains a global health problem resulting in economic and social burdens [1]. One of the most widespread of the human-infecting species is *Schistosoma mansoni*, which is estimated to infect more than 80 million people globally. Intestinal schistosomiasis caused by *S. mansoni* occurs in Africa, Madagascar, the Middle East, the Caribbean, Brazil, Venezuela and Suriname.

Infections with *S. mansoni* in humans are initiated by the release of cercariae by various species of freshwater snails of the genus *Biomphalaria*; cercariae penetrate the skin of people when exposed in water. Given the parasite

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Downregulation of autophagy-related gene ATG5 and GABARAP expression by IFN-λ1 contributes to its anti-HCV activity in human hepatoma cells

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ABSTRACT

Type-III interferon (IFN-λ), the most recently discovered family of IFNs, shares common features with type I IFNs, but also has many distinctive activities. It is not clear that whether IFN-λ has additional antiviral mechanisms. In this study, we investigated the effects of IFN-λ on autophagy, a cellular process closely related to hepatitis C virus (HCV) infection in human hepatoma Huh7 cells. Our results showed that IFN-λ1 treatment inhibit autophagic activity in Huh7 cells, as evidenced by the decreased expression of microtubule-associated protein 1 light chain 3B (LC3B)-II and conversion of LC3B-I to LC3B-II, decreased formation of GFP-LC3 puncta and accumulation of autophagosomes. IFN-λ1 could also inhibit HCV-induced or tunicamycin (a known inducer of autophagy with similar mechanism to HCV infection) -induced LC3B-II expression and autophagosome formation. Through PCR array, real time RT PCR, and western blot, two autophagy-related genes, ATG5 and GABARAP, were identified and verified to be down-regulated by IFN-λ1 treatment, either in HCV-uninfected Huh7 cells or in HCV JFH-1-infected cells. Overexpression of ATG5 and/or GABARAP could partly recover the IFN-λ1-inhibited HCV replication. Mechanism research demonstrated that IFN-λ1 could induce the expression of miR-181a and miR-

Abbreviations: IFN-λ, interferon-λ; HCV, hepatitis C virus; LC3B, microtubule-associated protein 1 light chain 3B; HCC, hepatocellular carcinoma; DAAs, directly acting antivirals; SVR, sustained virological response; PEG-IFN/RBV, polyethylene glycol interferon-α/ ribavirin; IFN-λR1, IFN-λ receptor 1; GWASs, genome-wide association studies; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HSV-1, herpes simplex virus 1; PRRs, pattern-recognition receptors; JAK, Janus kinase; TYK, tyrosine kinase; DMEM, Dulbecco's modified Eagle's medium; FBS, fetal bovine serum; NEAA, non-essential amino acids; MOI, multiplicity of infection; TEM, Transmission electron microscopy; ISGs, interferon-stimulated genes; ER, endoplasmic reticulum; PE, phosphatidylethanolamine; PAS, pre-autophagosomal structure; PAMP, pathogen-associated molecular pattern; RIG-I, retinoic acid−inducible gene I; Tu, tunicamycin.

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Molecular Cancer

RESEARCH Open Access

Epigenetic down regulation of G protein-coupled estrogen receptor (GPER) functions as a tumor suppressor in colorectal cancer

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Abstract

Background: Estrogenic signals are suggested to have protection roles in the development of colorectal cancer (CRC). The G protein-coupled estrogen receptor (GPER) has been reported to mediate non-genomic effects of estrogen in hormone related cancers except CRC. Its expression and functions in CRC were investigated.

Methods: The expression of GPER and its associations with clinicopathological features were examined. The mechanisms were further investigated using cells, mouse xenograft models, and clinical human samples.

Results: GPER was significantly ($p < 0.01$) down regulated in CRC tissues compared with their matched adjacent normal tissues in our two cohorts and three independent investigations from Oncomine database. Patients whose tumors expressing less ($n = 36$) GPER showed significant ($p < 0.01$) poorer survival rate as compared with those with greater levels of GPER ($n = 54$). Promoter methylation and histone H3 deacetylation were involved in the down regulation of GPER in CRC cell lines and clinical tissues. Activation of GPER by its specific agonist G-1 inhibited proliferation, induced cell cycle arrest, mitochondrial-related apoptosis and endoplasmic reticulum (ER) stress of CRC cells. The upregulation of reactive oxygen species (ROS) induced sustained ERK1/2 activation participated in G-1 induced cell growth arrest. Further, G-1 can inhibit the phosphorylation, nuclear localization, and transcriptional activities of NF-κB via both canonical IKKα/ IκBα pathways and phosphorylation of GSK-3β. Xenograft model based on HCT-116 cells confirmed that G-1 can suppress the in vivo progression of CRC.

Conclusions: Epigenetic down regulation of GPER acts as a tumor suppressor in colorectal cancer and its specific activation might be a potential approach for CRC treatment.

Keywords: GPER, G-1, CRC, NF-κB, ROS

Background

Colorectal cancer (CRC), also called colon cancer or large bowel cancer, is the second most common cause of cancer death and accounts for almost 10% of all reported cancer cases in the world [1]. Given the high incidence in the aging population and high mortality rates of CR, new prevention strategies are needed. Clinical data revealed that the incidence of colon cancer is significantly ($p < 0.05$) lower in women than in men, which may be due to the presence of estrogens [2]. Postmenopausal women receiving combined hormone replacement therapy will significantly reduce the risk of colorectal cancer [3, 4]. Further, young women (18–44 years old) of colorectal cancer have a better overall survival compared with men of the same age [5]. However, this protection is lost when a woman reaches menopause. Cellular and animal studies also suggested role of estrogens in the reduction of colon

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Parasites & Vectors

RESEARCH Open Access

Establishment of a medium-scale mosquito facility: optimization of the larval mass-rearing unit for *Aedes albopictus* (Diptera: Culicidae)

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Abstract

Background: Standardized larval rearing units for mosquito production are essential for the establishment of a mass-rearing facility. Two larval rearing units, developed respectively by the Guangzhou Wolbaki Biotech Co. Ltd. (Wolbaki) and Insect Pest Control Laboratory, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture (FAO/IAEA-IPCL), are tested to assess their potential uses to mass-rear the larval stages of *Aedes albopictus* in support of the establishment of a medium-scale mosquito facility for the application of mosquito genetic control strategies.

Methods: The triple *Wolbachia*-infected *Ae. albopictus* strain (HC strain) was used in this study. The effects of larval densities of two larval rearing trays (corresponding to 2.4, 3.0 and 3.6 larvae/cm^2) and tray size/position (top, middle and bottom layers) on the pupae production and larval survival were assessed when trays were stacked within the larval rearing units. The male pupae production, female pupae contamination after sex separation, and male mating competitiveness were also studied by using both larval rearing units in their entirety.

Results: The optimal larval rearing density for Wolbaki-tray (Wol-tray) was 6,600 larvae (equal to 3.0 larvae/cm^2) and 18,000 larvae (3.6 larvae/cm^2) for the FAO/IAEA-IPCL tray (IAEA-tray). No significant difference in pupae production was observed when trays were stacked within top, middle or bottom layers for both units. At thirty-four hours after the first pupation, the average male pupae production was (0.89×10^5) for the Wol-unit and (3.16×10^5) for the IAEA-unit. No significant difference was observed in female pupae contamination between these two units. The HC males showed equal male mating competitiveness to wild type males for mating with wild type females in large cages, regardless of whether they were reared in the Wol-unit or IAEA-unit.

Conclusions: The current study has indicated that both the Wol-unit and IAEA-unit are suitable for larvae mass-rearing for *Ae. albopictus*. However, the IAEA-unit, with higher male production and less space required compared to the Wol-unit, is recommended to be used in support of the establishment of a medium-sized mosquito facility.

Keywords: Mosquito facility, Larval rearing units, Mass-rearing, *Aedes albopictus*

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Establishment of mouse leukemia cell lines expressing human CD4/CCR5 using lentiviral vectors

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Abstract A low-cost rodent model of HIV infection and which presents high application value is an effective tool to investigate HIV infection and pathogenesis. However, development of such a small animal model has been hampered by the unsuitability of rodent cells for HIV-1 replication given that the retrovirus HIV-1 has high selectivity to its host cell. Our study used the mouse leukemia cell lines L615 and L1210 that were induced by murine leukemia virus and transfected with hCD4/CCR5 loaded-lentiviral vector. Lentiviral vectors containing the genes hCD4/CCR5 under the transcriptional control of cytomegalovirus promoter were designed. Transfection efficiencies of human CD4 and CCR5 in L615 and L1210 cells were analyzed by quantitative real-time polymerase chain reaction (RT-PCR) and Western blot assay. Results showed that hCD4 and CCR5 proteins were expressed on the cell surface, demonstrating that the L615 and L1210 cells were humanized and that they possess the characteristics necessary for HIV infection of human host cells. Moreover, the sensitivity of human CD4/CCR5 transgenic mouse cells to HIV infection was confirmed by RT-PCR and ELISA. Mouse leukemia cell lines that could express hCD4 and CCR5 were thus established to facilitate normal entry of HIV-1 so that a human CD4/CCR5 transgenic mice cell model can be used to investigate the transmission and pathogenesis of HIV/AIDS and potential antiviral drugs against this disease.

Keywords HIV-1 · Mouse leukemia cell lines (L615 and L1210) · Gene transfer · Lentiviral vectors · CD4 · CCR5

Introduction

Establishment of appropriate cell models of acquired immune deficiency syndrome (AIDS) is critical in better understanding the pathogenesis of immune deficiency

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PLOS ONE

RESEARCH ARTICLE

Estimating the basic reproduction rate of HFMD using the time series SIR model in Guangdong, China

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Data Availability Statement: Due to ethical restrictions, part of relevant data are within the paper and its Supporting Information files. A confidential agreement concerning the disclosure of the HFMD cases data has been signed between the authors and China Center for Disease Control and Prevention (China CDC). All interested readers may contact China CDC to request the data (data@chinacdc.cn).

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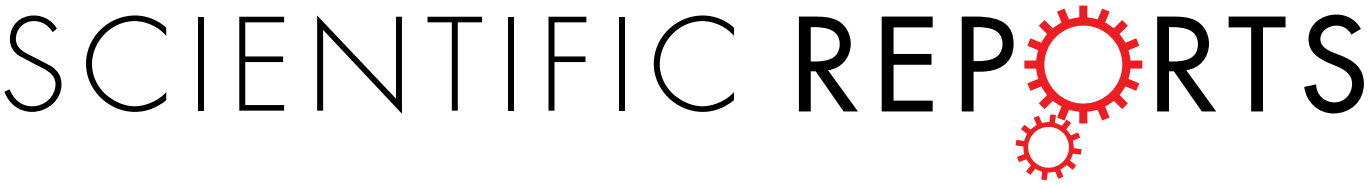
Abstract

Hand, foot, and mouth disease (HFMD) has caused a substantial burden of disease in China, especially in Guangdong Province. Based on notifiable cases, we use the time series Susceptible-Infected-Recovered model to estimate the basic reproduction rate (R0) and the herd immunity threshold, understanding the transmission and persistence of HFMD more completely for efficient intervention in this province. The standardized difference between the reported and fitted time series of HFMD was 0.009 (<0.2). The median basic reproduction rate of total, enterovirus 71, and coxsackievirus 16 cases in Guangdong were 4.621 (IQR: 3.907–5.823), 3.023 (IQR: 2.289–4.292) and 7.767 (IQR: 6.903–10.353), respectively. The heatmap of R0 showed semiannual peaks of activity, including a major peak in spring and early summer (about the 12th week) followed by a smaller peak in autumn (about the 36th week). The county-level model showed that Longchuan (R0 = 33), Gaozhou (R0 = 24), Huazhou (R0 = 23) and Qingxin (R0 = 19) counties have higher basic reproduction rate than other counties in the province. The epidemic of HFMD in Guangdong Province is still grim, and strategies like the World Health Organization's expanded program on immunization need to be implemented. An elimination of HFMD in Guangdong might need a Herd Immunity Threshold of 78%.

Introduction

Hand, foot and mouth disease (HFMD) is a major public health issue in China, affecting over two million children annually [1, 2]. Particularly, the incidence of HFMD in Guangdong Province exceeded 30/10,000 per year, which was more than three times the national average [3, 4]. An efficient intervention, a necessary and important action to prevent and control the spread of diseases, hinges on a complete understanding of the transmission and persistence of HFMD.



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Excessive fruit consumption during the second trimester is associated with increased likelihood of gestational diabetes mellitus: a prospective study

Wu-Qing Huang[1,*], Ying Lu[1,2,*], Ming Xu[1], Jing Huang[1], Yi-Xiang Su[3] & Cai-Xia Zhang[1]

This study aimed to investigate the association between fruit consumption during the second trimester and the occurrence of gestational diabetes mellitus (GDM). A prospective study with 772 female participants was conducted in China from April 2013 to August 2014. Dietary intake was assessed in face-to-face and telephone interviews using a 3-day food record. GDM was ascertained using a standard 75 g 2 hour oral glucose tolerance test. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) after adjustment for various confounders. Of the 772 participants, 169 were diagnosed with GDM during the period under study. Greater total fruit consumption during the second trimester was associated with a higher likelihood of GDM (highest vs. lowest quartile: adjusted OR4.82, 95% CI 2.38 to 9.76). Fruits with a moderate or high glycaemic index (GI) were positively associated with the occurrence of GDM. Fruit subgroups were also categorised by polyphenol content, and tropical-fruit and citrus-fruit consumption was found to be positively related to the occurrence of GDM. These findings suggest that the excessive consumption of fruit, especially fruit with moderate or high GI values, tropical-fruit and citrus-fruit, increases the likelihood of GDM.

The recorded prevalence of gestational diabetes mellitus (GDM) in China has increased sharply, from about 5% to more than 16%, since the implementation of a new method of diagnosing GDM in December 2011[1,2]. GDM is associated with an increased risk of adverse pregnancy and perinatal outcomes and long-term adverse health consequences for both mother and child[3]. Therefore, it is urgently necessary to identify risk factors for GDM. Dietary factors are amongst the most important modifiable factors. With the improvement of living standards, fruit consumption in China has drastically increased, to the extent that an appreciable proportion of pregnant women in China today consume fruit to excess[4]. Fruit is abundant in fibre, antioxidants and phytochemicals, which have beneficial health effects[5,6]. However, some kinds of fruit also contain high levels of sugar (e.g., fructose), the excessive intake of which is likely to be harmful to human health[7,8]. Epidemiological studies have generated mixed results regarding the relationship between fruit consumption and type 2 diabetes (T2D) risk[9–12]. Although the Nurses' Health Study (NHS) II investigated the association between pre-pregnancy habitual fruit consumption and GDM risk, the specific effects of fruit consumption during pregnancy have not yet been examined[13]. One study investigated the association between dietary habits and GDM risk among Cantonese women in China. The results revealed a tendency for excessive fruit consumption by Cantonese women during pregnancy and a positive association between the consumption of fruit with a high glycaemic index (GI) and GDM risk[4].

In addition, the GI and polyphenol content, which have been suggested to be related to blood-glucose metabolism, differ substantially between types of fruit[14,15]. One study indicated that fruits with a moderate GI played a protective role in T2D[16]. Meanwhile, interest in polyphenols has increased notably over the past decade due to

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JLB

Article

Expansion and activation of granulocytic, myeloid-derived suppressor cells in childhood precursor B cell acute lymphoblastic leukemia

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ABSTRACT

Precursor B cell acute lymphoblastic leukemia (B-ALL) is a B cell–derived, malignant disorder with the highest incidence among children. In addition to the genetic abnormality, a dysregulated immune system also has an important role in the pathogenesis of B-ALL. Myeloid-derived suppressor cells (MDSCs) represent one of the key drivers in immune tolerance against tumor cells, including various solid tumors and hematologic malignancies. The role of MDSCs in B-ALL remains poorly understood. Here, we showed that the granulocytic (G)-MDSC population was significantly elevated in both the peripheral blood and BM of patients with B-ALL, when compared with age-matched healthy controls. G-MDSCs levels correlated positively with clinical therapeutic responses and B-ALL disease prognostic markers, including minimal residual disease, and the frequencies of $CD20^+$ and blast cells. The immunosuppressive function of B-ALL–derived G-MDSCs was mediated through the production of reactive oxygen species and required direct cell–cell contact, with the potential participation of STAT3 signaling. Overall, the results of our study support accumulation and activation of G-MDSCs as a novel mechanism of immune evasion of tumor cells in patients with B-ALL and may be a new therapeutic target. *J. Leukoc. Biol.* 102: 449–458; 2017.

Introduction

B-ALL is a malignancy of precursor B cells with the highest incidence among children [1]. Although most children with B-ALL can be cured by current chemotherapy, relapsed patients remain at a very high risk of death, and adult patients with ALL have even worse clinical outcomes [2]. In addition to genetic abnormalities, a dysregulated immune system facilitates the immune evasion of cancer cells in hematologic malignancies, including B-ALL [3–5]. Understanding the mechanism of immune dysfunction in B-ALL will benefit the discovery of effective immunotherapy.

MDSCs are a heterogeneous population of progenitor and immature myeloid cells that acquire potent immunosuppressive functions [6]. In mice, MDSCs are defined as $CD11b^+Gr1^+$ cells [7]. Human MDSCs usually express the common myeloid markers CD33 and CD11b but lack expression of HLA-DR [8]. Because of their heterogeneous nature, MDSCs can be further divided into 2 subsets: M-MDSCs and G-MDSCs or polymorphonuclear MDSCs [9]. These 2 subsets differ in many aspects, including cellular morphology, gene profiling, tissue distribution, and suppressive functions [10, 11]. M-MDSCs suppress T cell responses in an Ag-nonspecific manner, predominantly by up-regulating arginase-1 and iNOS [12]. G-MDSCs suppress Ag-specific T cell responses by enhancing the generation of ROS [13, 14].

The expansion and activation of MDSCs are driven by soluble factors secreted from the tumor microenvironment. These factors include IL-6, granulocyte-Mϕ CSF, and vascular endothelial growth factor, among others [15]. The expansion of MDSCs represents a major driver of immunotolerance in cancer-bearing hosts, including solid tumors and hematologic malignancies [16–18]. The expanded MDSCs exert strong suppressive effects on antitumor immunity by inhibiting effector immune

Abbreviations: B-ALL = precursor B cell acute lymphoblastic leukemia, B-ALL-DX = B-ALL before treatment, BM = bone marrow, G-MDSC = granulocytic myeloid-derived suppressor cell, MDSC = myeloid-derived suppressor cell, MM = multiple myeloma, M-MDSC = monocytic myeloid-derived suppressor cell, MRD = minimal residual disease, qRT-PCR = quantitative reverse transcription–PCR, ROS = reactive oxygen species

The online version of this paper, found at www.jleukbio.org, contains supplemental information.

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Expansion of monocytic myeloid-derived suppressor cells in endometriosis patients: A pilot study

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ABSTRACT

Endometriosis is a chronic inflammation disease and is closely associated with immune dysregulation. Myeloid-derived suppressor cells (MDSCs) are a negative regulator of the immune system. The aim of this study was to evaluate the possible role of MDSCs in endometriosis patients. We collected the peripheral blood and peritoneal fluid from endometriosis patients and controls and analyzed M-MDSCs level using specific monoclonal antibodies recognizing HLA-DR, CD33, CD11b, CD14 markers by flow cytometry. We found that there existed abnormal expansion of monocytic MDSCs (M-MDSCs) (HLA-DR$^{-/low}$CD33^{+} CD11b^{+} CD14^{+}) in peripheral blood and peritoneal fluid of patients with endometriosis. Functional studies revealed that M-MDSCs from endometriosis patients significantly suppressed T-cell responses and produced high level of reactive oxygen species (ROS). The elevation of M-MDSCs from endometriosis patients may contribute to the disease progression.

1. Introduction

Endometriosis is a chronic disease in which endometrial tissue is found outside the uterus, mainly on the pelvic peritoneum and/or ovaries. The symptoms caused by endometriosis include chronic pelvic pain, menstrual disorders, pelvic inflammatory reactions and infertility [1–2].

Multiple lines of evidence have suggested that endometriosis is associated with the changes of local and systemic immunity. However, the underlying mechanisms are diverse, including dysfunction of T and B cells; increased levels of various proinflammatory cytokines and angioregulatory cytokines, such as IL-6, IL-1 and TNF-α; reduced NK cell activity and the production of auto-antibodies [1–5]. One recent study showed that the percentage of CD25^{high}Foxp3^{+} Treg cells was significantly increased in endometriosis patients [6]. These studies collectively suggest a close relationship between endometriosis and the impaired immune response. Other immune cells with immunosuppression function may participate in the pathogenesis of endometriosis.

Myeloid-derived suppressor cells (MDSCs), are a heterogeneous population of myeloid progenitor cells that cannot fully differentiate into mature myeloid cells under some pathological conditions, such as cancer, autoimmune disorders and inflammatory diseases [7–12]. The main feature of MDSCs is their immunosuppression function, especially towards T cells in a context-dependent manner [8]. Human MDSCs with the phenotype of HLA-DR$^{-/low}$CD11b^{+}CD33^{+}, can be further divided into two major subsets: monocytic MDSCs (M-MDSC), which are CD14^{+}CD15^{-} cells and granulocytic MDSCs (G-MDSC), which express CD15 but not CD14 [8–9]. These two subsets differ in many aspects, such as immunosuppressive activity, tissue distribution, morphology and surface markers [8–9].

To our knowledge, little is known about the role of MDSCs in the pathogenesis of endometriosis, though MDSCs were found to be important in maintaining materno–fetal tolerance [13–14]. Therefore, the aim of our present study was to investigate the level and function of MDSCs in the peripheral blood and peritoneal fluid of patients with endometriosis.

2. Materials and methods

2.1. Subjects

In this study, Endometriosis (Endo) patients were recruited at Affiliated Guangzhou Women and Children's Medical Center, Guangzhou, China. A number of 32 women (mean age 29 years, range 18–38)

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Research Article

Favorable Outcomes of Chinese HCV-Related Cirrhotic Patients with Sustained Virological Response after Pegylated Interferon Plus Ribavirin Treatment

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Few studies have conducted follow-up investigations of the clinical course in HCV-related cirrhotic patients who achieved a sustained virological response (SVR) with pegylated interferon plus ribavirin treatment (PegIFN + RBV). We investigated the clinical course and laboratory data in a prospective cohort study enrolling HCV-related cirrhotic patients who received PegIFN + RBV between August 2008 and July 2013 in China. Complete blood counts, liver function tests, and HCV-RNA were serially examined. Liver-related complications were recorded. To detect hepatocellular carcinoma (HCC), alpha-fetoprotein assays, and ultrasound scans were repeated at 6-month intervals. Twenty-five patients were enrolled, including 8 patients with decompensation events before treatment. Eighteen patients achieved SVR with a mean follow-up period of 25.78 months. During the follow-up period, only one patient exhibited HCV-RNA positivity and no decompensation events were detected, but 4 patients developed HCC after SVR. APRI decreased more in patients with SVR than in patients with non-SVR (median, −1.33 versus 0.86, $P < 0.001$). The albumin levels and platelet counts significantly increased during the follow-up period after SVR (44.27 ± 4.09 versus 42.63 ± 4.37, $P = 0.037$ and 173.89 ± 87.36 versus 160.11 ± 77.97, $P = 0.047$). These data indicated that HCV-related cirrhotic patients with SVR after PegIFN + RBV may have a favorable clinical course and improvements in laboratory data. Moreover, HCC should be monitored.

