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

2018 年年报

中山大学中山医学院

广 州

2019 年 1 月

目　录

一、基本概况

中山大学热带病防治研究教育部重点实验室于 2003 年正式批准成立，2007 年通过验收并开放运行，2010 年和 2016 年教育部重点实验室评估获得“优秀”。重点实验室依托于中山医学院管理，充分发挥学科历史优势和地处广东的区位优势，以保障国家生物安全和国民健康为导向，开展重要热带病的防治基础和相关前沿研究，将其建设成为全球热带病防治应用基础和前沿研究、技术创新、人才培养和学术交流的主要基地之一。

实验室有固定人员 72 人，其中具有博士学位人员 58 人（80%），高级职称 48 人。主体科研场所集中于中山大学北校园医学科技楼 11～15 楼和生物安全楼 6～8 楼，总面积达 9200 平方米。目前实验室仪器设备总值 8000 多万元，其中价值超 10 万元仪器共 80 台，仪器全量、全方位、全覆盖、全时共享预订和使用。

二、定位与方向

本重点实验室围绕热带病防控和生物安全等领域的科学前沿问题，重点研究解决严重危害人类健康的热带传染性疾病的病原和发病机制、临床和诊治、媒介和防控等关键问题,是国际领先的学术研究中心、技术研发中心和人才培养基地，为消灭、控制和预防热带病、保障国家生物安全、提升国家国际影响力作出重要贡献。

热带病防治教育部重点实验室以重要热带寄生虫病、热带病毒病、热带细菌病为主要研究对象，主要围绕四个方向开展研究：（1）重要寄生虫病与媒介防控（2）重要虫媒病毒并几其他热带病毒病的防治研究；（3）结核病及细菌耐药机制研究；（4）生物安全技术和反向病原学研究。

三、总体运行情况

1、承担科研任务

本年度2018年新增纵向科研项目56项，横向项目2项，合同经费达9092.1万元，到账经费4797.1万元。新增科研项目中，国家级项目21项，省部级18项。其中，传染病重大项目主持1项；国家自然科学基金重点项目2项，优青1项，面上项目10项。

2018年实验室新增科研项目

序	项目名称	项目编号	负责人	项目类别	立项日期	合同经费（万元）
1	艾滋病精准诊治标志物的鉴定	2018ZX10302-103	张辉	重大专项传染病重大专项主持项目	2018-01-01	1843.15
2	TCR-T与CAR-T联合免疫治疗清除储存库临床研究	/	潘婷	重大专项传染病重大专项参与项目	2018-01-01	1363.69
3	利用膜蛋白组学方法筛查潜伏感染细胞表面新型标志物（张辉分本）	/	潘婷	重大重点项目分本重大专项校内分本	2018-01-01	133.25
4	单泛素化NEMO网络失控促DNA损伤炎症诱发恶性转化的分子机制	81830082	李隽	国家自然科学基金重点项目	2018-08-18	293
5	质粒介导多粘菌素耐药新机制 MCR-1的传播和进化及抑制剂研究	81830103	田国宝	国家自然科学基金重点项目	2018-08-18	294
6	超保守非编码 RNA uc.243 诱导卵巢癌顺铂耐药的分子机制	91740119	李隽	国家自然科学基金重大研究计划/培育项目	2018-01-01	100
7	临床细菌耐药与感染	81722030	田国宝	国家自然科学基金优秀青年科学基金项目	2018-01-01	130