1. Introduction

Approximately 25–50 million Chinese were infected with hepatitis C virus (HCV) [1]. Without treatment, 16% of patients with HCV progress to liver cirrhosis within 20 years after infection, and 41% develop liver cirrhosis within 30 years [2]. As the patients infected with HCV age, the risk of developing life-threatening complications (decompensated cirrhosis or hepatocellular carcinoma) is expected to increase [3]. The annual risk of developing decompensated liver diseases has been shown to be 4% in cirrhotic patients. The annual mortality is 13% for patients with decompensated liver disease, and the ten-year survival rate is only 25% [4]. Thus, these cirrhotic patients infected with HCV make a significant burden on public health.

Before the introduction of direct-acting antiviral agents (DAAs), the combination of pegylated interferon and ribavirin (subsequently referred to as PegIFN + RBV) was the approved treatment for chronic hepatitis C (CHC) [5]. The incidence of developing hepatic events (decompensation, hepatocellular carcinoma (HCC) and death) reduced in patients with sustained virological response (SVR) [6–8]. A report showed that interferon therapy could be associated with a reduction of HCC development even in patients without SVR [8]. Moreover, successful antiviral therapy in selected patients waiting for liver transplantation could delay

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BMC Genetics

METHODOLOGY ARTICLE Open Access

Generalized disequilibrium test for association in qualitative traits incorporating imprinting effects based on extended pedigrees

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Abstract

Background: For dichotomous traits, the generalized disequilibrium test with the moment estimate of the variance (GDT-ME) is a powerful family-based association method. Genomic imprinting is an important epigenetic phenomenon and currently, there has been increasing interest of incorporating imprinting to improve the test power of association analysis. However, GDT-ME does not take imprinting effects into account, and it has not been investigated whether it can be used for association analysis when the effects indeed exist.

Results: In this article, based on a novel decomposition of the genotype score according to the paternal or maternal source of the allele, we propose the generalized disequilibrium test with imprinting (GDTI) for complete pedigrees without any missing genotypes. Then, we extend GDTI and GDT-ME to accommodate incomplete pedigrees with some pedigrees having missing genotypes, by using a Monte Carlo (MC) sampling and estimation scheme to infer missing genotypes given available genotypes in each pedigree, denoted by MCGDTI and MCGDT-ME, respectively. The proposed GDTI and MCGDTI methods evaluate the differences of the paternal as well as maternal allele scores for all discordant relative pairs in a pedigree, including beyond first-degree relative pairs. Advantages of the proposed GDTI and MCGDTI test statistics over existing methods are demonstrated by simulation studies under various simulation settings and by application to the rheumatoid arthritis dataset. Simulation results show that the proposed tests control the size well under the null hypothesis of no association, and outperform the existing methods under various imprinting effect models. The existing GDT-ME and the proposed MCGDT-ME can be used to test for association even when imprinting effects exist. For the application to the rheumatoid arthritis data, compared to the existing methods, MCGDTI identifies more loci statistically significantly associated with the disease.

Conclusions: Under complete and incomplete imprinting effect models, our proposed GDTI and MCGDTI methods, by considering the information on imprinting effects and all discordant relative pairs within each pedigree, outperform all the existing test statistics and MCGDTI can recapture much of the missing information. Therefore, MCGDTI is recommended in practice.

Keywords: Generalized disequilibrium test, Genomic imprinting, Monte Carlo sampling, Qualitative trait

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Research paper

Genetic analyses of Chinese isolates of *Toxoplasma gondii* reveal a new genotype with high virulence to murine hosts

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ABSTRACT

A great deal of evidence demonstrates that a strongly clonal population structure of *Toxoplasma gondii* strains exists in humans and animals in North America and Europe, while the strains from South America are genetically separate and more diverse. Potential differences in virulence between different strains mean that an understanding of strain diversity is important to human and animal health. However, to date, only one predominant genotype, ToxoDB#9 (Chinese I), and a few other genotypes, including ToxoDB#205, have been identified in China. By using DNA sequence-based phylogenetic analyses, we have re-evaluated the population structure of *T. gondii* strains collected from China and compared them with other global strains. Based on phylogenetic analysis of restriction fragment length polymorphisms, multilocus sequence typing and intron sequences from *T. gondii*, we propose that the Chinese isolates described as Chinese I are divided into two groups called Chinese I and Chinese III. Our results demonstrate that significant differences were found in mouse mortality caused by some Chinese strains, and also the archetypal I, II, III strains in mice. Furthermore, a comparison of cyst loading in the brains of infected rats showed some Chinese strains to be capable of a high degree of cyst formation. Furthermore we show that genotyping using neutral genetic markers may not be a useful predictor of pathogenic phenotypes.

1. Introduction

Toxoplasma gondii is an important, globally distributed, intracellular parasite and provides a valuable model system to understand the evolution of intracellular pathogens. It not only infect large numbers of warm blooded animals including birds, livestock and humans, but also marine mammals (Dubey, 2010; Montoya and Liesenfeld, 2004). Animals and humans are mainly infected by ingesting food or water contaminated with *T. gondii* oocysts or consuming raw or undercooked meat containing parasite cysts (Dubey and Beattie, 1988). The life cycle of the parasite includes domestic cats and other felids as definitive hosts (Frenkel et al., 1970) while virtually all warm-blooded vertebrates can act as intermediate hosts (Dubey and Beattie, 1988). In the intermediate hosts, *T. gondii* undergoes asexual reproduction as either tachyzoites, during acute infection, or bradyzoites (cysts) during chronic infection. In the definitive host it goes through sexual reproduction to produce a high output (many millions daily) of the highly infective oocyst stage.

However, despite the sexual reproductive phase in the life cycle, initially only a few genotypes were recognized in *T. gondii* and were referred to as type I, II, and III. These archetypal types, all together, accounted for 95% of the strains isolated in North America and Europe (Ajzenberg et al., 2002; Howe and Sibley, 1995). In addition, these strains (type I, II, and III) also predominate in chickens from Africa, where a higher prevalence of type II and III were found (Velmurugan et al., 2008). Intriguingly, although the differences at the genomic level among the three main lineages are less than 1%, the virulence phenotypes in mice can differ markedly. Typically, type I strains are uniformly lethal ($LD_{100} = 1$) to mice; in contrast, types II and III strains are less virulent ($LD_{50} \geq 10^5$) (Howe and Sibley, 1995; Khan et al., 2009; Sibley and Boothroyd, 1992). These archetypal strains are typically identified by techniques such as restriction fragment length polymorphism (RFLP) (Pena et al., 2008) or microsatellite analysis (Lehmann et al., 2006). These techniques have been widely used for genotyping a broad range of organisms (Anderson et al., 2000; Cameron et al., 1988; Hide and Tait, 2009; Widmer et al., 2004; Severson et al.,

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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Genome-wide SNPs reveal the drivers of gene flow in an urban population of the Asian Tiger Mosquito, *Aedes albopictus*

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Data Availability Statement: Aligned sequences for 152 *Aedes albopictus* have been deposited at NCBI SRA (https://www.ncbi.nlm.nih.gov/sra/), with accession numbers SAMN07738910 - SAMN07739061. Geographical coordinates of each sample have also been deposited and are retrievable with the above.

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Abstract

Aedes albopictus is a highly invasive disease vector with an expanding worldwide distribution. Genetic assays using low to medium resolution markers have found little evidence of spatial genetic structure even at broad geographic scales, suggesting frequent passive movement along human transportation networks. Here we analysed genetic structure of *Aedes albopictus* collected from 12 sample sites in Guangzhou, China, using thousands of genome-wide single nucleotide polymorphisms (SNPs). We found evidence for passive gene flow, with distance from shipping terminals being the strongest predictor of genetic distance among mosquitoes. As further evidence of passive dispersal, we found multiple pairs of full-siblings distributed between two sample sites 3.7 km apart. After accounting for geographical variability, we also found evidence for isolation by distance, previously undetectable in *Ae. albopictus*. These findings demonstrate how large SNP datasets and spatially-explicit hypothesis testing can be used to decipher processes at finer geographic scales than formerly possible. Our approach can be used to help predict new invasion pathways of *Ae. albopictus* and to refine strategies for vector control that involve the transformation or suppression of mosquito populations.

Author summary

Aedes albopictus, the Asian Tiger Mosquito, is a highly invasive disease vector with a growing global distribution. Designing strategies to prevent invasion and to control *Ae. albopictus* populations in invaded regions requires knowledge of how *Ae. albopictus* disperses. Studies comparing *Ae. albopictus* populations have found little evidence of genetic structure even between distant populations, suggesting that dispersal along human transportation networks is common. However, a more specific understanding of dispersal processes has been unavailable due to an absence of studies using high-resolution genetic markers.

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Microbiome

RESEARCH Open Access

Gut symbiont enhances insecticide resistance in a significant pest, the oriental fruit fly *Bactrocera dorsalis* (Hendel)

Daifeng Cheng[1†], Zijun Guo[1†], Markus Riegler[2], Zhiyong Xi[3,4], Guangwen Liang[1] and Yijuan Xu[1*]

Abstract

Background: Symbiotic bacteria affect insect physiology and ecology. They may also mediate insecticide resistance within their hosts and thereby impact pest and vector control practices. Here, we document a novel mechanism of insecticide resistance in which a gut symbiont of the tephritid pest fruit fly *Bactrocera dorsalis* enhances resistance to the organophosphate insecticide trichlorphon.

Results: We demonstrated that the gut symbiont *Citrobacter* sp. (CF-BD) plays a key role in the degradation of trichlorphon. Based on a comparative genomics analysis with other *Citrobacter* species, phosphatase hydrolase genes were identified in CF-BD. These CF-BD genes had higher expression when trichlorphon was present. *Bactrocera dorsalis* inoculated with isolated CF-BD obtained higher trichlorphon resistance, while antibiotic-treated flies were less resistant confirming the key role of CF-BD in insecticide resistance.

Conclusions: Our findings suggest that symbiont-mediated insecticide resistance can readily develop in *B. dorsalis* and may represent a more widely relevant insecticide resistance mechanism than previously recognized.

Keywords: Symbiotic bacteria, Insecticide resistance, Trichlorphon, *Bactrocera dorsalis*, Oriental fruit fly

Background

Insects can possess symbiotic microorganisms in their gut lumen, in specialized organs, or within cells [1–4]. In general, such microbial partners can contribute to the nutrition of various insect groups [5], defense against natural enemies [6], reproductive traits [7], and other physiological and ecological properties of insects [8–12]. Some symbiotic bacteria also mediate detoxification of insect diets [13–16] and, similarly, of insecticides, therefore conferring insecticide resistance to their hosts as it has originally been discovered for the apple maggot *Rhagoletis pomonella* [17] and more recently demonstrated for stinkbugs [18, 19].

Chemical insecticides have been widely used to control insect pests and vectors [20]; however, many insect pests and vectors have evolved strong resistance to a diverse range of insecticides. The mechanisms underlying insecticide resistance vary across pesticides and include changes of drug target sites, increased expression of degrading enzymes, and enhanced drug excretion [21, 22]. The frequent failure of chemical control has globally drawn major research attention to resistance mechanisms and management. For example, it has been determined that certain bacteria also possess the ability to degrade pesticides [23, 24], suggesting that symbiotic bacteria of insects may also contribute to insecticide resistance. However, besides the examples of *R. pomonella* [17] and stinkbugs [18], it is not known whether bacterially facilitated insecticide resistance also occurs in other insect pest taxa of economic significance and, further, what the general mechanisms of symbiont-facilitated insecticide resistance are.

Previous studies have found that intensive insecticide application can accelerate insecticide biodegradation in the environment [25, 26], including by bacteria that are capable of degrading organophosphorus compounds [27]. Studies have found that the biochemistry of organophosphorus compound degradation is identical in most bacteria. The functional enzyme in this process, organophosphate hydrolase or phosphotriesterase, is an

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Identification of a novel compound targeting the nuclear export of influenza A virus nucleoprotein

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Abstract

Although antiviral drugs are available for the treatment of influenza infection, it is an urgent requirement to develop new antiviral drugs regarding the emergence of drug-resistant viruses. The nucleoprotein (NP) is conserved among all influenza A viruses (IAVs) and has no cellular equivalent. Therefore, NP is an ideal target for the development of new IAV inhibitors. In this study, we identified a novel anti-influenza compound, ZBMD-1, from a library of 20,000 compounds using cell-based influenza A infection assays. We found that ZBMD-1 inhibited the replication of H1N1 and H3N2 influenza A virus strains *in vitro*, with an IC_{50} ranging from 0.41–1.14 μM. Furthermore, ZBMD-1 inhibited the polymerase activity and specifically impaired the nuclear export of NP. Further investigation indicated that ZBMD-1 binds to the nuclear export signal 3 (NES3) domain and the dimer interface of the NP pocket. ZBMD-1 also protected mice that were challenged with lethal doses of A/PR/8/1934 (H1N1) virus, effectively relieving lung histopathology changes, as well as strongly inhibiting the expression of pro-inflammatory cytokines/chemokines, without inducing toxicity effects in mice. These results suggest that ZBMD-1 is a promising anti-influenza compound which can be further investigated as a useful strategy against IAVs in the future.

Keywords: influenza A virus • compound ZBMD-1 • nucleoprotein • nuclear export

Introduction

Influenza A virus (IAV) is an important human viral pathogen that is responsible for periodic human pandemics as well as seasonal influenza, resulting in substantial human morbidity and mortality and a worldwide financial burden annually [1–3]. Vaccines are currently available to control infections in humans. However, mutations in the haemagglutinin (HA) and neuraminidase (NA) proteins of circulating viruses easily escape the surveillance by the host immune system [4]. Specific antiviral drugs are available for prophylaxis and therapeutic treatment for individuals infected with IAV. Two classes of Food and Drug Administration (FDA)-approved anti-influenza drugs are currently used in the treatment of IAV infections including NA inhibitors such as oseltamivir and zanamivir [5], and matrix protein 2 (M2) ion channel inhibitors such as amantadine and rimantadine [6, 7]. However, resistance development is a serious problem for antiviral drugs, particularly when the target viral proteins continuously undergo a high frequency of antigenic drift [8–10]. Most human influenza viruses, including pandemic 2009 H1N1 and H7N9, are currently resistant to amantadine/rimantadine or oseltamivir [11–14]. Therefore, identification of novel antiviral targets and development of antiviral drugs for the treatment of influenza virus infections are imperative.

The viral nucleoprotein (NP) of influenza A virus has recently been identified as a target for development of antiviral drugs [15–19].

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Microbiome

RESEARCH Open Access

Gut symbiont enhances insecticide resistance in a significant pest, the oriental fruit fly *Bactrocera dorsalis* (Hendel)

Daifeng Cheng[1†], Zijun Guo[1†], Markus Riegler[2], Zhiyong Xi[3,4], Guangwen Liang[1] and Yijuan Xu[1*]

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Results: We demonstrated that the gut symbiont *Citrobacter* sp. (CF-BD) plays a key role in the degradation of trichlorphon. Based on a comparative genomics analysis with other *Citrobacter* species, phosphatase hydrolase genes were identified in CF-BD. These CF-BD genes had higher expression when trichlorphon was present. *Bactrocera dorsalis* inoculated with isolated CF-BD obtained higher trichlorphon resistance, while antibiotic-treated flies were less resistant confirming the key role of CF-BD in insecticide resistance.

Conclusions: Our findings suggest that symbiont-mediated insecticide resistance can readily develop in *B. dorsalis* and may represent a more widely relevant insecticide resistance mechanism than previously recognized.

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Previous studies have found that intensive insecticide application can accelerate insecticide biodegradation in the environment [25, 26], including by bacteria that are capable of degrading organophosphorus compounds [27]. Studies have found that the biochemistry of organophosphorus compound degradation is identical in most bacteria. The functional enzyme in this process, organophosphate hydrolase or phosphotriesterase, is an

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Full length article

Immune response induced by oral delivery of *Bacillus subtilis* spores expressing enolase of *Clonorchis sinensis* in grass carps (*Ctenopharyngodon idellus*)

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ABSTRACT

Clonorchiasis, caused by the consumption of raw or undercooked freshwater fish containing infective metacercariae of *Clonorchis sinensis*is (*C.sinensis*), remains a common public health problem. New effective prevention strategies are still urgent to control this food-borne infectious disease. The previous studies suggested *Bacillus subtilis* (*B. subtilis*) spores was an ideal vaccines delivery system, and the *C.sinensis* enolase (*Cs*ENO) was a potential vaccine candidate against clonorchiasis. In the current study, we detected *Cs*ENO-specific IgM levels by ELISA in sera, intestinal mucus and skin mucus in grass carps (*Ctenopharyngodon idella*) through oral administration with *B. subtilis* spores surface expressing *Cs*ENO. In addition, immune-related genes expression was also measured by qRT-PCR. Grass carps orally treated with *B. subtilis* spores or normal forages were used as controls. The results of ELISA manifested that specific IgM levels of grass carps in *Cs*ENO group in sera, intestine mucus and skin mucus almost significantly increased from week 4 post the first oral administration when compared to the two control groups. The levels of specific IgM reached its peak in intestine mucus firstly, then in sera, and last in skin mucus. qRT-PCR results showed that 5 immune-related genes expression had different degree of rising trend in *Cs*ENO group when compared to the two control groups. Our study demonstrated that orally administrated with *B. subtilis* spores expressing *Cs*ENO induced innate and adaptive immunity, systemic and local mucosal immunity, and humoral and cellular immunity. Our work may pave the way to clarify the exact mechanisms of protective efficacy elicited by *B. subtilis* spores expressing *Cs*ENO and provide new ideas for vaccine development against *C. sinensis* infection.

1. Introduction

Clonorchiasis is a serious zoonotic parasitic disease, which is widely prevalent in most Southeast Asian regions such as China, Korea, Vietnam and Russia. It is estimated that approximately 15 million people are infected with this neglected tropical disease globally, of whom nearly 13 million are in China, accounting for more than 85%, and it still presents increment trend [1]. In spite of using many integrated control tactics, it was still hard to eradicate this food-borne parasitosis.

People who infected with *Clonorchis sinensis* (*C. sinensis*) are mainly because of eating raw or undercooked freshwater fish containing infective metacercariae, so cutting off transmission route by interrupting the formation of metacercaria in freshwater fish would be an effective strategy to control clonorchiasis. Vaccine is one of the most effective way to prevent infectious diseases. Studies have shown that fish could be vaccinated by injection, immersion or oral administration. Oral vaccination would be an ideal method for its easy operation, needle-free and feasibility of large-scale promotion.

Our previous studies had found that *C. sinensis* enolase (*Cs*ENO) was the key molecule in the development of metacercaria, and good immune protective efficacy had been obtained by applying it

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ORIGINAL ARTICLE

IRF7 regulates the development of granulocytic myeloid-derived suppressor cells through S100A9 transrepression in cancer

Q Yang[1,2,3], X Li[2,4], H Chen[2], Y Cao[2], Q Xiao[2], Y He[2], J Wei[2] and J Zhou[1,2,3,5]

Accumulation of myeloid-derived suppressor cells (MDSCs) is one of the major obstacles against achieving appropriate anti-tumor immune responses and successful tumor immunotherapy. Granulocytic MDSCs (G-MDSCs) are common in tumor-bearing hosts. However, the mechanisms regulating the development of MDSCs, especially G-MDSCs, remain poorly understood. In this report, we showed that interferon regulatory factor 7 (IRF7) plays an important role in the development of G-MDSCs, but not monocytic MDSCs. IRF7 deficiency caused significant elevation of G-MDSCs, and therefore enhanced tumor growth and metastasis in mice. IRF7 deletion did not affect the suppressive activity of G-MDSCs. Mechanistic studies showed that S100A9, a negative regulator of myeloid cell differentiation, was transrepressed by the IRF7 protein. S100A9 knockdown almost completely abrogated the effects of IRF7 deletion on G-MDSC development and tumor metastasis. Importantly, IRF7 expression levels negatively correlated with the G-MDSC frequency and tumor metastasis, as well as S100A9 expression, in cancer patients. In summary, our study demonstrated that IRF7 represents a novel regulator of G-MDSC development in cancer, which may have predictive value for tumor progression.

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INTRODUCTION

Myeloid-derived suppressor cell (MDSC) expansion has established roles in suppressing anti-tumor immunity in tumor-bearing hosts.[1,2] Targeting MDSCs, therefore, has become a promising strategy for tumor immunotherapy.[3] Some important transcription factors and signaling pathways have been implicated in regulating tumor-derived MDSCs.[4–11] The detailed mechanisms, however, remain to be fully elucidated.

Mouse MDSCs are characterized by coexpression of the myeloid markers Gr1 and CD11b, and can be further classified into monocytic (M-MDSCs) and granulocytic (G-MDSCs) subsets, based on expression of the Ly6G and Ly6C epitopes, respectively.[12] Human MDSC phenotypes are context-dependent, usually HLA-$DR^-CD33^+CD11b^+$, and subtypes are determined by the expression of CD14, CD15 and other markers.[13] These 2 subsets differ with respect to functions, tissue distribution and regulatory mechanisms.[14] Interestingly, most tumor-derived MDSCs are granulocytic.[15] Elucidation of the signaling events controlling MDSC subsets, which is poorly understood, will facilitate the development of effective MDSC-based tumor immunotherapy.

To gain insight into the mechanism underlying the expansion of tumor-derived MDSCs, we performed a microarray analysis of splenic MDSCs from tumor-bearing mice and corresponding control cells from naive mice. Interferon regulatory factor 7 (IRF7) was highly differentially expressed between MDSCs and control cells. IRF7 exerts broad biological functions.[16] For example, IRF7 plays a critical role in interferon (IFN)-mediated anti-viral immunity by transcriptionally controlling IFN-α and IFN-β in plasmacytoid dendritic cells (DCs).[17] IRF7 also participates in tumor progression, although conflicting results have been reported by different groups.[18–20] Bidwell *et al.* found that silencing IRF7 expression promoted breast cancer metastasis to the bones in an IFN-dependent manner, which may have involved host immunity. IRF7 expression inversely correlated with tumor progression and clinical outcomes.[20] Compared with the understanding of IRF7 in tumor biology, its function in tumor immunology remains poorly understood.[21]

In this study, we found that mice lacking IRF7 showed an increased rate of tumor metastasis, which was caused by enhanced G-MDSC development. The myeloid cell regulator S100A9, identified as novel target of IRF7, mediated the effects of IRF7 on MDSCs. Results from cancer patients further support the importance of IRF7 in regulating G-MDSC levels and tumor progression.

RESULTS

IRF7 deficiency in the host facilitates tumor metastasis

To study the effect of IRF7 expression on tumor progression, we established tumor growth and tumor metastasis models in wild type (WT) and IRF7 knockout (KO) mice, using the B16-F10 melanoma and Lewis lung carcinoma (LLC) tumor cell lines.[7,22,23] The results showed that mice lacking IRF7 displayed moderately faster tumor growth than did WT controls (Supplementary Figure S1). In addition, a dramatically higher metastatic rate was observed in IRF7-KO mice, as indicated by the percentage of

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ORIGINAL ARTICLE

Kallistatin inhibits lymphangiogenesis and lymphatic metastasis of gastric cancer by downregulating VEGF-C expression and secretion

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Abstract

Background Tumor-induced lymphangiogenesis and lymphatic metastasis are predominant during the metastasis of many types of cancers. However, the endogenous inhibitors that counterbalance the lymphangiogenesis and lymphatic metastasis of tumors have not been well evaluated. Kallistatin has been recognized as an endogenous angiogenesis inhibitor.

Methods and results Our recent study showed for the first time that the lymphatic vessel density (LVD) was reduced in lung and stomach sections from kallistatin-overexpressing transgenic mice. Kallistatin expresses anti-lymphangiogenic activity by inhibiting the proliferation, migration, and tube formation of human lymphatic endothelial cells (hLECs). Therefore, the present study focuses on the relationships of changes in kallistatin expression with the lymphangiogenesis and lymphatic metastasis of gastric cancer and its underlying mechanisms. Our results revealed that the expression of kallistatin in cancer tissues, metastatic lymph nodes, and plasma of gastric cancer patients was significantly downregulated and that the plasma level of kallistatin was negatively associated with the phase of lymph node metastasis. Furthermore, treatment with kallistatin recombinant protein decreased LVD and lymph node metastases in the implanted gastric xenograft tumors of nude mice. Mechanically, kallistatin suppressed the lymphangiogenesis and lymphatic metastasis by downregulating VEGF-C expression and secretion through the LRP6/IKK/IκB/NF-κB signaling pathway in gastric cancer cells.

Conclusions These findings demonstrated that kallistatin functions as an endogenous lymphangiogenesis inhibitor and has an important part in the lymphatic metastasis of gastric cancer.

Keywords Kallistatin · Lymphangiogenesis · LRP6 · NF-κB · VEGF-C · Lymph node metastasis · Gastric cancer

Caiqi Ma, Chuanghua Luo, and Haofan Yin contributed equally to this study.

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Trials

STUDY PROTOCOL Open Access

Laser peripheral iridotomy versus laser peripheral iridotomy plus laser peripheral iridoplasty in the treatment of multi-mechanism angle closure: study protocol for a randomized controlled trial

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Abstract

Background: China has the largest burden of primary angle-closure glaucoma (PACG) worldwide. The mechanism of the angle closure is complex and includes pupillary block and non-pupillary block. Currently, opinion is that laser peripheral iridotomy (LPI) alone is not sufficient to prevent disease progression. Laser peripheral iridoplasty (LPIP) is an alternative and effective way of widening the angle recess in eyes that are affected by primary angle closure (PAC). However, it is not known if greater benefit would be achieved using LPI plus LPIP for PAC with multiple mechanisms (MAC). Thus, the aim of this study is to demonstrate if LPI plus LPIP would be more effective than single LPI in controlling the progression of PAC with multiple mechanisms, based on ultrasound biomicroscopy (UBM) classification. A secondary aim is to determine whether or not this would result in the use of less medication and/or prolong the time to antiglaucoma surgery.

Methods: This multiple-mechanism angle-closure study will comprise a 3-year, multicenter, randomized, parallel-group, open-label, superiority trial, the aim of which will be to evaluate the safety and efficacy of LPI plus LPIP versus LPI for PAC. It is anticipated that 240 adults, diagnosed with PAC (the mechanism of angle closure will be assessed by UBM and it will be determined whether or not it involves multiple mechanisms) will be recruited from ten ophthalmic centers in China. Participants will be randomly allocated to receive either single LPI or LPI plus LPIP. Participant assessment will be designed to test the rate of disease progression and who will be followed up for 3 years. The primary outcome will be the disease progression rate and a comparison will be made between the LPI and LPI plus LPIP groups using Pearson's χ^2 test. Logistic regression analysis will be performed to account for the central effect.

(Continued on next page)

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REVIEW

Lessons from a 15-year-old boy with advanced schistosomiasis japonica in China: a case report

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Abstract Schistosomiasis is a chronic, parasitic disease caused by flukes (trematodes) of the genus *Schistosoma*, which presents the most important global burden of the 17 neglected tropical diseases listed by the World Health Organization. China has made great achievements in schistosomiasis control, and now China is planning to move forward, to eliminate schistosomiasis within 2020, but the fact cannot be denied that the possibility of schistosome infection is still there in some endemic due to its zoonotic nature as well as wide distribution of its intermediate hosts (snails). Thus, how to interrupt the transmission in areas with distribution of schistosomes and intermediate snails becomes a very serious challenge that China is facing. In this paper, it is reported an advanced schistosomiasis japonica case of a 15-year-old boy which is extremely rare in the current schistosomiasis control in China. Thus, it is supposed to strengthen health education of school children and to train professional physicians of local hospitals.

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Keywords *Schistosoma japonicum* · Advanced schistosomiasis · P. R. China

Introduction

Schistosomiasis is a disease of poverty, caused by a chronic infection with parasitic platyhelminthes of the genus *Schistosoma*, presenting the greatest public health and global burden of the 17 neglected tropical diseases listed by the World Health Organization (WHO 2006, 2010, 2015). People acquire such an infection by regular exposure to the cercaria-contaminated water (Colley et al. 2014). Of the five schistosome species infecting humans, *Schistosoma japonicum* is the only blood fluke that occurs in the People's Republic of China (China) (WHO 2016). After years of endeavors, including strengthening health systems, mass chemotherapy, clean water supply, health education, and snail control, China has been able to reduce morbidity, and prevalence of schistosomiasis japonica profoundly and succeeded even to interrupt transmission in many endemic areas (Zhang et al. 2016; Xu et al. 2016; Utzinger et al. 2005). Critical issues confronting China are that the distribution areas infested with *Oncomelania hupensis* snail, which is the intermediate host of *S. japonicum*, remains broad despite continued and intensified control efforts. Due to its zoonotic nature, the potential risk of getting a schistosome infection still exists even in previously cleaned endemic areas (He et al. 2001; Zheng et al. 2013). Although the number of schistosomiasis cases declines constantly, the number of advanced stage patients sustained, probably due to the pathological process as well as large-scale screening and aid program of advanced schistosomiasis which started in 2005 (Song et al. 2016). The disease burden of schistosomiasis is mainly attributed to the advanced stage, associated with diffuse hepatic fibrosis, liver cirrhosis, portal

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RESEARCH Open Access

Levels of hepatic Th17 cells and regulatory T cells upregulated by hepatic stellate cells in advanced HBV-related liver fibrosis

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Abstract

Background: Liver fibrosis which mainly occurs upon chronic hepatitis virus infection potentially leads to portal hypertension, hepatic failure and hepatocellular carcinoma. However, the immune status of Th17 and Treg cells in liver fibrosis is controversial and the exact mechanisms remain largely elusive.

Methods: Liver tissues and peripheral blood were obtained simultaneously from 32 hepatitis B virus infected patients undergoing surgery for hepatocellular carcinoma at the medical center of Sun Yat-sen University. Liver tissues at least 3 cm away from the tumor site were used for the analyses. Levels of Th17 cells and regulatory T cells were detected by flow cytometry analysis and immunohistochemistry. In vitro experiment, we adopted magnetic cell sorting to investigate how hepatic stellate cells regulate the levels of Th17 cells and regulatory T cells.

Results: We found that hepatic Th17 cells and regulatory T cells were increased in patients with advanced stage HBV-related liver fibrosis. Hepatic stellate cells upregulated the levels of Th17 cells and regulatory T cells via PGE2/EP2 and EP4 pathway.

Conclusions: We found that the increased levels of Th17 cells and regulatory T cells were upregulated by hepatic stellate cells. These results may provide insight into the role of hepatic stellate cells and Th17 cells and regulatory T cells in the persistence of fibrosis and into the occurrence of hepatocellular carcinoma following cirrhosis.

Keywords: Th17 cells, Regulatory T cells, Hepatic stellate cells, Liver fibrosis, HCC

Background

Liver fibrosis is the wound-healing response of the liver to many causes of chronic injury, of which hepatitis B virus (HBV) infection is the most common in China [1]. Hepatic stellate cells (HSC) have dominated studies exploring mechanisms of liver fibrosis over the last two decades [2]. Characterizing the interaction of HSC with immune cells is a research priority, yet has been largely overlooked until recently [3]. Moreover, chronic liver injury is associated with varying degrees of hepatic fibrosis, yet its relationship to immune cells status is unknown. In recent studies, we have established that activated HSC from patients suffering from hepatitis B can modulate the phenotype and function of monocytes and NK cells [4–6]. These findings support the hypothesis that HSC from hepatitis B patients plays an important role in regulating the immune status of hepatic fibrosis.

IL17-producing CD4+ T (Th17) cells and regulatory T cells (Tregs) have been recognized as unique subsets of effector T cells that are distinct from the Th1 and Th2

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REVIEW

Liver fluke infection and cholangiocarcinoma: a review

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Abstract Parasites are significant groups for carcinogenesis among which liver flukes, including *Opisthorchis viverrini* and *Clonorchis sinensis*, are typical representatives causing cholangiocarcinoma (CCA), the second most common primary hepatic malignancy with dismal prognosis. *O. viverrini* is prevalent in Southeast Asia, infecting 10 million people while *C. sinensis* has a wider distribution in East Asia and several Southeast Asian countries, affecting more than 35 million people's health. These two worms have some common characteristics and/or discrepancies in life cycle, genome, and transcriptome. As hot spots in recent years, genome and transcriptome research has extracted numerous novel fluke worm-derived proteins, which are excellent for carcinogenic exploration. However, just a handful of these studies have focused on the metabolic pathway. In this study, the main mechanisms of carcinogenesis of both worms, in terms of mechanical damage, metabolic products and immunopathology, and other possible pathways, will be discussed in detail. This review retrospectively describes the main traits of *C. sinensis* and *O. viverrini*, their molecular biology and core carcinogenic mechanisms in a contrast pattern.

Keywords *Clonorchis sinensis* · *Opisthorchis viverrini* · Cholangiocarcinoma · Omics · Carcinogenic mechanism

Introduction

Parasites are infamous infectious sources for humans and other mammals. In particular, the infection of helminths caused by *Opisthorchis viverrini* and *Clonorchis sinensis* remains a major public health problem in the Southeast and East Asia. This kind of infection leads to chronic inflammation in the host's biliary tract or even more severe problems (Silakit et al. 2015). Epidemiological and experimental evidence strongly indicate that *C. sinensis* and *O. viverrini* are the etiological agents of cholangiocarcinoma (CCA) (Yothaisong et al. 2015). CCA, the second largest contributor to primary liver cancer, is a devastating cancer arising from bile duct epithelial cells; CCA has been characterized as having very poor prognosis and poor response to current therapies (Mihalache et al. 2010; Sithithaworn et al. 2014). In order to gain some insight into these two worms and explore the cause of liver fluke related cancer, we review basic information related to *C. sinensis* and *O. viverrini*, and further discuss genome, and transcriptome research and specific carcinogenic mechanisms.

Characteristics of *O. viverrini* and *C. sinensis*

In 1915, the first *O. viverrini* infection case was reported in Thailand (Leiper 1915). Later, opisthorchias became endemic Southeast Asia countries, including Laos, Cambodia, Thailand, Vietnam, and with some reported cases in Malaysia, Singapore,

Shuohan Zheng, Yuan Zhu and Zijun Zhao contributed equally to this work.

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SHORT COMMUNICATION

Mast cell activator compound 48/40 is not an effective adjuvant for UV-attenuated *Toxoplasma gondii* vaccine

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Abstract *Toxoplasma gondii* (*T. gondii*, *Tg*) is a globally distributed parasitic protozoan causing different forms of toxoplasmosis in humans. Mast cells (MCs) play a role during *T. gondii* infection. Several studies suggest that MC activator compound 48/80 (C48/80) may be an effective vaccine adjuvant resulting in a potent and protective antigen-specific immune response against bacteria or virus infections. The present study was performed to determine whether C48/80 had adjuvant activity for ultraviolet (UV)-attenuated *T. gondii* vaccine to induce protective immune responses against *T. gondii* in mouse model. Kunming mice were divided into the following groups: naive mice, naive mice administrated with C48/80 intraperitoneal (i.p.) injection, mice infected by i.p. injection of 10^4 *T. gondii* RH strain alone (*Tg* group), mice infected with 10^4 RH tachyzoites plus C48/80 administration (*Tg* + C48/80), mice immunized with UV-*Tg* alone, and mice immunized with UV-*Tg* plus C48/80 administration (UV-*Tg* + C48/80). All the vaccinated mice were challenged with 10^4 tachyzoites of *T. gondii* RH strain at the same time as the primary infection. The survival rates, liver histopathologies, liver parasite burdens, and mRNA expression levels of Th1 and Th2 cytokines in the livers and spleens detected by quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) were compared among the aforementioned groups after primary infection or challenge infection. The results showed that, compared to the *Tg* group or *Tg* + C48/80 group, the UV-*Tg* + *Tg* group and UV-*Tg* + C48/80 + *Tg* group had significantly prolonged survival time, lower liver histopathological scores, decreased liver parasite burdens, and increased levels of Th1 and Th2 cytokines in the livers and spleens. There was no significant difference of survival time between the UV-*Tg* + *Tg* group and the UV-*Tg* + C48/80 + *Tg* group; however, the UV-*Tg* + C48/80 + *Tg* group showed higher parasite burden, more severe liver histopathology, and decreased IL-4 level compared to the UV-*Tg* + *Tg* group. These results indicate that C48/80 had no adjuvant activity for the immunization induced by UV-attenuated *T. gondii* vaccine.

Keywords UV-attenuated *T. gondii* · Compound 48/80 · Adjuvant · Mice

Introduction

Toxoplasma gondii (*T. gondii*, *Tg*) infects various warm-blooded animals including humans. It estimated that about one third of the world population has been infected with this parasite (Hill and Dubey 2002). *T. gondii* infection in human can cause serious symptoms including encephalitis, chorioretinitis, pneumonitis, and disseminated toxoplasmosis with multi-organ involvement in immunocompromised individuals (Khurana and Batra 2016). Currently, there is still lack of effective drugs against chronic stages of *T. gondii* infection. Live attenuated *T. gondii* vaccine strain

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Meropenem selection induced overproduction of the intrinsic carbapenemase as well as phenotype divergence in *Acinetobacter baumannii*

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ABSTRACT

Acinetobacter baumannii 37662 is a carbapenem-susceptible isolate with $bla_{OXA-51-like}$ as the sole carbapenemase gene. Following selection with meropenem (MEM) at a subinhibitory concentration, two morphologically different mutants, designated 37662RM1 and 37662RM2, were obtained and characterised. Compared with the parent strain, resistant mutant 37662RM1 grew at a slower rate and had impaired capsule synthesis, whereas 37662RM2 grew fast and abolished capsule synthesis. In addition, the latter resistant mutant also lost pathogenicity but showed significantly enhanced biofilm formation. Transposition of the insertion sequence IS*Aba1* and formation of IS*Aba1*–$bla_{OXA-51-like}$ was responsible for the upregulated expression of $bla_{OXA-51-like}$. The $bla_{OXA-51-like}$ gene of *A. baumannii* 37662 is a close variant of $bla_{OXA-138}$ and has been designated $bla_{OXA-508}$. Overproduction of OXA-508 conferred major carbapenem resistance to these two mutants. Overall, these results indicate that a subinhibitory concentration of MEM can induce phenotype divergence together with carbapenem resistance in *A. baumannii*.

1. Introduction

Acinetobacter baumannii, essentially as an opportunistic pathogen, is a serious cause of concern because of the increasing incidence of multidrug resistance globally. Carbapenems are considered the drugs of last resort [1]. The rapidly increasing number of carbapenem-resistant *A. baumannii* poses a threat to anti-infective therapy [2]. Several mechanisms underlying carbapenem resistance in *A. baumannii* have been described, including carbapenemase production, efflux pump overexpression, porin downregulation and penicillin-binding protein alterations [3]. Production of class D carbapenemases, or oxacillinases (OXA), is the most common resistance mechanism. Six major types of OXA-encoding genes have been identified in *A. baumannii*, including $bla_{OXA-23-like}$, $bla_{OXA-24-like}$, $bla_{OXA-58-like}$, $bla_{OXA-143-like}$, $bla_{OXA-235-like}$ and $bla_{OXA-51-like}$ [4–6]. The first five types are located either on plasmids or the chromosome, acquired through horizontal transfer [4–6]; in contrast, $bla_{OXA-51-like}$ mainly presents on the chromosome, naturally occurring in *A. baumannii* [5,7].

OXA-51-like proteins showed weak carbapenem-hydrolysing activity, but overproduction of OXA-51-like may confer carbapenem resistance [8,9]. Characterisation of carbapenem-resistant *A. baumannii* isolates has shown that overexpression of $bla_{OXA-51-like}$ is dependent on an upstream insertion sequence IS*Aba1*, which is suggested to function as a promoter [10–12]. In a rare case, IS*Aba9* has been identified within a truncated IS*Aba1*, and both ISs work together to drive the overexpression of downstream $bla_{OXA-51-like}$ [13]. Consistently, in the absence of IS*Aba1*, $bla_{OXA-51-like}$ is expressed little or not at all [11]. Many *A. baumannii* strains can potentially become carbapenem-resistant on their own since IS*Aba1* and $bla_{OXA-51-like}$ coexist ubiquitously [7,14]. Remarkably, the detection rate of *A. baumannii* containing IS*Aba1*–$bla_{OXA-51-like}$ in clinical isolates displays geographical differences, varying from an extremely low rate in one area to an extremely high rate in another [2,15,16]. Nonetheless, the risk factors facilitating the formation of IS*Aba1*–$bla_{OXA-51-like}$ have not yet been well characterised.

Some antibiotics at subinhibitory concentrations may potentially change bacterial gene expression profiles, either directly or indirectly, and thus cause alterations in resistance, metabolism, colony morphology, growth rate, virulence, biofilm formation or even host–pathogen interactions [17–19]. Multiple factors, such as

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Research Paper

Mesenchymal marker expression is elevated in Müller cells exposed to high glucose and in animal models of diabetic retinopathy

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ABSTRACT

Müller cells are retinal glial cells and exhibit a fibroblast-like phenotype and ability to migrate in diabetic retinopathy (DR). However, expression of mesenchymal markers, which promote fibrosis in various organs, has not been characterized in the diabetic retina. We examined changes in the expression of these markers in Müller cells exposed to high glucose and in animal models of diabetic retinopathy. High glucose conditions increased mesenchymal maker expression and migration in Müller cells. Snail, N-cadherin, Vimentin, β-catenin, and α-smooth muscle actin (α-SMA) levels were all dramatically increased in retinas from humans with diabetic retinopathy (DR) and from DR mouse models. In addition, Snail overexpression increased the expression of connective tissue growth factor (CTGF) and fibronectin, while Snail knockdown attenuated high glucose-induced increases in fibronectin and CTGF expression. These results demonstrate for the first time that mesenchymal markers are upregulated in retinas from a diabetic mouse model, and that Snail and N-cadherin levels are also increased in Müller cells exposed to high glucose. This suggests mesenchymal proteins may play a crucial role in the development of DR.

INTRODUCTION

Diabetic retinopathy (DR) is a severe complication of diabetes and the leading cause of blindness among working adults worldwide [1]. DR is classified as either non-proliferative (non-PDR) or proliferative (PDR) [2]. The main pathogenic features of PDR are preretinal neovascularization and the formation of fibrovascular membranes at the vitreoretinal interface. The presence of fibrovascular tissue often results in severe visual impairment due to vitreous hemorrhages and/or tractional retinal detachment [3]. Although retinal neovascularization has been considered the main characteristic of PDR, the fibrogenic process that occurs after new vessels are formed

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Methamphetamine induces hepatotoxicity via inhibiting cell division, arresting cell cycle and activating apoptosis: *In vivo* and *in vitro* studies

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ABSTRACT

Methamphetamine (METH) resulted in acute hepatic injury. However, the underlying mechanisms have not been fully clarified. In the present study, rats were treated with METH (15 mg/kg B.W.) for 8 injections (i.p.), and the levels of alanine transaminase, asparatate transaminase and ammonia in serum were significantly elevated over those in the control group, suggesting hepatic injury, which was evidenced by histopathological observation. Analysis of the liver tissues with microarray revealed differential expressions of a total of 332 genes in METH-treated rats. According to the GO and KEGG annotations, a large number of down-regulated cell cycle genes were screened out, suggesting that METH induced cell cycle arrest and deficient of cell cycle checkpoint. Related genes and proteins were confirmed by RT-qPCR and western blotting in rat livers, respectively. Moreover, treatment of Brl-3A cells with METH caused significant cytotoxic response and marked cell cycle arrest. Furthermore, overexpressions of Cidea, cleaved caspase 3 and PARP 1 in METH-treated rats indicated activation of apoptosis, while its inhibition alleviated cell death in Brl-3A cells, suggesting that activation of apoptosis took an important role in METH-induced hepatotoxicity. Taken together, the present study demonstrates that METH induced hepatotoxicity via inducing cell cycle arrest and activating apoptosis.

1. Introduction

Methamphetamine (METH) is a highly addictive psychostimulant drug of abuse, commonly referred to as “speed”, “crystal”, “crank”, “go”, and “ice” (Carvalho et al., 2012; Kayagaki et al., 2011). METH was firstly synthesized in 1893 in Japan (Hamamoto and Rhodus, 2009). METH causes both physical and psychological alterations, such as euphoric, stimulant, and hallucinogenic effects (Panenka et al., 2013). Abuse of METH triggers significant societal problems (Hostetler et al., 2016) and causes intense attention widespread in the world.

Neurotoxic effects induced by METH could be attributed to induction of pro-inflammatory cytokines (Shah et al., 2012), oxidative stress (Shah et al., 2013), hyperthermia (Kiyatkin and Sharma, 2009) and ER stress-mediated apoptosis (Shah and Kumar 2016). METH may induce hyperthermia via complex integration of the subsequent hyperlocomotion, altered metabolism, changes in hypothalamic neurotransmission, and vasoconstriction (Brown et al., 2007). It has been proved that hyperthermia induced by METH contributes significantly to hepatic injury and increases ammonia in peripheral plasma (Halpin et al., 2013). Increased ammonia in peripheral blood and brain (Felipo and Butterworth, 2002), as well as acute hepatic injury caused by METH may also contribute to its neurotoxicity (Halpin and Yamamoto, 2012).

Previous studies demonstrated that hepatic injury induced by METH was related to oxidative stress and subsequent mitochondrial collapse in hepatocytes (Eskandari et al., 2014), and the resultant hepatocellular necrosis and apoptosis (da Silva et al., 2013). However, the exact cellular and molecular mechanisms involved in this process have not been completely illuminated.