8	转录调节因子 PHF14 通过调控 TGF-β 信号通路促进非小细胞肺癌转移的分子机制研究	81802274	田寒	国家自然科学基金青年科学基金项目	2018-08-18	21
9	BRD4 对 PMN-MDSC 分化的调控作用及其在肿瘤中的病理意义	81873862	Dmitry Gabrilovich	国家自然科学基金面上项目	2018-08-17	57
10	寨卡病毒非结构蛋白负调节干扰素通路介导血脑屏障突破的分子机制研究	81870960	朱勋	国家自然科学基金面上项目	2018-08-16	56
11	PEDF 抑制乳腺癌异质血管生成的作用及机制	81872165	高国全	国家自然科学基金面上项目	2018-08-18	57
12	血吸虫感染所致胸腺萎缩对虫卵肉芽肿及纤维化发生的作用机制研究	81871682	吴忠道	国家自然科学基金面上项目	2018-08-16	57
13	EBV 早期裂解复制抑制炎症小体通路的机制和功能研究	81871643	况二胜	国家自然科学基金面上项目	2018-08-18	57
14	XPF/ERCC1 复合物在抗体类别转换中介导 DNA 双链断裂修复的机制研究	81871304	董俊超	国家自然科学基金面上项目	2018-08-18	57
15	基于非线性动力学驱动的癫痫发作预测深度学习研究	61876194	周毅	国家自然科学基金面上项目	2018-08-18	60
16	细胞发育谱系树比对算法的设计与应用	31871320	杨建荣	国家自然科学基金面上项目	2018-08-18	60
17	新型乙型肝炎病毒核衣壳组装抑制剂的设计合成及其抗病毒机制的研究	21877132	柏川	国家自然科学基金面上项目	2018-08-18	63
18	基于非线性动力学驱动的癫痫发作预测深度学习研究	/	周毅	国家自然科学基金面上项目	2018-08-16	60
19	细胞膜相关的长非编码 RNA 在肺癌发生发展中的生物学作用与调控机制	81820108025	黎孟枫	国家自然科学基金国际(地区)合作与交	2018-08-18	241

				流项目		
20	中英抗菌药物耐药研讨会	/	曾谷城	国家自然科学基金国际(地区)合作与交流项目	2018-10-01	1.5
21	国家寄生虫种质资源共享服务平台	平台-TDRC-22	吕志跃	科技部其他	2018-06-01	20
22	2018 年青年千人计划引进人才科研启动费 2（丁涛）	/	丁涛	人才项目“青年千人计划”引进人才配套经费	2018-06-05	300
23	2018 年青年千人计划引进人才科研启动费 2（陈俊）	/	陈俊	人才项目“青年千人计划”引进人才配套经费	2018-06-06	300
24	2017 年青年千人计划引进人才科研启动费（董俊超）	/	董俊超	人才项目“青年千人计划”引进人才配套经费	2018-01-01	200
25	2017 年青年千人计划引进人才科研启动费（杨建荣）	/	杨建荣	人才项目“青年千人计划”引进人才配套经费	2018-01-01	200
26	2017 年青年千人计划引进人才科研启动费（陈小舒）	/	陈小舒	人才项目“青年千人计划”引进人才配套经费	2018-01-01	300
27	2017 年青年千人计划引进人才科研启动费（丁俊军）	/	丁俊军	人才项目“青年千人计划”引进人才配套经费	2018-01-01	300
28	肝组织外泌体在日本血吸虫病肝纤维化中的作用及其机制	2018M640858	王立富	人事部中国博士后基金	2018-11-20	8
29	胚胎注射建立携带单型沃尔巴克菌	2018M643317	张东京	人事部中国博士后	2018-09-01	5

	wPip 白纹伊蚊蚊株研究			基金		
30	南海微生物来源的创新靶向药物研究	GDME-201 81004	黎孟枫	广东省科技计划重点项目	2018-05-31	500
31	华支睾吸虫病防治重大科技成果科普化	/	黄艳	广东省科技计划科技计划项目	2018-12-27	10
32	泌尿系肿瘤大数据人工智能精准诊疗新技术应用及研究	201803040 001	李博	广东省科技计划科技计划项目	2018-04-01	75
33	烟酸受体HCAR2介导的脂代谢抑制寨卡病毒复制的分子机理研究	2018A0505 06029	刘超	广东省科技计划省国际合作项目	2018-12-28	50
34	藏药来源的新型混源萜化合物的抗肿瘤活性及分子机制研	20181050	袁洁	广东省中医药局面上项目	2018-01-05	1
35	超保守非编码 RNA uc.243 诱导卵巢癌顺铂耐药的分子机制	2018B0303 11009	李隽	广东省自然科学基金重点项目	2018-05-01	50
36	基于磁性纳米颗粒及发光技术的日本血　吸虫感染早期诊断技术的研究	2018A0303 10108	邬燕琪	广东省自然科学基金博士启动项目	2018-06-30	10
37	华支睾吸虫与乙肝病毒相互作用的初步研究	2018A0303 130025	黄艳	广东省自然科学基金自由申请项目	2018-05-01	10
38	RFC4 作为肺癌转移早期诊断分子标志物的肿瘤生物学功能及机制研究	2018A0303 130260	刘蕾	广东省自然科学基金自由申请项目	2018-05-01	10
39	食管癌早期转移的诊断技术和临床转化研究	201803010 098	李隽	广州市科技计划科技攻关/生物医药专项	2018-04-01	100
40	肺癌转移早期诊断新型分子标志物的	201803010 039	黎孟枫	广州市科技计划科	2018-04-01	100

	研发及其肿瘤生物学功能研究			技攻关/生物医药专项		
41	重组弓形虫疫苗靶向免疫治疗胆管癌的新策略研究	201803010027	周兴旺	广州市科技计划科技攻关/生物医药专项	2018-03-01	100
42	血吸虫病人肝纤维化的全基因遗传标记鉴定和风险评估	201803010116	李淼新	广州市科技计划民生科技重大专项	2018-04-01	100
43	艾滋病功能性治愈新策略-临床与基础研究	/	张辉	广州市科技计划健康医疗协同创新重大专项	2018-04-01	112.5
44	面向临床高通量测序数据的高性能计算分析应用研究（后补助项目机动经费）	201604016136	周毅	广州市科技计划健康医疗协同创新重大专项	2018-12-17	80
45	基于 RORγt 活性抑制的靶标特异性自免疫药物研发	201807010042	黄朝峰	广州市科技计划科技攻关/国际合作	2018-04-01	100
46	Notch 信号在非小细胞肺癌中异常激活的分子机制和临床意义	/	刘蕾	广州市科技计划科学研究专项（一般项目）	2018-04-01	20
47	AcFAR-1 蛋白小分子拮抗剂抗广州管圆线虫感染效应研究	/	元冬娟	广州市科技计划科学研究专项（一般项目）	2018-04-01	20
48	新型乙肝病毒核衣壳组装抑制剂的高通量筛选及其抗病毒的机理研究	201806010118	潘婷	广州市科技计划创新人才培养计划-珠江科技新星专项	2018-03-31	30
49	中山大学医学标本馆科普基地运行补	/	陈琼珠	广州市科普广州市	2018-05-31	35

	助			科普		
50	2018 广州市科普游自由行	/	陈琼珠	广州市科普广州市科普	2018-03-01	1.056
51	超级增强子通过相分离介导染色体四维机构动态变化以诱导体细胞重编程	2018GZR110105007	丁俊军	其他项目实验室开放课题	2018-12-01	150
52	埃博拉病毒等高烈性传染病防治性小分子药物的研发	/	张辉	医学科研管理基金校内项目	2018-04-09	200
53	2018 年度国家科学技术奖申报资助经费（肿瘤侵袭转移的信号网络调控失衡机制及新治疗靶点的研究）	/	黎孟枫	医学科研管理基金校内项目	2018-04-04	10
54	表现遗传相关蛋白质机器对病毒特异性 CD8+T 细胞耗竭的调控机制-预研经费	/	邓凯	医学科研管理基金校内项目	2018-01-01	10
55	新型乙肝病毒核衣壳组装抑制剂的高通量筛选及其抗病毒的机理研究	/	张辉	医学科研管理基金校内项目	2018-01-01	30
56	核酸酶复合物 XPF/ERCC1 在 B 细胞抗体类别转换过程中介导 DNA 双链断裂修复的机制研究	18ykzd11	董俊超	高校基本业务费青年教师重点培育项目	2018-08-23	30
57	长期抗病毒治疗患者非 AIDS 相关疾病控制策略研究	/	张辉	国家科技部	2018-01-01	10
58	健康相关（美容护肤、医用消毒、生物医药、医疗器械、保健品）系列新技术和新产品研究开发	/	胡旭初	企事业单位委托科技项目	2018-01-15	500