In the present study, microarray was performed for a

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ORIGINAL ARTICLE

miR-146a Inhibits dengue-virus-induced autophagy by targeting TRAF6

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Abstract During dengue virus (DENV) infection, the virus manipulates different cellular pathways to assure productive replication, including autophagy. However, it remains unclear how this autophagic process is regulated. Here, we have demonstrated a novel role for the microRNA miR-146a in negatively regulating the cellular autophagic pathway in DENV-infected A549 cells and THP-1 cells. Overexpression of miR-146a significantly blocked DENV2-induced autophagy, and LNA-mediated inhibition of miR-146a counteracted these effects. Moreover, co-overexpression of TRAF6, a target of miR-146a, significantly reversed the inhibitory effect of miR-146a on autophagy. Notably, treatment with recombinant IFN-β fully restored the autophagic activity in TRAF6-silenced cells. Furthermore, our data showed that, in DENV2-infected A549 cells, autophagy promoted a pro-inflammatory response to significantly increase TNF-α and IL-6 production. Taken together, our results define a novel role for miR-146a as a negative regulator of DENV-induced autophagy and identify TRAF6 as a key target of this microRNA in modulating the DENV-autophagy interaction.

Jieying Pu and Siyu Wu contributed equally to this work.

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Introduction

Dengue virus (DENV) is a positive single-stranded RNA virus of the family *Flaviviridae*, which is serologically subdivided into four serotypes, DENV1, 2, 3, and 4 [1]. DENV infection can manifest itself either as the self-limiting disease dengue fever (DF) or as severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), and dengue has become one of the most prevalent arthropod-borne viral diseases in subtropical and tropical regions of the world [2]. Unfortunately, dengue pathogenesis and the interplay between the virus and the host immune system remains incompletely understood.

DENV infection can activate the cellular autophagic pathway [3, 4]. Autophagy is a highly conserved catabolic process by which host cells remove protein aggregates and damaged organelles for maintaining cellular homeostasis [5]. The autophagic cascade starts with engulfment of cytoplasmic cargo by an autophagosome, which then fuses with an endosome to form an autolysosome, exposing the inner compartment to lysosomal hydrolases for degradation [6]. It has been demonstrated that stresses, such as nutrient starvation and pathogenic infection, can also induce autophagy [7, 8]. Many protein factors that are important for autophagy have been identified. The microtubule-associated protein light-chain 3 (LC3), as one of these factors, is often used as

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RESEARCH Open Access

Molluscicidal activity and mechanism of toxicity of a novel salicylanilide ester derivative against *Biomphalaria* species

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Abstract

Background: Schistosomiasis mansoni is one of the most important, but often neglected, tropical diseases transmitted by snails of the genus *Biomphalaria*. Control of the intermediate host snail plays a crucial role in preventing the spread of schistosomiasis. However, there is only one molluscicide, niclosamide, recommended by the World Health Organization. Niclosamide has been used for several decades but is toxic to non-target organisms. Therefore, it is necessary to optimize the scaffold of niclosamide and develop novel molluscicides with enhanced potency and decreased toxicity to non-target organisms.

Methods: In this study, a candidate compound was analyzed by nuclear magnetic resonance and mass spectrometry. The molluscicidal potential against *Biomphalaria* species and cercaricidal potential against *S. mansoni* were evaluated using the immersion method. Furthermore, the preliminary mechanism was studied through cellular enzyme tests and electron microscopy.

Results: 5-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]phenyl-4-methoxybenzoate (salicylanilidate), a novel salicylanilide ester derivative, was derived from niclosamide. The 50% lethal concentration to *B. glabrata*, *B. straminea* and *B. pfeifferi* was 0.261 mg/l, 0.172 mg/l and 0.241 mg/l, respectively. The effective dose required to completely kill *S. mansoni* cercariae was 0.625 mg/l for salicylanilidate and 0.125 mg/l for niclosamide. However, salicylanilidate was approximately 100-fold less toxic to the fish *Danio rerio* than niclosamide. Furthermore, salicylanilidate reduced the enzymatic activities of nitric oxide synthase (NOS), lactate dehydrogenase (LDH) and acetylcholinesterase (AChE) in the snail, demonstrating that it could affect neurohypophysis transmission and energy metabolism. Severe swelling in the tentacle and deformation of cilia in the tentacle and mantle were observed through scanning electron microscopy. The results of transmission electron microscopy showed that salicylanilidate could damage critical organelles in hepatopancreas tissues, including degeneration of the endoplasmic reticulum and vacuolization in mitochondria. In addition, transcriptional levels of superoxide dismutase (SOD), acid phosphatase (ACP) and NOS in the hepatopancreas were significantly downregulated as shown by real-time quantitative polymerase chain reaction (RT-PCR). These results indicated that the hepatopancreas is a primary target organ of salicylanilidate.

Conclusions: Salicylanilidate not only had deleterious effects on *Biomphalaria* species and *S. mansoni* cercariae but also showed very low toxicity to *D. rerio*, suggesting that it has broad potential applications.

Keywords: *Biomphalaria*, *Schistosoma mansoni*, Cercaria, Niclosamide, Salicylanilidate

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ORIGINAL ARTICLE

Neuronal Apoptosis: Pathological Basis of Behavioral Dysfunctions Induced by *Angiostrongylus cantonensis* in Rodents Model

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Abstract: *Angiostrongylus cantonensis* invades the central nervous system (CNS) of humans to induce eosinophilic meningitis and meningoencephalitis and leads to persistent headache, cognitive dysfunction, and ataxic gait. Infected mice (nonpermissive host), admittedly, suffer more serious pathological injuries than rats (permissive host). However, the pathological basis of these manifestations is incompletely elucidated. In this study, the behavioral test, histological and immunohistochemical techniques, and analysis of apoptotic gene expression, especially caspase-3, were conducted. The movement and motor coordination were investigated at week 2 post infection (PI) and week 3 PI in mice and rats, respectively. The cognitive impairs could be found in mice at week 2 PI but not in rats. The plaque-like lesion, perivascular cuffing of inflammatory cells, and dilated vessels within the cerebral cortex and hippocampus were more serious in mice than in rats at week 3 PI. Transcriptomic analysis showed activated extrinsic apoptotic pathway through increased expression of TNFR1 and caspase-8 in mice CNS. Immunohistochemical and double-labeling for NeuN and caspase-3 indicated the dramatically increased expression of caspase-3 in neuron of the cerebral cortex and hippocampus in mice but not in rats. Furthermore, western-blotting results showed high expression of cleaved caspase-3 proteins in mice but relatively low expression in rats. Thus, extrinsic apoptotic pathway participated in neuronal apoptosis might be the pathological basis of distinct behavioral dysfunctions in rodents with *A. cantonensis* infection. It provides the evidences of a primary molecular mechanism for the behavioral dysfunction and paves the ways to clinical diagnosis and therapy for *A. cantonensis* infection.

Key words: *Angiostrongylus cantonensis*, eosinophilic meningitis, meningoencephalitis, apoptosis

INTRODUCTION

Angiostrongyliasis is caused by the rat lung worm, *Angiostrongylus cantonensis*, a kind of nematode that was first identified and reported by Chen at 1935 in wild rats in the vicinity of Canton in China [1]. Humans accidentally acquire infection with this nematode either by eating poorly cooked intermediate hosts (freshwater snails and slug) or carrier hosts (land crabs and freshwater shrimps) or by consuming the contaminated vegetables containing third-stage larvae [2-7]. The definitive hosts of *A. cantonensis* are divided into permissive (rat) and nonpermissive hosts (mice, guinea pigs, rabbits, rhesus monkeys, and humans) based on whether the worms invade the lung and eventually attain sexual maturity. In the permissive host, the worms can migrate to lungs without causing severe eosinophilic meningitis. But in nonpermissive hosts, larvae generally fail to migrate to the lungs and terminate their development at a young adult worm stage dwelling in CNS until death, which can cause meningitis or meningoencephalitis characterized by obviously increasing eosinophil infiltrations [8,9].

Clinical exploration revealed that *A. cantonensis* invading human CNS caused eosinophilic meningitis and meningoencephalitis, and resulted in a serial of neurological symptoms,

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Neutrophils and PMN-MDSC: Their biological role and interaction with stromal cells

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ABSTRACT

Neutrophils and polymorphonucler myeloid-derived suppressor cells (PMN-MDSC) share origin and many morphological and phenotypic features. However, they have different biological role. Neutrophils are one of the major mechanisms of protection against invading pathogens, whereas PMN-MDSC have immune suppressive activity and restrict immune responses in cancer, chronic infectious disease, trauma, sepsis, and many other pathological conditions. Although in healthy adult individuals, PMN-MDSC are not or barely detectable, in patients with cancer and many other diseases they accumulate at various degree and co-exist with neutrophils. Recent advances allow for better distinction of these cells and better understanding of their biological role. Accumulating evidence indicates PMN-MDSC as pathologically activated neutrophils, with important role in regulation of immune responses. In this review, we provide an overview on the definition and characterization of PMN-MDSC and neutrophils, their pathological significance in a variety of diseases, and their interaction with other stromal components.

1. Introduction

Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of pathologically activated myeloid precursors and relatively immature myeloid cells that accumulate under many pathological conditions [1,2]. Currently, MDSC could be further divided into two major subsets: polymorphonuclear (PMN)-MDSC and monocytic (M)-MDSC. PMN-MDSC share many morphological and phenotypic characteristics of neutrophils, whereas M-MDSC are similar to monocytes [3,4]. In both mice and humans PMN-MDSC represent the most abundant population of MDSC. In recent years an important biological role of PMN-MDSCs has emerged. These cells have been implicated in control of immune responses and their clinical relevance has been demonstrated in cancer and other pathologic conditions. In this review, we discuss main features of PMN-MDSC vis-a-vis neutrophils and their significance in cancer and infectious diseases.

2. Neutrophil differentiation

Neutrophils are the most abundant type of granulocytes [5,6]. The development of neutrophils occurs in the bone marrow (BM) and involves several defined steps including common myeloid progenitors, granulocyte–monocyte myeloid progenitors, myeloblasts, promyelocytes, myelocytes, metamyelocytes, band neutrophils and, finally, segmented neutrophils [7,8]. The granules formed during neutrophil maturation serve as a reservoir of anti-microbial factors and enzymes, such as myeloperoxidase (MPO), neutrophil elastase (NE), defensins, cathelicidins and matrix metalloproteinase (MMP), which protect hosts from infections and promote the resolution of inflammation [9,10]. After generation in the BM and brief period of circulation in peripheral blood, neutrophils migrate to the tissues. This migration is regulated by chemokines released by activated endothelial cells, fibroblasts, macrophages, and various products of microorganisms in case of infection. Apoptotic neutrophils are cleared primarily by resident tissue

Abbreviation: BM, bone marrow; BV8, prokineticin 2; CHOP, C/EBP homologous protein; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte–macrophage-colony stimulating factor; HBV, hepatitis B virus; HIV-1, human immunodeficiency virus; ICAM-1(-2), intracellular adhesion molecule-1 (-2); IL-6, (IL-8, IL-10), interleukin 6, (interleukin-8, interleukin-10); IRF8, interferon related factor 8; M-CSF, macrophage colony stimulating factor; MDSC, myeloid-derived suppressor cells; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NE, neutrophil elastase; NETs, neutrophil extracellular traps; NLR, neutrophil-to-lymphocyte ratio; NO, nitric oxide; NOS, nitric oxide synthase; LOX-1, lectin type oxidized LDL receptor 1; PGE2, prostaglandin E2; PMN, polymorphonuclear cells; ROS, reactive oxygen species; sXBP1, spliced X-box binding protein 1; TAN, Tumor associated neutrophils; TB, tuberculosis; TGF-β, transforming growth factor β; TNF- α, tumor necrosis factor α; VEGF, vascular endothelial growth factor

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Niclosamide inhibits lytic replication of Epstein-Barr virus by disrupting mTOR activation

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ABSTRACT

Infection with the oncogenic γ-herpesviruses Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) cause several severe malignancies in humans. Inhibition of the lytic replication of EBV and KSHV eliminates the reservoir of persistent infection and transmission, consequently preventing the occurrence of diseases from the sources of infection. Antiviral drugs are limited in controlling these viral infectious diseases. Here, we demonstrate that niclosamide, an old anthelmintic drug, inhibits mTOR activation during EBV lytic replication. Consequently, niclosamide effectively suppresses EBV lytic gene expression, viral DNA lytic replication and virion production in EBV-infected lymphoma cells and epithelial cells. Niclosamide exhibits cytotoxicity toward lymphoma cells and induces irreversible cell cycle arrest in lytically EBV-infected cells. The ectopic overexpression of mTOR reverses the inhibition of niclosamide in EBV lytic replication. Similarly, niclosamide inhibits KSHV lytic replication. Thus, we conclude that niclosamide is a promising candidate for chemotherapy against the acute occurrence and transmission of infectious diseases of oncogenic γ-herpesviruses.

1. Introduction

Two natural human oncogenic γ-herpesviruses, Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV), cause several types of severe malignancies (Ganem, 2010; Kutok and Wang, 2006). These viruses have two alternative lifecycles after their DNA genomes enter into the cellular nucleus: default latency and a small portion of lytic replication. Lytic replication provides a reservoir of infectious virion particles for expansion and transmission (Ganem, 2010; Kenney and Mertz, 2014). Thus, the blockade of lytic replication could effectively prevent the incidence of infection and diseases from their sources of infection. Although there are many antiviral drugs available (Siakallis et al., 2009; Skorenski and Sienczyk, 2014), few have been assessed in treating acute infection and lytic replication of these viruses.

Homologous EBV and KSHV share a high similarity of their viral DNA genomes and viral gene products (Damania, 2004; Nicholas, 2000). Consequently, these viruses employ a variety of common cellular pathways to facilitate their infection, replication and maintenance of viral genomes as well as tumorigenesis (Collins and Medveczky, 2002; Damania and Jung, 2001; de Oliveira et al., 2010; Filippakis et al., 2010; Hayward et al., 2006; Noguchi et al., 2007; Stevenson, 2004). Disruption of these pathways by inhibitors mostly leads to the inhibition of their infection and further pathogenesis; however, therapeutic clinical applications remain unavailable.

Niclosamide is one of the World Health Organization's essential medicines and is classified as an effective anthelmintic drug to treat worm infections, especially tapeworm infections (Craig and Ito, 2007). Niclosamide is also effective against intractable drug-resistant bacterial infections (Costabile et al., 2015; de Carvalho et al., 2011; Imperi et al., 2013; Rajamuthiah et al., 2015). As niclosamide inhibits mTORC1 signaling through disruption of cellular pH homeostasis (Balgi et al., 2009; Fonseca et al., 2012) and lysosome inhibition-induced Rag-mTORC1 signaling (Li et al., 2013), it can be used as a preclinical inducer of autophagy. Moreover, niclosamide uncouples mitochondrial respiration and disrupts cellular metabolism, which provides a potential approach for treating type 2 diabetes (Tao et al., 2014).

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Nicotinamide induces mitochondrial-mediated apoptosis through oxidative stress in human cervical cancer HeLa cells

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ABSTRACT

Aims: Nicotinamide participates in energy metabolism and influences cellular redox status and modulates multiple pathways related with both cellular survival and death. Recent studies have shown that it induced proliferation inhibition and apoptosis in many cancer cells. However, little is known about the effects of nicotinamide on human cervical cancer cells. We aimed to evaluate the effects of the indicated concentrations nicotinamide on cell proliferation, apoptosis and redox-related parameters in HeLa cells and investigated the apoptotic mechanism.

Materials and methods: After the treatment of the indicated concentrations nicotinamide, HeLa cell proliferation was evaluated by the CCK-8 assay and the production of ROS (reactive oxygen species) was measured using 2′,7′-Dichlorofluorescin diacetate. The apoptotic effect was confirmed by observing the cellular and nuclear morphologies with fluorescence microscope and apoptotic rate of HeLa cell apoptosis was measured by flow cytometry using Annexin-V method. Moreover, we examined the mitochondrial membrane potential by JC-1 method and measured the expression of apoptosis related genes using qRT-PCR and immunoblotting.

Key findings: Nicotinamide restrained the HeLa cell proliferation and significantly increased the accumulation of ROS and depletion of GSH at relatively high concentrations. Furthermore, nicotinamide promoted HeLa cell apoptosis via the intrinsic mitochondrial apoptotic pathway.

Significance: Our study revealed that nicotinamide induced the apoptosis through oxidative stress and intrinsic mitochondrial apoptotic pathways in HeLa cell. The results emerge that nicotinamide may be an inexpensive, safe and promising therapeutic agent or a neoadjuvant chemotherapy for cervical cancer patients, as well useful to find new drugs for cervical cancer therapy.

1. Introduction

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females [1]. Currently, surgery, radiotherapy and cisplatin-based chemotherapy are the primary methods for treating cervical cancer [2]. However, drug resistance of cervical cancer leading to the low efficacy of the clinical therapeutics and the high cost of the treatment became the major cause of the high incidence and the high mortality rate in developing parts of the world. Hence, it is urgent to find the safe, effective, and affordable treatment for cervical cancer. Human cervical cancer HeLa cell line, derived from cervical cancer cells taken on February from a patient named Henrietta Lacks who died of her cancer on October in 1951 [3], was selected as the experimental model in the present study.

Nicotinamide, the amide form of niacin (vitamin B3), is the necessary nutrient that provided by dietary source and supplement [4]. It also has been used to treat with pellagra clinically for a long time and lack of reported side effects [5]. Nicotinamide is a precursor of the coenzyme nicotinamide adenine dinucleotide (NAD^+), participating in the cellular energy metabolism in the mitochondrial electron transport chain [6]. In addition, nicotinamide also is essential for the synthesis of nicotinamide adenine dinucleotide phosphate ($NADP^+$) [7], which is involved in the synthesis of fatty acids and cell survival under oxidative stress condition [8]. And the reduced pyridine nucleotides, NAD(P)H, depending upon an adequate supply of $NAD(P)^+$ [8], also play a pivotal role in the regulation of cellular redox status.

So far, various studies have demonstrated that nicotinamide could modify redox balance in vivo and in vitro, from human fibroblasts [9] to mouse preadipocyte cells [10]. Additionally, emerging evidences reported that nicotinamide might be a potential candidate as anticancer agent or in combination with other chemotherapeutics in several cancer cell models, including pancreatic cancer [11], chronic lymphocytic leukemia [12] and prostate carcinoma [13], breast cancers [14].

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Nitric oxide blocks the development of the human parasite *Schistosoma japonicum*

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Human schistosomiasis, caused by *Schistosoma* species, is a major public health problem affecting more than 700 million people in 78 countries, with over 40 mammalian host reservoir species complicating the transmission ecosystem. The primary cause of morbidity is considered to be granulomas induced by fertilized eggs of schistosomes in the liver and intestines. Some host species, like rats (*Rattus norvegicus*), are naturally intolerant to *Schistosoma japonicum* infection, and do not produce granulomas or pose a threat to transmission, while others, like mice and hamsters, are highly susceptible. The reasons behind these differences are still a mystery. Using inducible nitric oxide synthase knockout (iNOS$^{-/-}$) Sprague–Dawley rats, we found that inherent high expression levels of iNOS in wild-type (WT) rats play an important role in blocking growth, reproductive organ formation, and egg development in *S. japonicum*, resulting in production of nonfertilized eggs. Granuloma formation, induced by fertilized eggs in the liver, was considerably exacerbated in the iNOS$^{-/-}$ rats compared with the WT rats. This inhibition by nitric oxide acts by affecting mitochondrial respiration and energy production in the parasite. Our work not only elucidates the innate mechanism that blocks the development and production of fertilized eggs in *S. japonicum* but also offers insights into a better understanding of host–parasite interactions and drug development strategies against schistosomiasis.

rat | *Schistosoma japonicum* | schistosomiasis | granuloma formation | mitochondria

Schistosomiasis, caused by *Schistosoma* species, is the second most important parasitic disease for public health after malaria. In 2015, it was estimated that 700 million people were at the risk of this disease and 218 million people required treatment in 78 countries (1). *Schistosoma japonicum* is widely distributed in South China, Indonesia, and the Philippines (1), with 170,438 patients being treated in China in 2015 (2). It is well known that viable egg production is the key for both transmission and pathogenesis (egg-induced granulomas in the liver and intestinal tissues) of this parasite. The female *S. japonicum* produces around 3,000 eggs per day, 10-fold more than the related species *Schistosoma mansoni*, and this has been proposed to cause a more severe pathology to patients (3). *S. japonicum* is one of the most difficult parasites to control, because more than 46 nonhuman mammals can be naturally infected, especially cattle, goats, dogs, pigs, and mice, and these play an important role in the transmission of this disease in endemic regions (4, 5). However, it is well known that some experimental animals, such as Norway rats (*Rattus norvegicus*), show an innate resistance to infection, in which *Schistosoma* spp. cannot develop well and do not cause typical granuloma formation in the liver (6–8). These phenomena are described as susceptible or "permissive" and resistant or "nonpermissive" based on the capacity of the host species to allow development of sexual maturation and oviposition by the parasite (7). Although such natural characteristics have been investigated for several decades, little direct evidence has been obtained to fully explain these phenomena, even despite the publication of the genome of *S. japonicum* and the great benefits provided by it (9). We are interested to know why such huge differences in resistance occur between mice and rats when they are infected with *S. japonicum*. What are the host factors that relate to innate resistance? Obviously, a better understanding of the mechanism of resistance would provide a better understanding of the pathogenesis of human schistosomiasis and the host–parasite interactions.

In recent decades, experiments have been carried out to investigate potential mechanisms that could mediate natural resistance to *Schistosoma* infection in rats. Capron and Capron (6) and Capron et al. (10), primarily using in vitro assays, argued that humoral immunity, particularly antibody-dependent, cell-mediated cytotoxicity, played a critical role in the resistance of the rat host. In addition, the anaphylactic antibodies (IgG2a and IgE) and effector cells, including eosinophils, macrophages, platelets, and mast cells, could mediate cytotoxicity, which might act directly against schistosomula in vivo (10, 11). However, some contrasting results have indicated that cell-mediated responses appeared to be insignificant in rat schistosomiasis (12). Moreover, some results also suggested that a Th2 type response was involved in such resistance, based on the observations of preferential expression of Th2 cytokines before rejection of worms

Significance

Viable egg production by *Schistosoma* species is the key pathogenic process causing granuloma formation in permissive hosts (e.g., mice), while nonpermissive hosts [e.g., Norway rats (*Rattus norvegicus*)] avoid such sequelae. Using inducible nitric oxide synthase knockout (iNOS$^{-/-}$) rats, we demonstrate that high expression levels of iNOS in rats play an important role in blocking the egg-induced granuloma formation of *Schistosoma japonicum*. The nitric oxide, produced by iNOS, inhibits parasite growth, reproductive organ development, egg production, and viability by interfering with mitochondrial function. This study solves the puzzle as to why rats are naturally resistant to *S. japonicum* infection and provides insights for understanding the pathogenesis of human schistosomiasis and the interactions between host and parasite.