2、研究进展

1 热带传病蚊媒生物防治技术研究及应用

2018 年 9 月，奚志勇主任在墨西哥蚊子工厂开幕仪式上讲话，标志着“以蚊治蚊”第一个海外工厂启动生产。

以伊蚊为代表的虫媒是重要的传病媒介，在登革热、疟疾、寨卡等重要热带传染性疾病传播过程中起到关键作用，给人类健康造成严重危害。目前缺乏行之有效的虫媒控制手段制约虫媒传播的热带病。建设期间，与平台共建的“中山大学-密歇根州立大学（MSU）热带病虫媒控制联合研究中心”，在教育部科学研究重大项目、广东省创新科研团队项目、美国国立卫生研究院和盖茨全球健康大挑战联合基金、国际原子能地区合作项目等项目资助下，集中开展了基于沃尔巴克氏体的新型伊蚊生物防治技术的开发及应用，取得了引领国际的蚊媒防控里程碑式科研成果。该成果建立稳定携带新型沃尔巴克氏体的蚊株。通过持续释放适量携带沃尔巴克氏体的雄蚊，使野外伊蚊种群数量降低至不足以引起蚊媒病传播流行。获农业部颁发的田间试验许可证，蚊媒释放田间实验（广州沙仔岛和大刀沙岛）结

果证实，该技术对白纹伊蚊成蚊压制效率可达 97%，有效实现热带病传播蚊媒的种群压制。2018 年开始，团队正与广州市疾控中心合作，在广州选择两个有代表性的登革热控制试点，其中一个试点是城中村，另一个是老城区有高楼大厦的地方，有望成为防控登革热和寨卡等热带病的革命性新策略。

目前，除在广州建成世界最大“蚊子工厂”外，在美国国际开发署和墨西哥政府的资助下在墨西哥梅利达建立了在海外的第一个蚊子工厂。在此基础上，中国政府向国际原子能机构推荐将广州的蚊子工厂建设成向周边国家辐射的亚洲蚊子工厂，提升东南亚和南亚国家的登革和塞卡防控能力。受我们的影响，新加坡、澳大利亚、台湾、国际原子能机构、美国夏威夷、斯里兰卡也相继启动以蚊治蚊技术，并生产由我们提供的蚊株。成果在 Science 和 PNAS 等杂志发表论文 10 篇，并获得国家授权发明专利 4 项。

2 重要热带寄生虫病关键技术建立及应用

血吸虫病、肝吸虫病、弓形虫病、疟疾等媒介传染热带病是我国和广大发展中国家面临的最严峻公共卫生问题之一，严重危害民众健康。重要热带寄生虫病防控存在以下关键难题：（1）生物学、代谢生理等信息不完整，且相应细胞和动物模型的难以建立；（2）快速、准确诊断存在很大困难。本平台汇聚了病原学、免疫学、分子流行病学、生物信息学等领域实力最强的科研团队。平台建设期间，在寄生虫病基础研究方向取得原创性成果：（1）rSj16 对葡聚糖硫酸酯钠诱导的结肠炎具有保护作用，其作用主要通过抑制过氧化物酶体增殖激活受体-alpha（PPAR-alpha）信号通路介导。提示 rSj16 可能是一种有效的治疗药物，PPAR-alpha 可能是治疗结肠炎的新靶点。（2）利用广州管圆线虫基因组测序数据和基因操作技术，对广州管圆线虫甘油二酯脂肪酶、Cystatin 及非适宜宿主特异性基因 CCL8 进行系统研究，深入提示寄生生物的寄生特性。（3）在鱼用华支

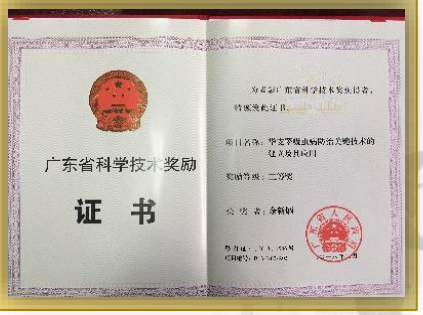
睾吸虫病诊断和疫苗、人体华支睾吸虫病诊疗等关键技术取得重大突破。在鱼用华支睾吸虫病诊断和疫苗、人体华支睾吸虫病诊疗等关键技术取得重大突破。目前鱼用疫苗已进入大田试验阶段，在中山市民众镇、黄圃镇、板芙镇约 60 亩鱼塘，对 300 万尾草鱼给予口服免疫，连续免疫三次后，检查成鱼，囊蚴免疫保护力可达 100%。预防淡水鱼肝吸虫感染生态疫苗研制技术的建立及应用获得国家科学技术进步二等奖和广东省科学技术二等奖。为有效降低我国食源性寄生虫病的临床危害做出了重要贡献。上述成果在 Progress in Lipid Research、Trends Parasitol 等热带病领域顶尖期刊上发表论文 8 篇，获得国内发明专利授权 9 项。

国家科学技术奖二等奖

疟疾、血吸虫病等重大寄生虫病防治关键技术的建立及其应用（余新炳、黄艳参与）

广东省科学技术奖一等奖

华支睾吸虫病防治关键技术的建立及其应用（黄艳徐劲，余新炳，胡旭初，李学荣参与）



余新炳教授赴中山市鱼用疫苗大田试点观察

3 结核病新型防治技术研发

结核（TB）是由结核分枝杆菌（Mtb）感染引起的一种“高感染率”、“高致病率”与“高致死率”传染病，是全球面临的最为严峻的公共卫生安全威胁之一。中国是结核病负担最重、耐药结核疫情最为严重的国家之一。世界卫生组织（WHO）2017 年的结核年报显示结核的年致死人数已经超过 AIDS/HIV；且越来越多的超级耐药（XDR-TB）及全耐药结核（TDR-TB）病例使得结核面临“无药可治”的危险处境。要解决结核预防、诊断与治疗等多个环节的一系列科学挑战，核心的工作是认识结核病发病机理，特别结核感染中的免疫调控机制，从而为开发新的疫苗、治疗与诊断技术提供新的科学基础。

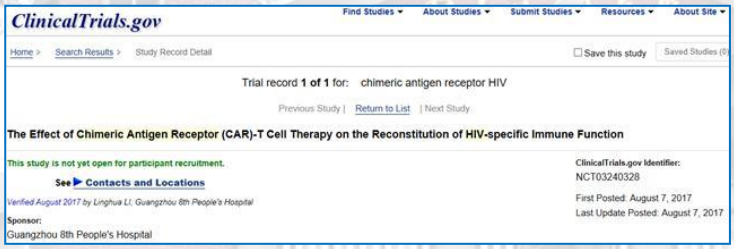
深圳市自然科学一等奖
Th17/Th22 细胞在结核病中的应答特征及其调控机制

实验室围绕控制结核感染中 T 细胞保护性免疫、免疫抑制或免疫过激分子机理等科学问题：（1）系统地研究了 IL-22 的抗结核免疫功能与机制，率先阐述了 IL-22 受 Tim-3“正调控”的新机制，为结核感染 T 细胞效应功能调控提供了新范例，为结核防治提供了新靶点。（2）深入研究了 CD8+T 细胞的抗结核保护性效应功能及其 lncRNA 调控新机制，为正在进行的结核新疫苗临床实验提供了重要实验证据支撑，为结核的防治提供了表观遗传新靶点。项目前期成果获得“深圳市自然科学一等奖”等成果。

4 重要热带病毒致病机制、检测与新型免疫疗法的临床实验

人免疫缺陷性病毒（HIV）、登革病毒（DENV）和寨卡病毒(ZIKV) 是严重威胁人类生命健康的传染疾病。本实验室在这 3 种病毒为代表的热带病毒研究上取得的成果分别简述如下：

免疫细胞过继治疗是 AIDS 功能性治愈的重要手段，其中，嵌合抗原受体（CAR）-T 细胞和 T 细胞受体（TCR）-T 细胞过继免疫治疗治疗，是当前最先进也最有前途的免疫疗法。本实验室取得以下成果：(1)将 HIV-1 广谱中和抗体 VRC01 来源的 scFv 序列和全新设计的第三代 CAR 分子胞内段序列连接在一起并转导 CD8+ T 细胞，产生了 HIV-1 特异性 VC-CAR-T 细胞，比已报道 CAR-T 治疗效果更加明显，并首次证明能有效清除 HIV-1 感染者样本中病毒储藏库（Journal of Virology, 2016）。该研究成果在 AIDS 功能性治愈领域处于国际领先地位。利用此项技术，我们开展了全球首例以广谱中和抗体为基础的 CAR-T 细胞疗法 I 期临床试验（已获临床伦理批准），正在对 20 例 HIV 感染者进行了 CAR-T 免疫治疗临床安全性和有效性实验。（2）此外，对 40 余位 HIV-1 感染患者进行了新型 TCR-T 细胞过继免疫治疗治疗的 I 期临床试验，所有患者均能较好耐受该疗法，证明该过继免疫策略安全。且过继免疫回输后，HIV-1 感染患者分泌干扰素 γ 细胞数量增加，显示该疗法对抗病毒免疫监控的提高有良好作用。