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Full length article

Oral delivery of *Bacillus subtilis* spores expressing cysteine protease of *Clonorchis sinensis* to grass carp (*Ctenopharyngodon idellus*): Induces immune responses and has no damage on liver and intestine function

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ABSTRACT

Clonorchis sinensis (*C. sinensis*) is a fish-borne trematode. Human can be infected by ingestion of *C. sinensis* metacercariae parasitized in grass carp (*Ctenopharyngodon idella*). For induction of effective oral immune responses, spores of *Bacillus subtilis* (*B. subtilis*) WB600 were utilized as vehicle to delivery *Cs*CP (cysteine protease of *C. sinensis*) cooperated with CotC (*B.s*-CotC-CP), one of coat proteins, to the gastrointestinal tract. After routine culture of 8–12 h in LB medium, *B. subtilis* containing CotC-*Cs*CP was transferred into the sporulation culture medium. SDS-PAGE, western blotting and the growth curve indicated that the best sporulation time of recombinant WB600 was 24–30 h at 37 °C with continuous shaking (250 rpm). Grass carp were fed with three levels of *B.s*-CotC-CP (1×10^6, 1×10^7, and 1×10^8 CFU g^{-1}) incorporated in the basal pellets diet. The commercial pellets or supplemented with spores just expressing CotC (1×10^7 CFU g^{-1}) were served as control diet. Our results showed that grass carp orally immunized with the feed-based *B.s*-CotC-CP developed a strong specific immune response with significantly ($P < 0.05$) higher levels of IgM in samples of serum, bile, mucus of surface and intestinal compared to the control groups. Abundant colonization spores expressing *Cs*CP were found in hindgut that is conducive to absorption and presentation of antigen. Moreover, *B. subtilis* spores appeared to show no sign of toxicity or damage in grass carp. Our cercariae challenge experiments suggested that oral administration of spores expressing *Cs*CP could develop an effective protection against *C. sinensis* in fish body. Therefore, this study demonstrated that the feed-based recombinant spores could trigger high levels of mucosal and humoral immunity, and would be a promising candidate vaccine against *C. sinensis* metacercariae formation in freshwater fish.

1. Introduction

The clonorchiasis caused by *Clonorchis sinensis* (*C. sinensis*) is a long chronic infection disease in definitive hosts, often accompanied by a broad range of hepatic and bile duct symptoms, such as cholangitis, cholecystitis, bile duct obstruction, cholelithiasis, and even cholangiocarcinoma and hepatic cirrhosis [1–3]. Clonorchiasis is mainly prevalent in Asian countries and regions, such as China, South Korea, northern Vietnam, and Russia [3]. It is estimated that

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REVIEW
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Parasite-Derived Proteins for the Treatment of Allergies and Autoimmune Diseases

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The morbidity associated with atopic diseases and immune dysregulation disorders such as asthma, food allergies, multiple sclerosis, atopic dermatitis, type 1 diabetes mellitus, and inflammatory bowel disease has been increasing all around the world over the past few decades. Although the roles of non-biological environmental factors and genetic factors in the etiopathology have been particularly emphasized, they do not fully explain the increase; for example, genetic factors in a population change very gradually. Epidemiological investigation has revealed that the increase also parallels a decrease in infectious diseases, especially parasitic infections. Thus, the reduced prevalence of parasitic infections may be another important reason for immune dysregulation. Parasites have co-evolved with the human immune system for a long time. Some parasite-derived immune-evasion molecules have been verified to reduce the incidence and harmfulness of atopic diseases in humans by modulating the immune response. More importantly, some parasite-derived products have been shown to inhibit the progression of inflammatory diseases and consequently alleviate their symptoms. Thus, parasites, and especially their products, may have potential applications in the treatment of autoimmune diseases. In this review, the potential of parasite-derived products and their analogs for use in the treatment of atopic diseases and immune dysregulation is summarized.

Keywords: parasite, product, hygiene hypothesis, autoimmune disease, allergy

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INTRODUCTION

Parasites, which have co-evolved with mammals, including humans, over a long period of time, can use various strategies to survive, such as secreting immune-evasion molecules to modulate the host immune system. However, consequently, parasites play a dual role in human health (Ditgen et al., 2014; Maizels and McSorley, 2016). On the one hand, parasites threaten human health by causing malnutrition, mechanical damage, and toxic effects. On the other hand, parasites induce potent immunomodulatory effects and can act as potential therapeutics for a variety of inflammatory diseases including asthma, rhinitis, intestinal inflammation disease, type 1 diabetes (T1D), and several other immune dysregulation disorders.

Conventional wisdom suggests that there are three consequences of parasitic infection: (1) The damage caused by the host response exceeds the ability of the parasites to adapt, the parasites are

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REVIEW

Parasites and asthma

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Abstract Nowadays, many studies have found low morbidity of asthma in epidemic areas of parasitic diseases, as shown by the hygiene hypothesis. It is obvious that some parasite infections can prevent asthma and studies have been carried out to clarify the mechanism of the preventive effect and search for the future asthmatic therapies. Previous findings have indicated that this mechanism may be related to the immune response switching from Th1 to Th2 and important cells induced by parasites, including the regulatory T cells, regulatory B cells, dendrite cells, and alternatively activated macrophages. Cytokine IL-10 also plays a nonredundant role in protection against allergic airway inflammation in asthma. This review focuses on the relationship between parasites and asthma, and the potential protection mechanism involved.

Keywords Parasite · Asthma · Prevention · Therapy

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Introduction

Asthma is a chronic inflammatory disease of the airways of the lungs, especially the bronchi and bronchioles. Inflammation can cause the hypertrophy, hyperplasia and increased contractibility of the smooth muscle of the airway, the hyperplasia of the glands, and infiltration of the inflammatory cell, especially the eosinophils (Maddox and Schwartz 2002). The characteristic symptoms of asthma are chest distress, breath shortness, wheezing, and coughing, occasionally with sputum. These symptoms often exacerbate at night, in the early morning, during exercising, and in cold air (British Thoracic Society Scottish Intercollegiate Guidelines N 2008). A variety of factors are associated with asthma, such as environmental factors and genes. For example, some allergens like dust mites and pollen can cause asthma, and air pollution like NO_2, O_3, and airborne traffic-related pollutants can result in exacerbation of asthma (Kelly and Fussell 2011). Infections of the respiratory syncytial virus (RSV) can also give rise to asthma (Gern and Busse 2002). In addition, many genes are closely related to asthma, like ADAM33, ADRB2, CD14, FCER1B, HLA-DQB1, HLA-DRB1, IL13, IL4, IL4RA, and TNF which are mainly located on chromosomes 5q31–33, 6p21, and 12q13–q24 (Ober and Hoffjan 2006). Now, there are many drugs available for treatment. β_2-agonists, such as salbutamol, are helpful to rapid symptoms, and inhaled corticosteroids are effective in long-term control (National Asthma and Prevention 2007). However, these treatments show no effect on some asthmatics. As more and more molecular studies on asthma are being performed, specific targeting therapy may be developed in the future (Gauthier et al. 2015).

Nowadays, along with the development of the hygiene hypothesis, many diseases have been linked to exposure to bacteria and parasites. What interests us is that parasites have

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Infectious Diseases of Poverty

LETTER TO THE EDITOR Open Access

Parasitology should not be abandoned: data from outpatient parasitological testing in Guangdong, China

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Abstract

Over the past six decades, the Chinese government made parasitoses with a high disease burden, including soil-transmitted nematode infections, malaria, leishmaniasis, filariasis, and schistosomiasis, a public health priority because they were seen to be crucial impediments to the development of rural areas. As a result, these debilitating parasitic diseases that used to be widely prevalent have been well controlled or eliminated. Consequently, less attention has been paid to parasitic infection during the rapid development of the economy, especially in developed areas. However, our investigations conducted in the parasitological laboratory of Sun Yat-sen University (Guangzhou, Guangdong, China) show that emerging parasitic diseases still threaten many people's health, with 340 of 880 outpatients (38.6%) receiving a diagnosis of parasitic disease, among whom 201 (59.1%) had clonorchiasis and 120 (35.3%) had taeniasis/cysticercosis. Furthermore, our doctors are not equipped with sufficient parasitology knowledge because this discipline is not able to maintain attraction. Many parasitic infections that result in severe consequences are treatable and preventable, but the phenomena of misdiagnosis and missed diagnosis are common and merit attention.

Keywords: Parasitic diseases, Parasitology, Guangdong Province, P. R. China

Multilingual abstracts

Please see Additional file 1 for translations of the abstract into the five official working languages of the United Nations.

Background

China used to suffer greatly from parasitic infections [1, 2]. For example, lymphatic filariasis was highly prevalent in China 60 years ago, with 31 million cases and 330 million people at risk of endemic infection living in 864 counties of 16 provinces, autonomous regions, and municipalities. Its most spectacular symptom is elephantiasis — edema with thickening of the skin and underlying tissues that causes dramatic loss of labour to society, followed by tremendous economic loss [3, 4]. To enhance the population's health, China spared no effort to fight against parasites over the past six decades, which led to great progress in parasitic disease control. For example, the conventional major parasitic diseases in China (soil-transmitted nematode infections, malaria, leishmaniasis, filariasis, and schistosomiasis) either have been eliminated or are well controlled [3–9]. Therefore, less attention is paid to parasite control than before. Instead, non-communicable chronic diseases such as cancer, diabetes, respiratory diseases, hypertension, and dementia are becoming common causes of disability and mortality [10, 11], and therefore, studies in this field are increasingly popular, and parasitology is no longer a hot discipline. Parasitology used to be a compulsory and key course for all medical students in China, but this is no longer the case. More and more medical schools have decided to devote fewer resources to the course. Hence, the scale of parasitology becomes smaller and smaller [12, 13]. As a result, departments of parasitology in China have been abrogated or integrated to pathogenic biology or pathogen and immunology [14]. Furthermore, the time spent studying parasitology has been significantly shortened in some medical schools in China [12, 15].

Parasitic infections are becoming neglected diseases, especially in well-developed areas with good sanitary and

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ORIGINAL ARTICLE

Plasma D-dimer Can Effectively Predict the Prospective Occurrence of Ascites in Advanced Schistosomiasis Japonica Patients

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Abstract: China still has more than 30,000 patients of advanced schistosomiasis while new cases being reported consistently. D-dimer is a fibrin degradation product. As ascites being the dominating symptom in advanced schistosomiasis, the present study aimed to explore a prediction model of ascites with D-dimer and other clinical easy-achievable indicators. A case-control study nested in a prospective cohort was conducted in schistosomiasis-endemic area of southern China. A total of 291 patients of advanced schistosomiasis were first investigated in 2013 and further followed in 2014. Information on clinical history, physical examination, and abdominal ultrasonography, including the symptom of ascites was repeatedly collected. Result showed 44 patients having ascites. Most of the patients' ascites were confined in the kidney area with median area of 20 mm^2. The level of plasma D-dimer and pertinent liver function indicators were measured at the initial investigation in 2013. Compared with those without ascites, cases with ascites had significantly higher levels of D-dimer (0.71±2.44 μg/L vs 0.48±2.12 μg /L, $P=0.005$), as well ALB (44.5 vs 46.2, g/L) and Type IV collagen (50.04 vs 44.50 μg/L). Receiver operating characteristic curve analyses indicated a moderate predictive value of D-dimer by its own area under curve (AUC) of 0.64 (95% CI: 0.54-0.73) and the cutoff value as 0.81 μg/L. Dichotomized by the cutoff level, D-dimer along with other categorical variables generated a prediction model with AUC of 0.76 (95% CI: 0.68-0.89). Risks of patients with specific characteristics in the prediction model were summarized. Our study suggests that the plasma D-dimer level is a reliable predictor for incident ascites in advanced schistosomiasis japonica patients.

Key words: *Schistosoma japonicum*, D-dimer, ascites, prediction, schistosomiasis japonica, China

INTRODUCTION

Schistosomiasis japonica, caused by the infection of *Schistosoma japonicum*, is a widely distributed parasitic zoonoses that threatens human's health and social economic development [1,2]. The epidemic situation of the disease used to be serious in China. Comprehensive schistosomiasis control strategies in the past decades decreased a concrete number of infected cases from 1.52 million in 1989 to 0.12 million in 2013, and most of the endemic areas are controlled within the status of transmission interruption [2]. However, new challenges emerged that the remaining disease transmission in the geographically complex areas turns to be more challengable and that more infected patients who were not treated thoroughly are now developing into the late stage, i.e., advanced schistosomiasis [3-5]. Meanwhile, a few patients who received the standard clinical treatment timely still keep on the development to advanced schistosomiasis [3,5-8]. According to a 2014 national wide report, 115,614 cases of *S. japonicum* infection were estimated, and 30,880 patients are suffering from advanced schistosomiasis. Advanced schistosomiasis is characterized by hepatosplenic conditions, such as periportal liver fibrosis, spleen enlargement and congestion, portal hypertension, and other serious sequelae. The late stage schistosomiasis is hitherto difficult, if not impossible, to be fully recovered. Thus, with an increasing proportion of advanced cases in the overall disease spectrum, researchers should provide effective prevention strategies with early detection, early diagnosis, and early treatment.

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Plasminogen kringle 5 suppresses gastric cancer via regulating HIF-1α and GRP78

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Inhibition of tumour angiogenesis has an important role in antitumour therapy. However, a recent study indicates that antiangiogenesis therapy may lead to glucose-related protein 78 (GRP78) associated antiapoptotic resistance. The present study aims to elucidate the dual effects of plasminogen kringle 5 (K5) on tumour angiogenesis and apoptosis induction by targeting hypoxia-inducible factor 1α (HIF-1α) and GRP78. Co-immunoprecipitation and western blotting were used for examining the ubiquitination of HIF-1α and analysing angiogenesis and apoptosis-associated proteins. K5 promoted the sumo/ubiquitin-mediated proteasomal degradation of HIF-1α by upregulating von Hippel-Lindau protein under hypoxia, resulting in the reduction of vascular endothelial growth factor and thus suppressing tumour angiogenesis. Furthermore, K5 decreased GRP78 expression via downregulation of phosphorylated extracellular-regulated protein kinase, leading to caspase-7 cleavage and tumour cell apoptosis. Blocking voltage-dependent anion channel abrogated the effects of K5 on both HIF-1α and GRP78. K5 significantly inhibited the growth of gastric carcinoma xenografts by inhibiting both angiogenesis and apoptosis. The dual effects suggest that K5 might be a promising bio-therapeutic agent in the treatment of gastric cancer, particularly in patients who exhibit the induction of GRP78.

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Gastric cancer is an aggressive malignancy that is frequently diagnosed at an advanced stage with poor prognosis. Although surgery and/or a combination of chemotherapy improve the survival rates, the 5-year relative survival rates of the patients receiving these treatments remains low at 30% and that of the patients with advanced disease is <1 year.[1,2] Therefore, it is necessary to develop more effective therapeutic strategies.

As the growth and survival of most tumour cells is dependent on oxygen and nutrient supply, angiogenesis has been a long-standing and attractive therapeutic target for treating malignant tumours.[3] Angiogenesis is induced by hypoxic conditions and regulated by hypoxia-inducible factor 1α (HIF-1α) and its major target gene, vascular endothelial growth factor (VEGF).[4] The expression of HIF-1α and VEGF is increased in many human cancers.[5,6] Close association between high-level expression of HIF-1α and VEGF and patient mortality have been demonstrated in cancers of brain, breast, cervix, oropharynx, ovary, and uterus.[7] Preclinical studies have shown that inhibition of VEGF pathway impedes tumour growth. VEGF-neutralizing antibody Avastin (bevacizumab) and VEGF receptor tyrosine kinase inhibitors (sorafenib and sunitinib) inhibit primary tumour growth in clinical applications and have been used as anticancer treatments in several tumour types.[8] However, clinical observations indicate that these therapies may have limited efficacy because the response has been mostly transient, in addition to the development of drug resistance.[9] Glucose-related protein 78 (GRP78) could be induced by severe glucose and oxygen deprivation resulting from antivascular and antiangiogenesis therapies, which could lead to drug resistance in an HIF-1α-independent manner.[10] In conditions of stress or hypoxia associated with oncogenesis, GRP78, a major endoplasmic reticulum chaperone, has an essential role in counteracting the apoptosis, which promotes cancer cell proliferation, survival, metastasis, and resistance to a wide variety of therapies.[11,12]

K5, the fifth kringle domain in human plasminogen, has been shown to display the most potent inhibitory effect on endothelial cells and angiogenesis.[13] Some studies have demonstrated the antiangiogenesis and antitumour effects of K5 both *in vivo* and *in vitro*.[14,15] Our previous study also

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BMJ Open

Predicting the hand, foot, and mouth disease incidence using search engine query data and climate variables: an ecological study in Guangdong, China

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ABSTRACT

Objectives Hand, foot, and mouth disease (HFMD) has caused a substantial burden in China, especially in Guangdong Province. Based on the enhanced surveillance system, we aimed to explore whether the addition of temperate and search engine query data improves the risk prediction of HFMD.

Design Ecological study.

Setting and participants Information on the confirmed cases of HFMD, climate parameters and search engine query logs was collected. A total of 1.36 million HFMD cases were identified from the surveillance system during 2011–2014. Analyses were conducted at aggregate level and no confidential information was involved.

Outcome measures A seasonal autoregressive integrated moving average (ARIMA) model with external variables (ARIMAX) was used to predict the HFMD incidence from 2011 to 2014, taking into account temperature and search engine query data (Baidu Index, BDI). Statistics of goodness-of-fit and precision of prediction were used to compare models (1) based on surveillance data only, and with the addition of (2) temperature, (3) BDI, and (4) both temperature and BDI.

Results A high correlation between HFMD incidence and BDI (r=0.794, p<0.001) or temperature (r=0.657, p<0.001) was observed using both time series plot and correlation matrix. A linear effect of BDI (without lag) and non-linear effect of temperature (1 week lag) on HFMD incidence were found in a distributed lag non-linear model. Compared with the model based on surveillance data only, the ARIMAX model including BDI reached the best goodness-of-fit with an Akaike information criterion (AIC) value of −345.332, whereas the model including both BDI and temperature had the most accurate prediction in terms of the mean absolute percentage error (MAPE) of 101.745%.

Conclusions An ARIMAX model incorporating search engine query data significantly improved the prediction of HFMD. Further studies are warranted to examine whether including search engine query data also improves the prediction of other infectious diseases in other settings.

Strengths and limitations of this study

- Using a 4 year large-scale provincial-wide surveillance dataset on hand, foot, and mouth disease (HFMD), a seasonal autoregressive integrated moving average (ARIMA) model incorporating search engine query data (ARIMAX) was fitted to facilitate accurate and timely detection, and the robustness of the model was shown.
- The assessment of the lag-specific associations between predictors and the HFMD incidence provided evidence for the importance of setting lag of the predictors in the ARIMAX model.
- The increasing internet penetration in China may lead to an overestimation of the increasing trend in the HFMD incidence rate.
- Ecological fallacy could not be ruled out because a higher web search frequency was unlikely to increase the risk of HMFD.

INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a major public health problem in China, affecting over two million children annually.[1 2] Notably, the incidence of HFMD in Guangdong Province exceeded 30 per 10 000 person years, which was more than four times the average national level.[3 4] Mathematical models including multiple factors for predicting an outbreak of HMFD are urgently needed to reinforce an integrated management for monitoring, control and prevention of HFMD.

The autoregressive integrated moving average (ARIMA) model was used to predict hepatitis incidence using the historical surveillance data.[5] In addition, the seasonal ARIMA models have also been used to predict the evolution of some major infectious diseases satisfactorily, such as malaria and hepatitis A,[6] influenza,[7] pneumonia,[8] and dengue fever.[9] Some studies showed that the addition of external variables (ARIMAX) in the ARIMA model (ie, Google search queries) might improve the prediction.[10 11] Google search queries are the most commonly used data

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ORIGINAL PAPER

Prevalence of *Toxoplasma gondii* infection in HIV-infected patients and food animals and direct genotyping of *T. gondii* isolates, Southern Ghana

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Abstract *Toxoplasma gondii* is of public health and veterinary importance causing severe diseases in immunocompromised individuals including HIV/AIDS patients and in congenital cases and animals. There is limited information on the epidemiology of *T. gondii* infection in humans, particularly HIV patients and food animals and the parasite genotypes in Ghana. A total of 394 HIV-infected patients from three hospitals were screened for *T. gondii* anti-IgG and IgM using ELISA. DNAs from blood samples of seropositve participants and 95 brain tissues of food animals were PCR assayed to detect *Toxoplasma gra6*. DNA positive samples were genotyped using multilocus nested polymerase chain reaction restriction fragment length polymorphism at 10 loci: *sag1*, *alt.sag2*, *sag3*, *btub*, *gra6*, *l358*, *c22-8*, *c29-2*, *pk1*, and *apico*. The overall seroprevalence was 74.37% (293/394). *Toxoplasma* DNAs were detected in 3.07% of the seropositive participants and 9.47% of the animals. Six of the human DNA positive samples were partly typed at *sag3*: 33.33, 50, and 16.67% isolates had type I, II, and III alleles, respectively. All nine isolates from food animals typed at nine loci except *apico* were atypical: six isolates were identical to ToxoDB #41 and #145, and one was identical to TgCkBrRj2 all identified in Brazil. The genotype of two isolates has not been reported previously and was named as TgCtGh1. *T. gondii* seroprevalence is high among the HIV-infected individuals with *T. gondii* circulating in Ghana being genetically diverse.

Keywords *Toxoplasma* · Human · Animals · HIV · Prevalence · Genotyping · Ghana

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Introduction

The protozoan *Toxoplasma gondii* (*T. gondii*) is a coccidian and an obligate intracellular parasite that infects warm-blooded animals (Howe and Sibley 1995). Felids, the only definitive host, are central in the transmission of this parasite. Infected felids excrete oocysts, the environmentally resistant form of *T. gondii* in their feces. In the environment, sporulated oocysts become infectious to many homeothermic vertebrates that act as the intermediate hosts. Within the intermediate hosts, *T. gondii* forms tissue cysts in many organs including those in the central nervous system, skeletal muscle, and visceral organs (Montoya and Liesenfeld 2004). Humans and animals become infected postnatally mainly by ingesting raw and undercooked infected meat containing viable *Toxoplasma* tissue cysts or food or drink contaminated with *Toxoplasma* oocysts excreted from the feces of infected cats. This makes toxoplasmosis a major foodborne (Torgerson et al.

Prevalence, risk factors, outcomes, and molecular epidemiology of *mcr-1*-positive Enterobacteriaceae in patients and healthy adults from China: an epidemiological and clinical study

Yang Wang, Guo-Bao Tian*, Rong Zhang*, Yingbo Shen*, Jonathan M Tyrrell, Xi Huang, Hongwei Zhou, Lei Lei, Hong-Yu Li, Yohei Doi, Ying Fang, Hongwei Ren, Lan-Lan Zhong, Zhangqi Shen, Kun-Jiao Zeng, Shaolin Wang, Jian-Hua Liu, Congming Wu, Timothy R Walsh, Jianzhong Shen*

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See Articles page 400

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Summary

Background The *mcr-1* gene confers transferable colistin resistance. *mcr-1*-positive Enterobacteriaceae (MCRPE) have attracted substantial medical, media, and political attention; however, so far studies have not addressed their clinical impact. Herein, we report the prevalence of MCRPE in human infections and carriage, clinical associations of *mcr-1*-positive *Escherichia coli* (MCRPEC) infection, and risk factors for MCRPEC carriage.