- 申请相关专利共计 57 项， 其中 PCT 专利 11 项，国内授权专利 31 项；（近 5 年）
- 获得国家十二五、十三五科技重大专项支持

在登革病毒和寨卡病毒研究方面：（1）本实验室发现 RNA 解旋酶 A 是 DENV 复制的重要宿主因子；DENV 可通过靶向 MAVS 来逃避宿主天然免疫。微

小 RNA miR-146a 和 miR-378 参与 DENV 感染，miR-146a 靶向 TRAF6 抑制病毒引起的细胞自噬，而 miR-378 靶向 gzmb 基因抑制病毒对 NK 细胞感染。在抗登革药物研究上，我们发现前体肽可防止 anti-prM 抗体介导的 DENV 感染抗体依赖性增强（ADE）现象。这些成果加深我们对登革病毒感染和逃避宿主防御的认识，为 DENV 防治提供了新的潜在策略和药物靶标。（2）在 ZIKV 研究上，我们建立了基因组稳定的 ZIKV 克隆并鉴定病毒复制必需 RNA 元件；发现 ZIKV 通过 NS1-Caspase-1 裂解 cGAS 引起炎症逃避宿主细胞的抗病毒反应。同时我们进行药物筛选发现非甾体抗炎药(NSAIDs)诱导 AXL 的降解来抑制 ZIKV 复制。在精确诊断上，我们采用树突状 Ru(bpy)32+-聚合物-扩增化学发光方法，构建了一种新型的液体活检系统，能高通量少用量（一滴血）的简单、准确检测 ZIKV，为 ZIKV 精确诊断和早期诊断提供新技术方法。

3、队伍建设

固定人员 72 名
博士学位 58 名 (80%)
高级职称 48 名 (60%)
≥50 岁 25 名(36%)
40-49 岁 22 名(32%)
<40 岁 22 名(32%)。

热带病防治研究大科研平台目前已形成一支高学历、学科知识结构和年龄结构合理的学术梯队。平台通过高端引进和自主培养相结合的方式构建平台的研究队伍梯队，汇聚不同领域、不同层次的优秀人才，人才队伍由量变到质变的聚合效应初步显现。实验室拥有国家“千人计划”入选人才 3 人、教育部“长江学者”特聘教授 3 人、国家杰出青年基金获得者 3 人、青年千人 6 人、国家优青 3 人、国家 973 首席科学家及国家重点研发计划项目负责人 3 人、国家特支计划科技创新领军人才 2 人、教育部“新世纪人才”2 人。平台共有省部级创新研究团队或工程中心 6 个，分别是人类病毒学研究团队、新型生物农药和虫媒病遗传控制研发团队、广东省抗病原微生物药物与免疫技术工程技术研究中心、

广东省媒介生物防控工程技术研究中心、广东省基因操作与生物大分子产物工程技术研究中心、中山大学临床与转化医学研究院国际科技合作基地（广东省国际科技合作基地）。发挥了科技创新和汇聚人才的重要作用。

2018 年 4 月，中山大学孙冬柏常务副校长出席热带病防治研究教育部重点实验室建设研讨会开幕式，并为奚志勇教授颁发实验室主任聘书。

本年度在人才培育和引进方面，依据实验室研究方向和团队建设的需求，新增千人计划人才 1 名（奚志勇），青年千人计划人才 6 名（陈俊、丁涛、董俊超、杨建荣、），国家优秀青年 1 名（田国宝）、百人计划引进人才 1 名(曾燕妮)，充分发挥实验室科技创新和汇聚人才的重要作用。其中奚志勇教授热带病防治研究教育部重点实验室主任，“重要寄生虫病与媒介防控研究”方向学术带头人，中山大学—密歇根州立大学热带病虫媒控制联合研究中心主任。主要研究方向是应用昆虫共生菌沃尔巴克氏体控制蚊媒及蚊媒病，作为先驱，在世界范围首次成功将沃尔巴克氏体引入登革(Xi, et al.2005.Science)和疟疾 (Bian, et al.2013. Science)蚊媒，开启利用沃尔巴克氏控制登革和疟疾的新领域。

实验室成员荣誉称号/学术机构任职情况

南粤优秀教师	郝元涛
“2018-2022 教育部高等教学指导委员会”	吴忠道　医学人文素养与全科医学类委员
广东省寄生虫学会（第九届）	吴忠道　理事长
广东省寄生虫学会（第九届）	李学荣　副理事长
广东省寄生虫学会（第九届）	吕志跃　秘书长
广东省寄生虫学会（第九届）	吕芳丽、吴瑜、黄艳　理事
广东省寄生虫学会（第九届）	孙希　监事
广东省寄生虫学会（第九届）	徐劲　荣誉副理事长

4、人才培养

实验室积极开展学生学术交流和竞赛活动，开拓学生视野，基础医学与临床医学相结合，为学生提供国际化、前沿化、专业化的交流平台。本年度主要有“粤港澳”生物医学研究生学术论坛和组队赴泰国参加泰国孔敬大学国际急诊医学挑战赛，并主办实验室徽标（LOGO）设计方案，多种方式让学生融入热带病科研平台。

2018 年 7 月 21 日至 24 日，中山医学院举办了“粤港澳”生物医学研究生学术论坛。本次学术论坛旨在进一步拓宽高校生物医学研究生的学术视野，搭建高水平的学术交流平台，帮助研究生做好未来的发展规划。本届论坛共分为三个部分，分别是知名专家报告专场、研究生报告专场和研究生壁报展示专场，各个部分环环相扣、精彩纷呈。25 位研究生代表分别展示了自己优秀的学术成果和严谨求实的学术风采，在场专家对研究生的工作给予了充分的肯定和赞赏，并提出了建设性的意见和建议。

“粤港澳”生物医学研究生学术论坛

泰国孔敬大学国际急诊医学挑战赛

孔敬大学急诊医学和基础医学知识国际挑战赛是由泰国孔敬大学医学院主办的一场国际赛事，本次竞赛吸引了包括孟加拉国、泰国、柬埔寨、菲律宾、中国、马来西亚、日本、越南、美国等 9 个国家和地区的 26 个队伍参加，竞赛内容主要包括内外妇儿的急诊处理和灾难管理、毒理学内容，并涉及生理学、药理学、微生物学、解剖学等基础学科。竞赛共分三轮，第一轮为选择题（MCQ）及客观结构化临床考试(OCSE)，第二轮为简答题，第三轮为高端模拟人实战演

练，层层晋级，最终角逐出前三名。通过竞赛，让学生认识到国内外医学教育的差异。不仅让学生重视急诊医学的学习、转变固化的临床思维，更重要的是提供一个世界各国医学生交流的平台。

5、科研与教学成果

本年度实验室获得国家科学技术奖二等奖一项（本单位为第二完成单位）、广东省科学技术二等奖一项。共发表论文 107 篇，其中 SCI 收录论文 91 篇，影响因子>10 的 7 篇，影响因子>5 的 34 篇，论文质量不断提升。申请国家专利 21 项，获得授权专利 16 项，获得国家医疗器械证书 9 项。

实验室以教育教学为主要任务，完成本科、研究生教学任务，并以科研创新

理念教导和培养学生。本年度共获得 3 项教学成果奖，其中 2 项为一等奖，1 项为二等奖，对传染病学、流行病学和寄生虫学等课程不断地探索和实践，务求跟上时代和学生的需求。

教学成果奖（2018 年公布）

奖励类别	获奖等级	获奖成果名称	完成人
2017 年广东省教育教学成果奖	一等奖	基于互联网的互动式教学-公共卫生核心课程《医学统计学》慕课建设与应用	郝元涛、张晋昕、方积乾、林爱华、顾菁、陈雯、曾芳芳、朱淑明
2017 年广东省教育教学成果奖	一等奖	以教材建设为抓手，提升《人体寄生虫学》课程教学质量的探索与实践	吴忠道、何蔼、吕志跃、吴瑜、吕芳丽、李学荣、郑小英、黄艳
2017 年广东省教育教学成果奖	二等奖	传染病学优才教育体系的研究与实践	高志良、张晓红、赵志新、吴元凯、林国莉、赖菁

本年度共出版教材 2 项，科技专著 2 项，并举行《生物化学与分子生物学》教材编写会，到会的编委和蔡编辑就精编速览的编写大纲及同步习题集题量、题型等进行了热烈讨论，最后达成一致共识。