Methods We undertook this study at two hospitals in Zhejiang and Guangdong, China. We did a retrospective cross-sectional assessment of prevalence of MCRPE infection from isolates of Gram-negative bacteria collected at the hospitals from 2007 to 2015 (prevalence study). We did a retrospective case-control study of risk factors for infection and mortality after infection, using all MCRPEC from infection isolates and a random sample of *mcr-1*-negative *E coli* infections from the retrospective collection between 2012 and 2015 (infection study). We also did a prospective case-control study to assess risk factors for carriage of MCRPEC in rectal swabs from inpatients with MCRPEC and *mcr-1* negative at the hospitals and collected between May and December, 2015, compared with *mcr-1*-negative isolates from rectal swabs of inpatients (colonisation study). Strains were analysed for antibiotic resistance, plasmid typing, and transfer analysis, and strain relatedness.

Findings We identified 21 621 non-duplicate isolates of Enterobacteriaceae, *Acinetobacter* spp, and *Pseudomonas aeruginosa* from 18 698 inpatients and 2923 healthy volunteers. Of 17 498 isolates associated with infection, *mcr-1* was detected in 76 (1%) of 5332 *E coli* isolates, 13 (<1%) of 348 *Klebsiella pneumoniae*, one (<1%) of 890 *Enterobacter cloacae*, and one (1%) of 162 *Enterobacter aerogenes*. For the infection study, we included 76 *mcr-1*-positive clinical *E coli* isolates and 508 *mcr-1*-negative isolates. Overall, MCRPEC infection was associated with male sex (209 [41%] *vs* 47 [63%], adjusted p=0·011), immunosuppression (30 [6%] *vs* 11 [15%], adjusted p=0·011), and antibiotic use, particularly carbapenems (45 [9%] *vs* 18 [24%], adjusted p=0·002) and fluoroquinolones (95 [19%] *vs* 23 [30%], adjusted p=0·017), before hospital admission. For the colonisation study, we screened 2923 rectal swabs from healthy volunteers, of which 19 were MCRPEC, and 1200 rectal swabs from patients, of which 35 were MCRPEC. Antibiotic use before hospital admission (p<0·0001) was associated with MCRPEC carriage in 35 patients compared with 378 patients with mcr-1-negative *E coli* colonisation, whereas living next to a farm was associated with mcr-1-negative *E coli* colonisation (p=0·03, univariate test). *mcr-1* could be transferred between bacteria at high frequencies (10^{-1} to 10^{-3}), and plasmid types and MCRPEC multi-locus sequence types (MLSTs) were more variable in Guangdong than in Zhejiang and included the human pathogen ST131. MCRPEC also included 17 unreported ST clades.

Interpretation In 2017, colistin will be formally banned from animal feeds in China and switched to human therapy. Infection with MRCPEC is associated with sex, immunosuppression, and previous antibiotic exposure, while colonisation is also associated with antibiotic exposure. MLST and plasmid analysis shows that MCRPEC are diversely spread throughout China and pervasive in Chinese communities.

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Introduction

The relentless increase in multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria is worrying and has led to several global initiatives to unify national and international agenda to combat MDR and XDR infections.[1–4] Global awareness was precipitated by the rapid dissemination of carbapenem resistance mechanisms such as NDM-1, KPC, and OXA-48/181, and the realisation of the small number of antibiotics left to treat serious infections, such as colistin.[5–8] Until recently, colistin resistance was reported to be mediated by chromosomal mutations and possibly imposed a fitness cost to the organism.[9,10] Resistance to colistin is common in *Klebsiella pneumoniae*

Rb Silencing Mediated by the Down-Regulation of MeCP2 Is Involved in Cell Transformation Induced by Long-Term Exposure to Hydroquinone

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Hydroquinone (HQ), a metabolite of benzene, is a well-known human carcinogen; however, its molecular mechanisms of action remain unclear. MeCP2 has been traditionally described as a transcriptional repressor, though growing evidence indicates that it also activates gene expression. Here, we investigated whether some epigenetic machinery genes are aberrantly expressed as target tumor suppressor genes in HQ-transformed TK6 lymphoblastoid cells. Our results showed that treatment with 5-Aza-2′-deoxycytidine or trichostatin A enhanced the expression of Rb, resulting in cell arrest in G1-phase, and subsequently, an increase in apoptosis and a decrease in cell growth. Moreover, we hypothesised that Rb was silenced by the down-regulation of MeCP2 in HQ-transformed cells, resulting in the dynamic expression of Rb and epigenetic machinery proteins in HQ-transformed cells at different time points. The expression of Rb and MeCP2 in patients with B-cell non-Hodgkin's lymphoma (B-NHL) showed that positive staining for MeCP2 or Rb was significantly lower in B-NHL tumor tissues, and these changes were significantly and negatively correlated with the grade of B-NHL. The restoration of MeCP2 in HQ-transformed cells enhanced the expression of Rb, promoted cell apoptosis, and inhibited cell growth. The changes in the expression patterns of MeCP2 and Rb were inversely correlated with the degree of DNA methylation. A ChiP assay revealed that MeCP2 proteins were recruited to the Rb promoter with lower 5′-methylcytosine levels. In conclusion, we demonstrated that the down-regulation of MeCP2 silences Rb, a process involved in cell transformation resulting from long-term exposure to HQ.

Key words: hydroquinone; Rb; MeCP2; DNA methylation; cell transformation

INTRODUCTION

Benzene is classified as a human carcinogen by the International Agency for Research on Cancer [1]. Exposure to benzene is a cause of acute myeloid leukaemia (AML) and myelodysplastic syndrome [2], as well as a probable cause of other haematological malignancies, such as non-Hodgkin lymphoma

Abbreviations: 5-AzaC, 5-aza-2′-deoxycytidine; AML, acute myeloid leukaemia; ATRX, alpha thalassaemia/mental retardation syndrome X linked; BCA, bicinchoninic Acid; BRM, human Brahma; ChIP, chromatin immunoprecipitation; CTCF, CCCTC-binding factor; CREB1, cAMP responsive element binding protein 1; DAB, diaminobenzidine tetrahydrochloride; DMSO, dimethyl sulphoxide; DNMT, DNA methyltransferase; E2f1/2, E2 F transcription factor 1/2; Foxp3, forkhead box P3; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; Glut3, glucose transporter type 3; HDAC, histone deacetylases; HQ, hydroquinone; IDM3, increased DNA methylation 3; LOI, loss of imprinting; MBP, methyl-CpG-binding proteins; MeCP2, methyl-CpG binding protein 2; MSP, methylation-specific PCR; NF1C, nuclear factor 1 transcription C; NF1X, nuclear factor 1 X; NHL, non-Hodgkin lymphoma; N-Myc, v-myc avian myelocytomatosis viral oncogene neuroblastoma-derived homologue; PTGS2, prostaglandin-endoperoxide synthase 2; Rb, retinoblastoma gene; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1; TSA, trichostatin A; TSG, tumor suppressor genes.

Conflicts of interest: The authors declare that there are no conflicts of interest.

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Parasites & Vectors

RESEARCH Open Access

Recombinant α-actinin subunit antigens of *Trichomonas vaginalis* as potential vaccine candidates in protecting against trichomoniasis

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Abstract

Background: Human trichomoniasis caused by *Trichomonas vaginalis* is one of the most common sexually transmitted diseases with more than 200 million cases worldwide. It has caused a series of health problems to patients. For prevention and control of infectious diseases, vaccines are usually considered as one of the most cost-efficient tools. However, until now, work on the development of *T. vaginalis* vaccines is still mainly focused on the screening of potential immunogens. Alpha-actinin characterized by high immunogenicity in *T. vaginalis* was suggested as a promising candidate. Therefore, the purpose of this study was to evaluate the protective potency of recombinant α-actinin against *T. vaginalis* infection in a mouse intraperitoneal model.

Methods: Two selected coding regions of α-actinin (ACT-F, 14–469 aa and ACT-T, 462–844 aa) amplified from cDNA were cloned into pET-32a (+) expression vector and transfected into BL21 cells. After induction with IPTG and purification with electroelution, the two recombinant fusion proteins were emulsified in Freund's adjuvant (FA) and used to immunize BALB/C mice. Following intraperitoneal inoculation with *T. vaginalis*, the survival rate of mice was monitored for the assessment of protective potency. After immunization, the antibody level in mouse serum was assessed by ELISA, splenocyte proliferation response was detected with CCK8 and cytokines in the supernatant of splenocytes were quantified with a cytometric bead-based assay.

Results: We successfully obtained purified ACT-F (70.33 kDa) and ACT-T (61.7kDa). Both recombinant proteins could provide significant protection against *T. vaginalis* challenge, especially ACT-T (with 100% protection within one month). Meanwhile, high levels of specific total IgG and subtypes (IgG1 > IgG2a) were detected in sera from the immunized mice. Our results also revealed a statistically significant increase in splenocyte proliferation and related cytokine (IFN-γ, IL-6, IL-17A and IL-10) production after repeated stimulation with the corresponding antigens in vitro.

Conclusions: Immunization with both ACT-F and ACT-T could confer partial to complete protection and trigger strong Th1/Th2 mixed humoral and cellular immune responses in the mouse host. This suggested that recombinant α-actinin subunit antigens may be promising vaccine candidates against trichomoniasis.

Keywords: *Trichomonas vaginalis*, Alpha-actinin, Recombinant protein, Vaccine

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Theranostics

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Research Paper

rSj16 Protects against DSS-Induced Colitis by Inhibiting the PPAR-α Signaling Pathway

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Abstract

Background: Epidemiologic studies and animal model experiments have shown that parasites have significant modulatory effects on autoimmune disorders, including inflammatory bowel disease (IBD). Recombinant Sj16 (rSj16), a 16-kDa secreted protein of *Schistosoma japonicum* (*S.japonicum*) produced by *Escherichia coli* (*E. coli*), has been shown to have immunoregulatory effects *in vivo* and *in vitro*. In this study, we aimed to determine the effects of rSj16 on dextran sulfate sodium (DSS)-induced colitis.

Methods: DSS-induced colitis mice were treated with rSj16. Body weight loss, disease activity index (DAI), myeloperoxidase (MPO) activity levels, colon lengths, macroscopic scores, histopathology findings, inflammatory cytokine levels and regulatory T cell (Treg) subset levels were examined. Moreover, the differential genes expression after treated with rSj16 were sequenced, analyzed and identified.

Results: rSj16 attenuated clinical activity of DSS-induced colitis mice, diminished pro-inflammatory cytokine production, up-regulated immunoregulatory cytokine production and increased Treg percentages in DSS-induced colitis mice. Moreover, DSS-induced colitis mice treated with rSj16 displayed changes in the expression levels of specific genes in the colon and show the crucial role of peroxisome proliferator activated receptor α (PPAR-α) signaling pathway. PPAR-α activation diminished the therapeutic effects of rSj16 in DSS-induced colitis mice, indicating that the PPAR-α signaling pathway plays a crucial role in DSS-induced colitis development.

Conclusions: rSj16 has protective effects on DSS-induced colitis, effects mediated mainly by PPAR-α signaling pathway inhibition. The findings of this study suggest that rSj16 may be useful as a therapeutic agent and that PPAR-α may be a new therapeutic target in the treatment of IBD.

Key words: parasites, rSj16, inflammatory bowel disease, protective effects, PPAR-α.

Introduction

Inflammatory bowel disease (IBD), which comprises Crohn's disease (CD) and ulcerative colitis (UC), is a chronic relapsing idiopathic disease characterized by epithelial barrier damage and inflammation homeostasis disruption in the intestinal tract [1, 2, 3]. The etiologies of both CD and UC remain unknown; however, it is generally believed that both diseases are associated with multiple pathogenic factors, including environmental changes, arrays of gene variants resulting in disease susceptibility, qualitative and quantitative gut microbiota abnormalities and broadly dysregulated

PLOS | NEGLECTED TROPICAL DISEASES

SYMPOSIUM

Case report: A rare case of urinary myiasis induced by the fourth instar larvae of *Telmatoscopus albipunctatus*

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Abstract

Telmatoscopus albipunctatus, a cosmopolitan fly, is widely distributed throughout moist environments. It is one of the most medically important insects (especially in urban environments) that may potentially cause myiasis. Urinary myiasis and other sites of infestation, including the intestine, nasal passages, lung, and derma, have been reported. This is the first case report of a Chinese middlescent woman infected with *T. albipunctatus* in Guangzhou, China. In the present report, a 50-year-old woman came to The Third Affiliated Hospital of Southern Medical University, Guangzhou, China, because larvae were found when urinating in the morning; this had occurred every two days within the past two months. She complained of frequent micturition and urgency. Urine tests indicated that all indexes were normal except for slight urinary tract infection. Subsequently, the larvae were sent to the diagnostic section for parasitic infection in the Department of Parasitology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China. The stereoscopic microscope and transmission electron microscope were used for morphological observation. On this basis, the cytochrome oxidase subunit 1 (*COX1*) gene was specifically amplified by PCR. Sequence analysis of the PCR product and phylogenetic analysis were used to identify the species. Morphological analysis combined with molecular biology methods indicated that the insect was the fourth instar larvae of *T. albipunctatus*. Our results show that this was a case of a 50-year-old woman infected with *T. albipunctatus* larvae in her urinary tract, and the findings suggest that clinicians should be vigilant for this infection.

Introduction

Psychodidae is a cosmopolitan fly that is tiny and hairy. It belongs to the family Nematoceran and is a medically important insect, especially in urban areas. Most of the adults are distributed throughout houses, stinking ditches, or septic tanks, and the larvae are bred in moist

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Parasites & Vectors

RESEARCH Open Access

Secreted phospholipase A2 of *Clonorchis sinensis* activates hepatic stellate cells through a pathway involving JNK signalling

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Abstract

Background: Secreted phospholipase A2 (sPLA2) is a protein secreted by *Clonorchis sinensis* and is a component of excretory and secretory products (*Cs*ESPs). Phospholipase A2 is well known for its role in liver fibrosis and inhibition of tumour cells. The JNK signalling pathway is involved in hepatic stellate cells (HSCs) activation. Blocking JNK activity with SP600125 inhibits HSCs activation. In a previous study, the protein *Css*PLA2 was expressed in insoluble inclusion bodies. Therefore, it's necessary to express *Css*PLA2 in water-soluble form and determine whether the enzymatic activity of *Css*PLA2 or cell signalling pathways is involved in liver fibrosis caused by clonorchiasis.

Methods: *Balb/C* mice were given an abdominal injection of MBP-*Css*PLA2. Liver sections with HE and Masson staining were observed to detect accumulation of collagen. Western blot of mouse liver was done to detect the activation of JNK signalling pathway. In vitro, HSCs were incubated with MBP-*Css*PLA2 to detect the activation of HSCs as well as the activation of JNK signalling pathway. The mutant of MBP-*Css*PLA2 without enzymatic activity was constructed and was also incubated with HSCs to check whether activation of the HSCs was related to the enzymatic activity of MBP-*Css*PLA2.

Results: The recombinant protein MBP-*Css*PLA2 was expressed soluble and of good enzymatic activity. A mutant of *Css*PLA2, without enzymatic activity, was also constructed. In vivo liver sections of *Balb/C* mice that were given an abdominal injection of 50 μg/ml MBP-*Css*PLA2 showed an obvious accumulation of collagen and a clear band of P-JNK1 could be seen by western blot of the liver tissue. In vitro, MBP-*Css*PLA2, as well as the mutant, was incubated with HSCs and it was proved that activation of HSCs was related to activation of the JNK signalling pathway instead of the enzymatic activity of MBP-*Css*PLA2.

Conclusions: Activation of HSCs by *Css*PLA2 is related to the activation of the JNK signalling pathway instead of the enzymatic activity of *Css*PLA2. This finding could provide a promising treatment strategy to interrupt the process of liver fibrosis caused by clonorchiasis.

Keywords: Phospholipase A2, *Clonorchis sinensis*, Enzyme, Liver fibrosis, Cholangiocarcinoma, JNK signalling pathway

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Health and Disability

Seeing the big picture: Broadening attention relieves sadness and depressed mood

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We examined whether the broadened attentional scope would affect people's sad or depressed mood with two experiments, enlightened by the meaning of "seeing the big picture" and the broaden-and-build model. Experiment 1 (n = 164) is a laboratory-based experiment, in which we manipulated the attentional scope by showing participants zoomed-out or zoomed-in scenes. In Experiment 2 (n = 44), we studied how depressed mood and positive and negative emotions were affected when participants watched distant versus proximal scenes for eight weeks in real life. Healthy participants in Experiment 1, who were induced to feel sad, could return to the baseline mood after having the broadened attention task but not after having the narrowed attention task, which indicated that immediate attention broadening manipulation could function as antidotes for the lingering effects of induced negative emotions. Participants with depressed mood in Experiment 2 showed reduced depressed mood, increased positive affect, and decreased negative affect after receiving attention broadening training compared to those receiving attention narrowing training. Our findings suggest a robust role of broadened attentional scope in relieving negative emotions and even mildly depressed mood in the long run.

Key words: Attentional scope, negative emotion, broadened attention, depressed mood.

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INTRODUCTION

In Western countries, it is considerably common to hear people say, "seeing the big picture," when they try to cheer someone up. Interestingly, language descriptors of "seeing the big picture" seem to be universal across cultures. In China, to encourage others to drive away negative emotions, people usually say, "Kan (4) Kai(1) Dian(3)," which means literally "seeing broadly." These language descriptions are intended to get people broaden their attentional scope in order to regulate their negative emotions, which is consistent with the broaden-and-build model (Fredrickson, 1998, 2001) and other research (e.g., Gable & Harmon-Jones, 2010; Srinivasan & Hanif, 2010; Wadlinger & Isaacowitz, 2006) suggesting the idea of a bi-directional relationship between emotion and attention: emotion modulates attention, and attention modulates emotion at the same time.

The broaden-and-build model (Fredrickson, 1998, 2001), which bridges emotion and attention, posits that positive emotions are able to broaden one's thought–action repertoires while negative emotions have the opposite effect. Specifically, positive emotions build lasting psychological resources (e.g., resilience; Fredrickson *et al*., 2003), while negative emotions prevent individuals from thinking broadly and from building enduring psychological resources. On the flip side, the broaden-and-build model implies that broadened thinking promotes positive emotions and narrowed thinking leads to negative emotions. Positive emotions and broadened thinking reciprocate each other and build a complementary "upward spiral" that would benefit emotional well-being. Negative emotions and the narrowed thinking influence each other and build a "downward spiral," which leads to emotional problems or even emotional disorders such as depression (Fredrickson & Joiner, 2002).

There is much evidence supporting the bi-directional emotion-attention relationship in line with the broaden-and-build model. On the one hand, the impact of emotion on attention has been well-documented through behavioral tests (e.g., Fredrickson & Branigan, 2005; Gasper & Clore, 2002), eye-tracking (Wadlinger & Isaacowitz, 2006) as well as brain imaging (Schmitz, De Rosa & Anderson, 2009; Soto, Funes, Guzman-Garcia, Warbrick, Rotshtein & Humphreys, 2009). Quite a few studies have consistently shown that positive emotions predict broadened attention and negative emotions predict narrowed attention (Basso, Schefft, Ris & Dember, 1996; Chajut & Algom, 2003; Derryberry & Tucker, 1994; Fenske & Eastwood, 2003; Gable & Harmon-Jones, 2010; Uddenberg & Shim, 2015). For instance, Gasper and Clore (2002) found that participants in positive moods were more likely to use the global information but less likely to use the local details than those in negative moods in an

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Parasites & Vectors

RESEARCH Open Access

Sequence analysis and characterization of pyruvate kinase from *Clonorchis sinensis*, a 53.1-kDa homopentamer, implicated immune protective efficacy against clonorchiasis

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Abstract

Background: *Clonorchis sinensis*, the causative agent of clonorchiasis, is classified as one of the most neglected tropical diseases and affects more than 15 million people globally. This hepatobiliary disease is highly associated with cholangiocarcinoma. As key molecules in the infectivity and subsistence of trematodes, glycolytic enzymes have been targets for drug and vaccine development. *Clonorchis sinensis* pyruvate kinase (*Cs*PK), a crucial glycolytic enzyme, was characterized in this research.

Results: Differences were observed in the sequences and spatial structures of *Cs*PK and PKs from humans, rats, mice and rabbits. *Cs*PK possessed a characteristic active site signature (IKLIAKIENHEGV) and some unique sites but lacked the N-terminal domain. The predicted subunit molecular mass (Mr) of *Cs*PK was 53.1 kDa. Recombinant *Cs*PK (r*Cs*PK) was a homopentamer with a Mr. of approximately 290 kDa by both native PAGE and gel filtration chromatography. Significant differences in the protein and mRNA levels of *Cs*PK were observed among four life stages of *C. sinensis* (egg, adult worm, excysted metacercaria and metacercaria), suggesting that these developmental stages may be associated with diverse energy demands. *Cs*PK was widely distributed in adult worms. Moreover, an intense Th1-biased immune response was persistently elicited in rats immunized with r*Cs*PK. Also, rat anti-r*Cs*PK sera suppressed *C. sinensis* adult subsistence both in vivo and in vitro.

Conclusions: The sequences and spatial structures, molecular mass, and expression profile of *Cs*PK have been characterized. r*Cs*PK was indicated to be a homopentamer. Rat anti-r*Cs*PK sera suppressed *C. sinensis* adult subsistence both in vivo and in vitro. *Cs*PK is worthy of further study as a promising target for drug and vaccine development.

Keywords: *Clonorchis sinensis*, Pyruvate kinase, Pentamer, Expression profile, Excretory/secretory products, Immune response, Drug target, Vaccine candidate

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ARTICLE

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Simultaneous overactivation of Wnt/β-catenin and TGFβ signalling by miR-128-3p confers chemoresistance-associated metastasis in NSCLC

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Cancer chemoresistance and metastasis are tightly associated features. However, whether they share common molecular mechanisms and thus can be targeted with one common strategy remain unclear in non-small cell lung cancer (NSCLC). Here, we report that high levels of microRNA-128-3p (miR-128-3p) is key to concomitant development of chemoresistance and metastasis in residual NSCLC cells having survived repeated chemotherapy and correlates with chemoresistance, aggressiveness and poor prognosis in NSCLC patients. Mechanistically, miR-128-3p induces mesenchymal and stemness-like properties through downregulating multiple inhibitors of Wnt/β-catenin and TGF-β pathways, leading to their overactivation. Importantly, antagonism of miR-128-3p potently reverses metastasis and chemoresistance of highly malignant NSCLC cells, which could be completely reversed by restoring Wnt/β-catenin and TGF-β activities. Notably, correlations among miR-128-3p levels, activated β-catenin and TGF-β signalling, and pro-epithelial-to-mesenchymal transition/pro-metastatic protein levels are validated in NSCLC patient specimens. These findings suggest that miR-128-3p might be a potential target against both metastasis and chemoresistance in NSCLC.

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Research Paper: Gerotarget(Focus on Aging)

Soluble antigens from the neurotropic pathogen *Angiostrongylus cantonensis* directly induce thymus atrophy in a mouse model

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Keywords: *Angiostrongylus cantonensis*, central nervous system, thymic atrophy, soluble antigens, intrathymic injection, Gerotarget

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ABSTRACT

The nematode *Angiostrongylus cantonensis* (*A.C.*) is a neurotropic pathogen; stage-*III* larva invade the human (non-permissive host) central nervous system (CNS) to cause eosinophilic meningitis or meningoencephalitis accompanied by immunosuppression. In an *A.C.*-infected mouse (another non-permissive host) model, CNS damage-associated T cell immune deficiency and severe inflammation were proposed to result from activation of the hypothalamic-pituitary-adrenal (HPA) axis. However, glucocorticoids are anti-inflammatory agents. Additionally, while defects in thymic stromal/epithelial cells (TECs) are the major reason for thymic atrophy, TECs do not express the glucocorticoid receptor. Therefore, activation of the HPA axis cannot fully explain the thymic atrophy and inflammation. Using an *A.C.*-infected mouse model, we found that *A.C.*-infected mice developed severe thymic atrophy with dramatic impairments in thymocytes and TECs, particularly cortical TECs, which harbor $CD4^+CD8^+$ double-positive thymocytes. The impairments resulted from soluble antigens (sAgs) from *A.C.* in the thymuses of infected mice, as intrathymic injection of these sAgs into live mice and the addition of these sAgs to thymic cell culture resulted in thymic atrophy and cellular apoptosis, respectively. Therefore, in addition to an indirect effect on thymocytes through the HPA axis, our study reveals a novel mechanism by which *A.C.* infection in non-permissive hosts directly induces defects in both thymocytes and TECs via soluble antigens.

INTRODUCTION

Angiostrongylus cantonensis (*A.C.*) is a zoonotic nematode. When *A.C.*-infected larvae (stage-*III* larva) invade suitable hosts, such as rats, they are transported via the blood to the brain and finally to the pulmonary arteries of the hosts, where they mature to adulthood and oviposit to complete their life cycles. However, when the larvae invade non-permissive hosts, such as humans and mice, the infective larvae cannot travel to the lung to finish their life cycles; instead, they remain in the central nervous system (CNS) until their death. In the non-permissive host CNS, the larvae cannot develop further and migrate, leading to severe inflammation in the brain. *A.C.*-induced acute inflammation in the brain is characterized by eosinophilic meningitis or meningoencephalitis [1]. Currently, angiostrongyliasis has been reported worldwide, particularly in tropical countries, and is regarded as a serious public health problem. In recent years, several outbreaks of human angiostrongyliasis have been reported in China and other countries, and the harmful effects on human health have been recognized [2-5]. Interestingly, *A.C.* larvae do not invade the thymus directly in these non-permissive hosts, although angiostrongyliasis can

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ORIGINAL PAPER

Spleen atrophy related immune system changes attributed to infection of *Angiostrongylus cantonensis* in mouse model

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Abstract The spleen is one of the most important peripheral immune organs, which is frequently affected in infectious diseases. Infectious diseases can induce splenic alterations including splenic atrophy and functional alteration, while splenic atrophy may in turn interferes with recovery of infectious diseases. Angiostrongyliasis is an infectious disease by *Angiostrongylus cantonensis* (*A. cantonensis*), which invade non-permissive hosts, such as humans and mice, to cause severe damage to the central nervous system (CNS) and acute inflammatory response. *A. cantonensis* infection-induced CNS injury has been confirmed to be due to profound immunopathology derived from peripheral immune components. However, the mechanism of immunopathology remains largely unknown. Here, we found that *A. cantonensis* invaded non-permissive hosts such as mice in the brain, but not in the other peripheral organs. However, this infection induced severe spleen atrophy. We further recognized that this atrophy is associated with a decrease of total splenocyte number and disruption of splenic structure due to reduced proliferation and increased apoptotosis. These also resulted in deterioration of T cell profile in the periphery with a low CD4/CD8 ratio and B/T cell ratio, and increased ratio of $CD4^+CD25^+Foxp3^+$ Treg, $CD8^+CD28^-$ T, and $CD38^+$T lymphocyte of spleen. Albendazole treatment can alleviate spleen atrophy and set T cell immune reconstitution in some extend. Our data showed that *A. cantonensis* infection can cause splenic atrophy. These results are suggested to put more emphasis to improve the function of immune system. Meanwhile, infection and treatment model will be useful to evaluate new therapeutic approaches which can prevent or reverse immunosuppression and infectious complications.

Keywords *Angiostrongylus cantonensis* · CNS · Spleen atrophy · Treg cells · CD28 · CD38

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Research Article

Stabilized β-Catenin Ameliorates ALPS-Like Symptoms of B6/*lpr* Mice

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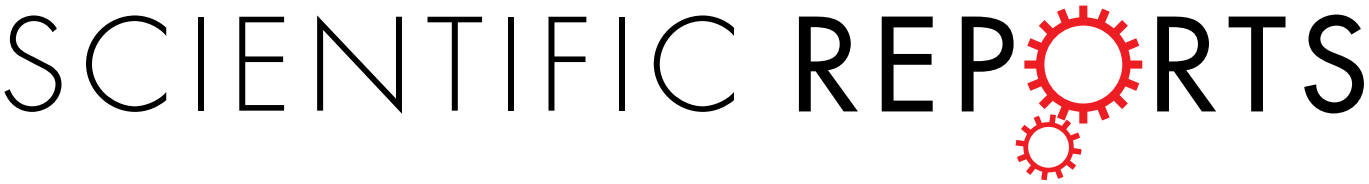
Autoimmune lymphoproliferative syndrome (ALPS) is an incurable disease mainly caused by the defect of Fas-mediated apoptosis and characterized by nonmalignant autoimmune lymphoproliferation. Stabilized β-catenin could not only potentiate Fas-mediated T cell apoptosis via upregulating the expression of Fas on activated T cells, but also potentiate T cell apoptosis via intrinsic apoptotic pathway. In the present study, we introduced β-cat^{Tg} into *lpr*/*lpr* mice and aimed to explore the potential role of stabilized β-catenin (β-cat^{Tg}) in the development of ALPS-like phenotypes of *lpr*/*lpr* mice. We found that the total splenocyte cells and some compositions were slightly downregulated in β-cat^{Tg}*lpr*/*lpr* mice, especially the CD4 and CD8 T_{EM} cells were significantly reduced. Meanwhile, stabilized β-catenin obviously decreased the numbers of spleen TCRβ^+CD4$^-$CD8$^-$ T (DNT) cells, and the levels of some serum proinflammatory factors also were lowered in β-cat^{Tg}*lpr*/*lpr* mice. Beyond that, stabilized β-catenin slightly lowered the levels of the serum autoantibodies and the scores of kidney histopathology of β-cat^{Tg}*lpr*/*lpr* mice compared with *lpr*/*lpr* mice. Our study suggested that stabilized β-catenin ameliorated some ALPS-like symptoms of *lpr*/*lpr* mice by potentiating Fas-independent signal-mediated T cell apoptosis, which might uncover a potential novel therapeutic direction for ALPS.

1. Background

To maintain homeostasis, apoptosis plays a critical role in lymphocyte development and activity. Excessive lymphocyte apoptosis can cause immune defects; however, inhibition of normal apoptosis can lead to the autoimmune disease or the occurrence of lymphoma [1]. So the immune system has developed some apoptotic mechanisms, in which activation-induced cell death (AICD) can be used to inhibit the excessive proliferation of T lymphocytes [1, 2]. Previous study reported that the proteins encoded by Fas and FasL genes were involved in the apoptosis of lymphocytes [3, 4]. As a major suppressing regulation, the AICD controls the homeostasis of T cell during immune response, in which activated T lymphocytes upregulate the expression of Fas (CD95), then interact with the Fas Ligand (FasL, CD95L) on activated B and T lymphocyte surface through the Fas-activating death domain (FADD) to trigger the caspase cascade, leading to proteolysis, DNA degradation, and induction of cell apoptosis [5].

β-Catenin, encoded by the CTNNB1 gene, is a multifunctional protein. It has dual roles in the cell, one of which is as the most important information molecule in the canonical Wnt pathway to regulate cell growth, differentiation and apoptosis, and so forth [6]. In the absence of Wnt signal stimulation, the target genes are usually kept inactive and bound by transcriptional corepressors. A cytosolic β-catenin "destruction" complex is composed of the adenomatous polyposis



OPEN

Suppression of autophagy by mycophenolic acid contributes to inhibition of HCV replication in human hepatoma cells

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Previous studies have shown that mycophenolic acid (MPA) has an anti-HCV activity. However, the mechanism of MPA-mediated inhibition of HCV replication remains to be determined. This study investigated whether MPA has an effect on autophagy, a cellular machinery required for HCV replication, thereby, inhibits HCV replication in Huh7 cells. MPA treatment of Huh7 cells could suppress autophagy, evidenced by decreased LC3B-II level and conversion of LC3B-I to LC3B-II, decreased autophagosome formation, and increased p62 level compared to MPA-untreated cells. Tunicamycin treatment or HCV infection could induce cellular autophagy, however, MPA also exhibited its inhibitory effect on tunicamycin- or HCV infection-induced autophagy. The expression of three autophagy-related genes, Atg3, Atg5, and Atg7 were identified to be inhibited by MPA treatment. Over-expression of these genes could partly recover HCV replication inhibited by MPA; however, silencing their expression by siRNAs could enhance the inhibitory effect of MPA on HCV. Collectively, these results reveal that suppression of autophagy by MPA plays a role in its anti-HCV activity. Down-regulating the expression of three autophagy-related genes by MPA involves in its antiviral mechanism.

Hepatitis C virus (HCV) infection is a global public health problem, with 170 million infected individuals worldwide, which represents ~3% of the world's population[1,2]. It is estimated 350 to 500 thousands deaths due to HCV-related hepatic diseases each year. The HCV epidemic can not be ignored in China where the estimated infection number is 5~10 million[3]. The end-stage hepatic diseases associated with HCV infection is a major reason of liver transplantation in the United States and Europe[4], which has become the effective operation for treatment of end-stage hepatic diseases[5]. However, the recurrence of HCV infection is the most common and serious complication of liver transplant HCV-infected patients, in post-transplantation which occurs in 70~80% of recipients, of whom 10~21% develop fibrosis and cirrhosis[4]. To prevent post-transplant graft rejection, the immunosuppressiants have also been applied widely in liver transplantation. Acting as a double-edged sword, the immunosuppression may accelerate viral replication, resulting in progression of chronic hepatitis C to severe allograft, fibrosis and cirrhosis[6].

Mycophenolate mofetil (MMF) has been considered to be an effective and safe immunosuppressive agent in organ transplantations[7] and treatments of autoimmune diseases[8]. Compared with calcineurin inhibitors (Cyclosporine and FK506), MMF lacks the nephrotoxicity. It is often used as a substitute or combined agent of

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TCF1 deficiency ameliorates autoimmune lymphoproliferative syndrome (ALPS)-like phenotypes of *lpr/lpr* mice

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Abstract

Autoimmune lymphoproliferative syndrome (ALPS) is an incurable disease, which is characterized by non-malignant autoimmune lymphoproliferation. TCF1 is a key effector in the canonical Wnt/β-catenin pathway, regulating the development, activation and function of T cells. In this study, we aimed to explore the potential role of TCF1 in the development of ALPS-like phenotypes of *lpr/lpr* mice. We acquired TCF1$^{-/-}$*lpr/lpr* double mutant mice by crossing TCF1 deficiency mice with *lpr/lpr* mice. Splenocyte compositions, serum cytokines levels, antidsDNA antibody production and kidney pathology were examined in the TCF1$^{-/-}$*lpr/lpr* mice. With these examinations, we revealed that TCF1 deficiency relieved most manifestations of ALPS-like phenotype, which were caused by Fas mutation in TCF1$^{-/-}$*lpr/lpr* mice. Splenocyte total numbers and compositions were down-regulated to the similar levels with wildtype mice. T_E and T_{EM} cells were decreased in TCF1$^{-/-}$*lpr/lpr* compared with *lpr/lpr* mice. The levels of autoantibodies and proinflammatory factors in serum, and the histopathology changes and the relative mRNA levels of proinflammatory factors in kidney all displayed parallel tendency in TCF1$^{-/-}$*lpr/lpr* mice. Our study demonstrated that TCF1 deficiency ameliorated the ALPS-like phenotypes of TCF1$^{-/-}$*lpr/lpr* mice, which might indicate a potential therapeutic direction for ALPS.

Introduction

TCF1, encoded by Tcf7 gene, is a key effector in downstream of the canonical Wnt/β-catenin pathway, which has been reported to regulate the regeneration of stem cells, the organogenesis of kidney and the multiple developmental processes of reproductive systems[1]. TCF1 regulates the various aspects of T cell development and the activation and function of mature CD4 and CD8 T cells. TCF1 also plays an important role in thymocytes development by multiple stages[2]. It promotes complete commitment in the T cell lineage, β-selection and the maturation of DN thymocytes to the DP stage[3, 4]. The differentiation of mature CD4+ T cells to T helper 2 (Th2) and Th17, and the formation and persistence of memory CD8+ T cells all are regulated by TCF1[5]. TCF1 also has an essential role in the development of natural killer T (NKT) cells from common CD4(+) CD8(+) thymocyte precursors[6]. The functions of CD8 T cell also have been regulated by Wnt, β-catenin and TCF1, and the memory-like phenotype of CD8 T cells and functions are induced by β-catenin transgene[5].

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by non-malignant autoimmunity lymphoproliferation caused by the defect of Fas-mediated apoptosis. The majority of patients with ALPS had mutations in the genes for the TNF receptor-family member Fas and its receptor Fas ligand (FasL)[7]. Fas and Fas ligand interaction triggered the caspase cascade, leading to proteolysis, DNA degradation and apoptosis. Activated T lymphocytes upregulated the expression of Fas, which interacted with Fas Ligand that were upregulated on activated B and T lymphocytes surface, and induced the cells apoptosis[8]. The *lpr/lpr* and *gld/gld* mice were two commonly used for ALPS disease murine models, and respective with Fas and FasL mutation[9, 10]. In these models, *lpr/lpr* and *gld/gld* mice all displayed a raised DNT subset, abnormal lymphoproliferation and syndrome of systemic lupus erythematosus(SLE)[9, 10].

Lpr/lpr mice showed the lupus-like diseases with a subset of symptoms similar to those observed in human ALPS, including increased autoantibody production, high level lymphocytes activation and proliferation, and lupus nephritis[11]. The lupus nephritis is common in Fas

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The Characteristics of Naive-like T Cells in Tumor-infiltrating Lymphocytes From Human Lung Cancer

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*Jian Yong Zou,‡ Yu Qing Zhang,‡ Rong Fu Wang,§ and Hai Hong**

Summary: Adoptive cell therapy using autologous tumor-infiltrating lymphocytes (TILs) or genetically modified lymphocytes from TILs is a new effective approach, but the application of TIL immunotherapy is still limited in many solid tumors. Knowledge of the classification and function of TILs is important to develop personalized immunotherapy with TILs in non–small lung cancer (NSCLC). In this study, we show the characteristics of T-cell subsets in TILs isolated from NSCLC. $CD3^+$ $CD8^+$ $CD45RA^+$ T cells outnumbered $CD3^+$ $CD4^+$ $CD45RA^+$ T cells in $CD45RA^+$ TILs, but it was the opposite in $CD45RO^+$ TILs. Effector memory $CD4^+$ T cells predominated in $CD4^+$ TILs; about 10% of the stem cell-like memory T cells (Tscm) were detected in TILs. To further analyze their functions, we stimulated TILs from NSCLC patients by mitogens to examine cytokine production. Our data demonstrated that naive-phenotype T cells in TILs secret IFN-γ in abundance; TNF-α-producing T cells were significantly increased in TILs; there were more IL-17-expressing $CD4^+$ Tscm cells than other subtypes of $CD4^+$ T cells in TILs. Our findings indicate that the $CD4^+/CD8^+$ naive-phenotype T cells and Tscm cells in TILs from lung cancer exhibit distinct composition and strong cytokine production. Attributes of Tscm cells from a naive-like T-cell population in TILs are the promising cell type for adoptive cell therapy in human lung cancer.

Key Words: T cell, tumor-infiltrating lymphocytes, lung cancer

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Tumor-infiltrating lymphocytes (TILs) were first described in 1863 by Robert Virchow and were found in proximity of the tumor.[1] TILs are identified as a heterogenous cell group, include effector T cells, T regulatory cells, natural killer cells, macrophages, dendritic cells, myeloid-derived suppressor cells, and other immune cell types.[1] The major populations of TILs that grow from tumors are $CD8^+$ T cells and $CD4^+$ T cells in vitro culture.[2] The frequency of TILs was correlated with a better prognosis in patients with different types of tumors,[3–5] including non–small lung cancer (NSCLC).[6,7] The subtypes of TILs in NSCLC have been reported with different prognostic effect. Mori et al's[8] report indicates that the number of $CD8^+$ TILs in NSCLC is not with a favorable prognosis; $CD4^+$ T cells, not $CD8^+$ T cells, in NSCLC cancer nests are associated with a favorable prognosis.[9] Hiraoka et al's[10] study demonstrated that the infiltration of $CD8^+$ and $CD4^+$ TIL cells are a favorable prognostic factor in NSCLC. In 2010, another report shows that a high frequency of $CD8^+$ TILs in NSCLC tissues is correlated with a favorable prognosis.[11] In light of recent studies of immunotherapy, adoptive cell therapy (ACT) immunotherapy with autologous TILs with the memory phenotype yields drastic regression of malignant melanoma,[12–15] whereas transferring terminal differentiation of TILs have poor antitumor immunity and short-term persistence.[12,16] In other human advanced cancer (such as NSCLC), the efficacy of TIL therapy is uncertain. To further improve the antitumor effect and therapeutic potential of ACT with TILs in NSCLC, it is necessary to identify the composition and function of T cells in TILs.

According to the surface marker, the function and proliferation capacity, T cells can be categorized into naive T cells (Tn), effector T cells (Teff), and memory T cells (Tm); memory T cells include central memory T cells (Tcm), effector memory T cells (Tem), stem cell-like memory T cells (Tscm), and tissue-resident memory T cells (Trm).[17,18] The distribution and function of Tscm cells in human lung cancer in the peripheral blood and lymph nodes have been studied.[19] In this study, we investigated the characteristics of T cells in TILs from NSCLC. We found that $CD3^+$ $CD8^+$ $CD45RA^+$ T cells outnumbered $CD3^+$ $CD4^+$ $CD45RA^+$ T cells, whereas $CD3^+$ $CD4^+$ $CD45RO^+$ T cells outnumbered $CD3^+$ $CD8^+$ $CD45RO^+$ T cells. $CD4^+$ Tem cells predominated in $CD4^+$ TILs, the proportion of $CD8^+$ Teff cells was higher than that of $CD4^+$ Teff cells. About 12% of $CD4^+$ Tscm and 10% of $CD8^+$ Tscm were detected in TILs. To further analyze the function of T-cell subsets in TILs, we stimulated TILs from NSCLC patients with mitogens to examine cytokine production. Our data demonstrate that naive-phenotype T cells in TILs secret interferon-γ (IFN-γ) in abundance; tumor necrosis factor (TNF)-α-producing T cells were significantly increased, but fewer $CD8^+$ Tscm cells produced TNF-α than $CD4^+$ Tscm cells in TILs; there were more interleukin-17 (IL-17)-expressing $CD4^+$ Tscm cells than other subtypes of $CD4^+$ T cells in TILs. An accurate understanding of the subsets of T cells in TILs from NSCLC is critical for the prognosis and personalized medicine with TILs immunotherapy.

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ORIGINAL ARTICLE

The distribution and function of human memory T cell subsets in lung cancer

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Abstract The distribution and function of T lymphocytes in human lung cancer remain limited. In this study, we investigated the properties of human T cell subsets in the blood of non-small cell lung cancer (NSCLC) patients. We found a relatively normal level of CD4+ subsets in the blood of NSCLC patients, but CD8+ effector T cells increased and CD8+ effector memory cells declined compared to the healthy donors. To further analyze their properties, we stimulated the peripheral blood mononuclear cells (PBMCs) of NSCLC patients by mitogens to examine cytokine production. Our data suggest that both CD4+ and CD8+ naïve cells in NSCLC patients significantly reduced IFN-γ and TNF-α production. Additionally, fewer CD8+ effector cells produced IFN-γ and TNF-α in NSCLC patients than in healthy subjects. Moreover, similar results were observed for CD4+ or CD8+ memory cells in NSCLC patients for the production of IFN-γ, TNF-α, and IL-17. Therefore, our results strongly suggest that the function of CD4+ and CD8+ T lymphocytes in NSCLC patients is compromised or dysregulated. The development of vaccines and antitumor immunotherapy may be essential for the treatment of lung cancer patients.

Keywords Human memory T cell · Lung cancer

Si Yuan Sheng and Yong Gu are co-first author.

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Introduction

Immunological memory is critical for long-term immunity and protection from infection. After naïve T cells are activated by the antigen, naïve T cells differentiate into effector T cells, depending on the anatomical position and phenotypic characteristics; effector T cells display different functions [1]. However, only a small fraction of effector T cells becomes long-lived memory T cell to provide lifelong protection against the previously encountered pathogens [2, 3]. With respect to the tissue homing-related molecular expression, memory T cells can be divided into two categories, central memory T cells (Tcm) and effector memory T cells (Tem) [4]. Recent data revealed that adoptively transferred different subsets of memory T cells have different antitumor activity in mouse models [5]. The distribution and function of human memory T cells have been identified in healthy subjects [6], but the physiological distribution and function of human T cell subsets in lung cancer are still limited. Clearly, the understanding of the compartmentalization of memory T cell subsets will provide valuable basis for designing tumor immunotherapy.

Current studies focus on the frequency of the tumor-infiltrating lymphocytes (TILs) to predict the prognosis of cancer patients [7]. The high frequency of CD4+ T cells in TILs and malignant pleural effusions (MPEs) correlates with a favorable prognosis in lung cancer patients [8, 9]; however, other studies indicate that the high number of CD8+ T cells, not CD4+ T cells, in TILs has a good clinical outcome [10–12]. The distinct distribution of CD4+ and CD8+ T cell

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

The interplay of climate, intervention and imported cases as determinants of the 2014 dengue outbreak in Guangzhou

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Data Availability Statement: The number of daily reported new cases can be downloaded freely from the Health Department of Guangdong Province (http://www.gdwst.gov.cn/a/yiqingxx/). The monthly average mosquito surveillance data was provided in the supporting information file S1 Table of Ref. 7 (http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004417). The number of foreign tourists staying overnight in Guangzhou and the number of tourists who travelled from Guangzhou with tour groups are provided in S1 Table.

Abstract

Dengue is a fast spreading mosquito-borne disease that affects more than half of the population worldwide. An unprecedented outbreak happened in Guangzhou, China in 2014, which contributed 52 percent of all dengue cases that occurred in mainland China between 1990 and 2015. Our previous analysis, based on a deterministic model, concluded that the early timing of the first imported case that triggered local transmission and the excessive rainfall thereafter were the most important determinants of the large final epidemic size in 2014. However, the deterministic model did not allow us to explore the driving force of the early local transmission. Here, we expand the model to include stochastic elements and calculate the successful invasion rate of cases that entered Guangzhou at different times under different climate and intervention scenarios. The conclusion is that the higher number of imported cases in May and June was responsible for the early outbreak instead of climate. Although the excessive rainfall in 2014 did increase the success rate, this effect was offset by the low initial water level caused by interventions in late 2013. The success rate is strongly dependent on mosquito abundance during the recovery period of the imported case, since the first step of a successful invasion is infecting at least one local mosquito. The average final epidemic size of successful invasion decreases exponentially with introduction time, which means if an imported case in early summer initiates the infection process, the final number infected can be extremely large. Therefore, dengue outbreaks occurring in Thailand, Singapore, Malaysia and Vietnam in early summer merit greater attention, since the travel volumes between Guangzhou and these countries are large. As

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The Maternally Inheritable *Wolbachia* *w*AlbB Induces Refractoriness to *Plasmodium berghei* in *Anopheles stephensi*

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The endosymbiont *Wolbachia* *w*AlbB induces refractoriness to *Plasmodium falciparum* in *Anopheles stephensi*, the primary mosquito vector of human malaria in the Middle East and South Asia. However, it remains unknown whether such refractoriness can be extended to other malaria species. In particular, it was reported that under very specific conditions, *w*AlbB can enhance *Plasmodium* infection in some hosts. Here, we measured the impact of *w*AlbB on the rodent malaria parasite *Plasmodium berghei* in *A. stephensi* by comparing the load of oocysts and sporozoites in midguts and salivary glands, respectively, between *w*AlbB-infected and -uninfected mosquitoes. To investigate whether *w*AlbB modulated mosquito immune defense against parasites, we compared the expression of the immune genes, which were previously reported to involve in antimalarial response, in both midguts and the remaining carcass tissues of mosquitoes. The stable association of *w*AlbB with *A. stephensi* resulted in reduction of parasites by more than half at the oocyst stage, and up to 91.8% at the sporzoite stage. The anti-*plasmodium* immune genes, including *TEP1*, *LRIM1*, Toll pathway gene *Rel1* and the effector *Defensin 1*, were induced by *w*AlbB in different mosquito body tissues. These findings suggest that immune priming is a potential cause of *w*AlbB-mediated antimalarial response in *A. stephensi*. More importantly, no evidence was found for any enhancement of *Plasmodium* infection in *A. stephensi* stably infected with *w*AlbB. We discuss these findings with possible implementations of *Wolbachia* for malaria control in disease endemic areas.

Keywords: *Wolbachia*, *Plasmodium*, malaria, population replacement, vector-borne disease, innate immunity

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INTRODUCTION

Transmitted by *Anopheles* mosquitoes, malaria is one of the world's deadliest diseases caused by protozoan parasites of the genus *Plasmodium*. Although significant efforts and resources have been devoted to malaria control, especially over the past decade, there are still 3.2 billion people currently living in areas of high malaria risk, with about 214 million cases of clinical malaria and 438,000 malaria-related deaths in WHO (2015). Given the lack of a highly effective vaccine and the

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Original Article

The plasmid-mediated fosfomycin resistance determinants and synergy of fosfomycin and meropenem in carbapenem-resistant *Klebsiella pneumoniae* isolates in Taiwan

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KEYWORDS
Fosfomycin;
Carbapenem resistance;

Abstract *Background:* Epidemiology of fosfomycin susceptibility and the plasmid-mediated fosfomycinase genes of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) isolates in Taiwan remain unclear.
Methods: 642 CRKP clinical isolates were collected from a nation-wide surveillance study (16 hospitals) in Taiwan in 2012–2013. Antimicrobial susceptibilities were determined. PFGE and

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Translational Neurodegeneration

REVIEW Open Access

The role of gene variants in the pathogenesis of neurodegenerative disorders as revealed by next generation sequencing studies: a review

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Abstract

The clinical diagnosis of neurodegenerative disorders based on phenotype is difficult in heterogeneous conditions with overlapping symptoms. It does not take into account the disease etiology or the highly variable clinical course even amongst patients diagnosed with the same disorder. The advent of next generation sequencing (NGS) has allowed for a system-wide, unbiased approach to identify all gene variants in the genome simultaneously. With the plethora of new genes being identified, genetic rather than phenotype-based classification of Mendelian diseases such as spinocerebellar ataxia (SCA), hereditary spastic paraplegia (HSP) and Charcot-Marie-Tooth disease (CMT) has become widely accepted. It has also become clear that gene variants play a role in common and predominantly sporadic neurodegenerative diseases such as Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). The observation of pleiotropy has emerged, with mutations in the same gene giving rise to diverse phenotypes, which further increases the complexity of phenotype-genotype correlation. Possible mechanisms of pleiotropy include different downstream effects of different mutations in the same gene, presence of modifier genes, and oligogenic inheritance. Future directions include development of bioinformatics tools and establishment of more extensive public genotype/phenotype databases to better distinguish deleterious gene variants from benign polymorphisms, translation of genetic findings into pathogenic mechanisms through in-vitro and in-vivo studies, and ultimately finding disease-modifying therapies for neurodegenerative disorders.

Keywords: Next generation sequencing, Neurodegenerative diseases, Genetics, Pleiotropy

Background

Traditionally, neurological disorders have been classified and diagnosed based on clinical features such as symptom-onset and disease course, and characterization of physical signs to allow localization of abnormalities in the nervous system. While most acute neurological conditions can be diagnosed with reasonable certainty, the same cannot be said to be true in chronic neurodegenerative conditions, where the definitive diagnosis can often only be ascertained by specific pathologic findings. For example, studies have shown that the accuracy of Parkinson's disease (PD) diagnosis by neurologists was only 65–75%, which has not changed significantly in the last two decades [1].

Even in diseases that are hereditary with a clear genetic contribution, the clinical diagnosis remains difficult due to significant heterogeneity both in clinical features and genetic causes. This is evident in spinocerebellar ataxias (SCA) and hereditary spastic paraplegia (HSP). To date, 40 SCAs have been characterized, and 28 causal genes have been identified [2]. Genetically defined HSPs are assigned the symbol SPG (spastic gait) followed by a number. It is a highly heterogeneous group of disorders, with more than 80 genes or loci implicated [3]. There is significant overlap in clinical features of the two syndromes that

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Exosomes Derived from Dendritic Cells Treated with *Schistosoma japonicum* Soluble Egg Antigen Attenuate DSS-Induced Colitis

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Exosomes are 30–150 nm small membrane vesicles that are released into the extracellular medium via cells that function as a mode of intercellular communication. Dendritic cell (DC)-derived exosomes modulate immune responses and prevent the development of autoimmune diseases. Moreover, *Schistosoma japonicum* eggs show modulatory effects in a mouse model of colitis. Therefore, we hypothesized that exosomes derived from DCs treated with *S. japonicum* soluble eggs antigen (SEA; SEA-treated DC exosomes) would be useful for treating inflammatory bowel disease (IBD). Exosomes were purified from the supernatant of DCs treated or untreated with SEA and identified via transmission electron microscopy, western blotting and NanoSight. Acute colitis was induced via the administration of dextran sulfate sodium (DSS) in drinking water (5.0%, wt/vol). Treatment with exosomes was conducted via intraperitoneal injection (i.p.; 50 μg per mouse) from day 0 to day 6. Clinical scores were calculated based on weight loss, stool type, and bleeding. Colon length was measured as an indirect marker of inflammation, and colon macroscopic characteristics were determined. Body weight loss and the disease activity index of DSS-induced colitis mice decreased significantly following treatment with SEA-treated DC exosomes. Moreover, the colon lengths of SEA-treated DC exosomes treated colitis mice improved, and their mean colon macroscopic scores decreased. In addition, histologic examinations and histological scores showed that SEA-treated DC exosomes prevented colon damage in acute DSS-induced colitis mice. These results indicate that SEA-treated DC exosomes attenuate the severity of acute DSS-induced colitis mice more effectively than DC exosomes. The current work suggests that SEA-treated DC exosomes may be useful as a new approach to treat IBD.

Keywords: soluble egg antigen, dendritic cell, exosomes, dextran sulfate sodium, inflammatory bowel disease

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MINI REVIEW
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The Roles of Mast Cells in Parasitic Protozoan Infections

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Protozoan parasites such as *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., and *Toxoplasma gondii* are major causes of parasitic diseases in both humans and animals. The immune system plays a critical role against protozoa, but their immune mechanism remains poorly understood. This highlights the need to investigate the function of immune cells involved in the process of parasite infections and the responses of host immune system to parasite infections. Mast cells (MCs) are known to be central players in allergy and anaphylaxis, and it has been demonstrated that MCs have crucial roles in host defense against a number of different pathogens, including parasites. To date, there are many studies that have examined the interaction of helminth-derived antigens and MCs. As one of the major effector cells, MCs also play an important role in the immune response against some parasitic protozoa, but their role in protozoan infections is, however, less well characterized. Herein, we review the current knowledge about the roles of MCs and their mediators during infections involving highly pathogenic protozoa including *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., and *T. gondii*. We offer a general review of the data from patients and experimental animal models infected with the aforementioned protozoa, which correlate MCs and MC-derived mediators with exacerbated inflammation and disease progression as well as protection against the parasitic infections in different circumstances. This review updates our current understanding of the roles of MCs during parasitic protozoan infections, and the participation of MCs in parasitic protozoan infections could be of a potential therapeutic target.

Keywords: mast cell, *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., *Toxoplasma gondii*

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INTRODUCTION

Plasmodium spp., *Leishmania* spp., *Trypanosoma* spp., and *Toxoplasma gondii* are some of the most important medical protozoan parasites that cause diseases in humans. *Plasmodium* spp. is a group of mosquito-borne parasitic protozoa. After being bitten by an *Anopheles* mosquito, sporozoites penetrate the liver cells of the host and produce thousands of free merozoites, which invade erythrocytes and then burst the cells to release the merozoites to invade other erythrocytes and cause clinical symptoms (1). *Leishmania* spp. comprises several species and causes leishmaniasis, which affects more than 300 million people worldwide (2). This parasite has a complex life cycle composed of two distinct stages: the promastigote form found in the female sandfly vector and the amastigote form replicated in the mammalian host (3). *Trypanosoma brucei* causes the fatal illness human African trypanosomiasis (4), which is adapted to parasitize the mammalian bloodstream

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REVIEW

Therapeutic potential of helminths in autoimmune diseases: helminth-derived immune-regulators and immune balance

Meng Wang[1,2] · Linxiang Wu[1,2] · Rennan Weng[1,2] · Weihong Zheng[1,2] · Zhongdao Wu[1,2,3] · Zhiyue Lv[1,2,3]

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Abstract Helminths have accompanied human throughout history by releasing immune-evasion molecules that could counteract an aberrant immune response within the host. In the past decades, helminth infections are becoming less prevalent possibly due to the developed sanitation. Meanwhile, the incidence of autoimmune diseases is increasing, which cannot be exclusively explained by the changes of susceptibility genes. While the hygiene hypothesis casts light on the problem. The infections of helminths are believed to interact with and regulate human immunity with the byproduct of suppressing the autoimmune diseases. Thus, helminths are potential to treat or cure the autoimmune diseases. The therapeutic progresses and possible immune suppression mechanisms are illustrated in the review. The helminths that are studied most intensively include *Heligmosomoides polygyrus, Hymenolepis diminuta*, *Schistosoma mansoni, Trichinella spiralis*, and *Trichuris suis*. Special attentions are paid on the booming animal models and clinical trials that are to detect the efficiency of immune-modulating helminth-derived molecules on autoimmune diseases. These trials provide us with a prosperous clinical perspective, but the precise mechanism of the down-regulatory immune response remains to be clarified. More efforts are needed to be dedicated until these parasite-derived immune modulators could be used in clinic to treat or cure the autoimmune diseases under a standard management.

Keywords Helminths · Autoimmune diseases · Therapeutic potential · Immune balance

Introduction

Helminths are parasitic worms that are composed of several categories named monogeneans, cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes). Each worm parasites in the specific host. It is believed the secretion of immune-evasion molecules which could counteract an aberrant immune response within the host that accounts for the parasitic phenomenon (Hewitson et al. 2009; Keiser and Utzinger 2009).

Autoimmune diseases, by classical definition, occur when the normal body molecules are pathologically attacked by the immune system. It is a large category of disorders that contain more than 70 diseases, of which the representatives include multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), inflammatory bowel disease (IBD), sarcoidosis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and etc. (Patt et al. 2013). More than 5% of the western people are affected by the autoimmune disease with more female patients than male (Bashi et al. 2015; Osada and Kanazawa 2010). Growing evidences have shown that the structure of one's microbial community is particularly associated with autoimmune diseases (Diamanti et al. 2016; Lin and Zhang 2017). Microbiota, settling in host's skin, oral cavity and intestinal tract, as well as their products are closely related

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Original Article

TIMELESS confers cisplatin resistance in nasopharyngeal carcinoma by activating the Wnt/β-catenin signaling pathway and promoting the epithelial mesenchymal transition

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ABSTRACT

This study investigated the expression, clinicopathological significance and mechanism of action of TIMELESS, a mammalian homolog of a Drosophila circadian rhythm gene, in nasopharyngeal carcinoma. Quantitative real-time PCR, western blotting and immunohistochemistry revealed TIMELESS was upregulated in NPC cell lines (n = 8 vs. NP69 cells), and freshly-frozen (n = 6) and paraffin-embedded human NPC specimens (n = 108 vs. normal samples/non-tumor cells). TIMELESS expression was associated with T category ($P = 0.002$), N category ($P = 0.001$), clinical stage ($P < 0.001$), metastasis ($P = 0.047$), vital status ($P = 0.013$) and serum Epstein–Barr DNA ($P = 0.005$). High TIMELESS expression was associated with poorer overall survival (80.7% vs. 95.9%; $P = 0.004$) and progression free survival (68.1% vs. 88.0%; $P = 0.005$). Univariate and multivariate analysis revealed TIMELESS was an independent prognostic factor for overall survival and progression free survival. Stable ectopic overexpression of TIMELESS in NPC cell lines conferred resistance to cisplatin-induced apoptosis *in vitro* and *in vivo*, promoted an epithelial-to-mesenchymal transition phenotype, and activated the Wnt/β-catenin pathway and downstream gene transcription; knockdown of TIMELESS had the opposite effects. TIMELESS may play a role in the development of NPC and could represent a valuable prognostic factor and potential therapeutic target.

Introduction

Nasopharyngeal carcinoma (NPC) has a distinct ethnogeographic distribution and high incidence in Guangdong, Southern China [1,2], where environmental factors, genetic predisposition and Epstein–Barr virus (EBV) infection contribute to its pathogenesis [3,4]. Concurrent chemoradiotherapy (CCRT) with cisplatin-based regimens is the standard treatment and intensity-modulated radiotherapy (IMRT) results in excellent locoregional control [5–14]. However, chemoresistance remains a major obstacle in NPC, and can result in distant metastasis and local recurrence after CCRT [15,16]. Multiple mechanisms lead to cisplatin resistance [17], including reduced cisplatin uptake and accumulation, alterations to DNA repair mechanisms and DNA mismatch repair [18] and inhibition of apoptosis, via various cell

List of abbreviations: NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival; EBV, Epstein–Barr virus; CCRT, concurrent chemoradiotherapy; IMRT, intensity-modulated radiotherapy; UICC, Union for International Cancer Control; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

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Opinion

Unpacking 'Artemisinin Resistance'

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Artemisinin and its derivatives, in combination with partner drugs, are currently the most effective treatments for malaria parasite infection. Even though artemisinin has been widely used for decades, its mechanism of action had remained controversial until recently. Artemisinin combination therapies (ACTs) have recently been found to be losing efficacy in Southeast Asia. This 'artemisinin resistance', defined by a delayed parasite clearance time, has been associated with several genetic mutations. As with any other drug resistance phenotype, resistance can best be understood based on its mechanism of action. Recently, it was demonstrated that artemisinin attacks multiple parasitic targets, suggesting that mutations in drug targets are unlikely to cause high-level artemisinin resistance. These findings will help us to better understand the mechanisms of artemisinin resistance and suggest protocol modifications that may improve the efficacy of ACTs.

Trends

Artemisinin and its derivatives are prodrugs that require heme for activation.

Heme-activated artemisinins are free radicals and promiscuously bind hundreds of parasite proteins.

'Artemisinin resistance', manifesting as a delayed parasite clearance time, is due to changes in parasite life-cycle progression and enhanced stress response pathways rather than the parasite becoming insensitive to artemisinin throughout its life cycle.

Optimizing current ACTs holds the promise to overcome 'artemisinin resistance'.

Artemisinin Combination Therapies and Resistance

ACTs are now the standard of care for the treatment of malaria, particularly that caused by *Plasmodium falciparum* infection [1–4]. The therapies include one artemisinin derivative plus a second, slower-acting, antimalarial drug with a longer half-life [5,6]. There are many different ACTs on the market, all of which are administered for 3 days [4,7]. It has been known since the 1980s that a 3-day course of artemisinin monotherapy is not curative [7–14]. Thus, ACTs rely on the cooperation of artemisinin and its partner drug to cure malaria infection. Given that artemisinin is so fast acting, the early decline in parasitemia (often called the 'parasite clearance time' or PCT) is due to the artemisinin component of the treatment mix. The remaining parasites are effectively mopped up by the second drug.

There have be many recent reports of persistent parasitaemias after a 3-day course of ACT, triggering concerns over the emergence of artemisinin resistance [15–19]. Indeed, incomplete parasite clearance after a 3-day course of ACT has become the definition of artemisinin resistance. It is important to note that no malaria parasite strains, regardless of their origin and genetic backgrounds, have been shown to be insensitive to artemisinin tested by standard *in vitro* killing assays. Thus, while there is clear evidence showing the emergence and spread of parasites in Southeast Asia that require longer clearance times (more than 3 days) [18,20–27], it is still controversial whether the delayed PCT is truly a predictor of artemisinin resistance [11,28–31].

A better understanding of the working mechanism of artemisinin at a molecular level could lead to a better understanding of resistance and the survival strategies that parasite use. Here, we review more than two decades of studies on the mechanism of action of artemisinin. Together with recent work on the physiological characteristics of malaria parasites requiring longer clearance times, these findings provide the biochemical foundation to unpack 'artemisinin resistance' [32–39].

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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Genome-wide SNPs reveal the drivers of gene flow in an urban population of the Asian Tiger Mosquito, *Aedes albopictus*

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Abstract

Aedes albopictus is a highly invasive disease vector with an expanding worldwide distribution. Genetic assays using low to medium resolution markers have found little evidence of spatial genetic structure even at broad geographic scales, suggesting frequent passive movement along human transportation networks. Here we analysed genetic structure of *Aedes albopictus* collected from 12 sample sites in Guangzhou, China, using thousands of genome-wide single nucleotide polymorphisms (SNPs). We found evidence for passive gene flow, with distance from shipping terminals being the strongest predictor of genetic distance among mosquitoes. As further evidence of passive dispersal, we found multiple pairs of full-siblings distributed between two sample sites 3.7 km apart. After accounting for geographical variability, we also found evidence for isolation by distance, previously undetectable in *Ae. albopictus*. These findings demonstrate how large SNP datasets and spatially-explicit hypothesis testing can be used to decipher processes at finer geographic scales than formerly possible. Our approach can be used to help predict new invasion pathways of *Ae. albopictus* and to refine strategies for vector control that involve the transformation or suppression of mosquito populations.

Author summary

Aedes albopictus, the Asian Tiger Mosquito, is a highly invasive disease vector with a growing global distribution. Designing strategies to prevent invasion and to control *Ae. albopictus* populations in invaded regions requires knowledge of how *Ae. albopictus* disperses. Studies comparing *Ae. albopictus* populations have found little evidence of genetic structure even between distant populations, suggesting that dispersal along human transportation networks is common. However, a more specific understanding of dispersal processes has been unavailable due to an absence of studies using high-resolution genetic markers.

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REVIEW

Recent advances in the identification of the host factors involved in dengue virus replication

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Dengue virus (DENV) belongs to the genus *Flavivirus* of the family *Flaviviridae* and it is primarily transmitted via *Aedes aegypti* and *Aedes albopictus* mosquitoes. The life cycle of DENV includes attachment, endocytosis, protein translation, RNA synthesis, assembly, egress, and maturation. Recent researches have indicated that a variety of host factors, including cellular proteins and microRNAs, positively or negatively regulate the DENV replication process. This review summarizes the latest findings (from 2014 to 2016) in the identification of the host factors involved in the DENV life cycle and Dengue infection.

KEYWORDS dengue virus (DENV); host factors; replication; proteins; miRNAs

INTRODUCTION

The dengue virus (DENV) is a positive-sense single-stranded RNA virus that belongs to family *Flaviviridae*. Currently, four DENV serotypes have been identified (DENV1–4) (Casseb et al., 2016). All of these serotypes are able to cause a flu-like disease (dengue fever) as well as more severe diseases, such as dengue hemorrhagic fever and dengue shock syndrome (Gubler, 1998). The DENV genome is approximately 11 kb in length with a 5′ type I m^7G cap structure, and it encodes a polyprotein. The polyprotein is post-translationally cleaved by host and viral proteases into three structural proteins (the capsid, C; premembrane/membrane, prM/M; envelope, E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (Green et al., 2014).

The DENV virions enter their target cells via receptor-mediated endocytosis in a clathrin-dependent manner (Acosta et al., 2008; Savidis et al., 2016). In an acidified endosomal vesicle, the virion undergoes conformational changes that enable fusion with the endosomal membrane, releasing the genome RNA into the cytosol (Zaitseva et al., 2010). After the initial translation and cleavage of the polyprotein, DENV triggers the formation of a replication complex in the perinuclear endoplasmic reticulum, where RNA replication and protein translation occur (Welsch et al., 2009). The newly synthesized positive-sense RNA is then packaged by the C protein and assembled into an enveloped virion that is covered with prM/E heterodimers. When the vesicles containing the immature virions move through the Golgi apparatus, prM is cleaved by a furin protease. Finally, the immature virions become mature or partially mature virions, which are secreted (Yu et al., 2008).

Research indicates that the ten proteins encoded by the compact DENV genome are insufficient for viral replication. The virus has evolved many strategies to hijack and utilize host factors throughout its life cycle. Host factors have been implicated in the promotion of almost every step of the viral life cycle, including entry, RNA synthesis, protein expression, assembly, egress, and maturation. On the other hand, research has indicated that some host factors protect cells from virus infection and replication.

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