教　材

★ 人体寄生虫学实验知道（八年制配教 第 3 版），北京人民卫生出版社，何蔼

★ 全球健康研究方法，北京人民卫生出版社，郝元涛、陈心广、丁元林、袁兆康、孙强

中国医药科技出版社全国高等教育五年制临床医学专业教材精编速览+同步习题集《生物化学与分子生物学》教材编写会专家合影

科技专著

★ 肝吸虫病看名医，广州中山大学出版社，余新炳

★ 丙型肝炎病毒感染的基础与临床，北京：科学技术文献出版社，龚国忠 ，成军 ，高志良

6、学术交流

2018 年度实验室出访交流 26 人次，来访交流 54 人次，主办或承办国内外学术会议 2 场，包括 2018 年热带医学和生物安全论坛暨粤港澳大湾区热带病防控联盟启动会、基于沃尔巴克氏体技术控制登革热和疟疾国际研讨会。本实验室坚持对外开放、交流与合作，面向全球，开展实质性的国际合作。中山大学与密歇根州立大学两校已合作 7 年，在沃尔巴克氏体技术控制登革热和疟疾等研究方面有着密切的交流。合作多年来重要的会议都在本校举办，进一步加深该项目与国际原子能机构的合作，同时凸显了广州（蚊子工厂、2 个试点现场）在此项目中的重要地位。2018 年，更推动与印度国家疟疾研究所、约翰霍普金斯大学等建立国际合作团队，启动印度疟疾现场测试的研究，进一步提高了本平台在东南亚地区的辐射能力，促进了对“一带一路”国家技术输出。此外，墨西哥蚊子工厂的开幕，也将该技术的应用在发展中国家，乃至全球范围内进行推广应用。该项目的发展对于科研项目的合作、成果转化、社会经济、国民健康以及大众科普教育等方面有着重要的推动作用。此外，2018 年 11 月实验室奚志勇主任、吴忠道常务副主任陪同中山大学常务副校长孙冬柏访问国际原子能机构，推进“国际原子能机构区域蚊媒防控合作中心”项目的实施。

基于沃尔巴克氏体技术控制登革热和疟疾国际研讨会（2018，广州）

启动基于沃尔巴克氏体技术控制印度疟疾的现场测试研究，促进对“一带一路”国家技术输出，提升国际辐射力。

2018 年 11 月奚志勇主任、吴忠道常务副主任
赴奥地利维也纳国际原子能机构部长级会议

此外，本实验室拟建“粤港澳大湾区输入性热带病防控联盟”，邀请广州、深圳、珠海、香港、澳门等共 19 家科研机构、医院等作为共同发起单位，建立长期伙伴合作关系，推动大湾区科研与医疗合作，共同打造以粤港澳大湾区为基地的热带病防控网络，提升湾区热带医学研究水平和热带病区域性防控及应急能力。

2018 年热带医学和生物安全论坛暨粤港澳大湾区热带病防控联盟启动会

2018 年，本实验室作为“一带一路”热带医学联盟的发起单位与副理事长单位，加入由海南医学院海南医学院主办的“一带一路”热带医学联盟（BRTMA），旨在加强“一带一路”沿线国家和地区热带医学的全面深入合作，望在这个学术研究、信息交流、资源共享、合作共赢的平台上，与各理事单位共商合作大计，为中国和亚洲热带医学事业的发展和繁荣做出贡献。

2018 年 9 月，吴忠道教授带队前往深圳华大生命科学研究院和深圳国家基因库进行学术交流，我院生物信息学相关研究领域的相关教授、副教授共十四人参加了本次学术活动。希望通过此次交流，探讨深化双方交流合作的有效机制和运作模式 。

中国援助桑给巴尔血吸虫病防治项目是中国重要援非项目之一，桑给巴尔方高度评价并积极融入我国“一带一路”发展战略。探索和实施适合当地的血吸虫病防治策略，推动桑给巴尔最终实现消除血吸虫病的防治目标。此项目是我国积极落实"一带一路"倡议和习近平主席提出的"中非公共卫生合作计划"，在联合国

中山医学院-上海市免疫学研究所“免疫学前沿及其临床运用”交流研讨会

2018 年 9 月 19 日至 20 日，应上海市免疫学研究所邀请，我院免疫学学科群考察交流团对该所进行了访问。考察交流团由我院青年千人、百人计划引进人才、免疫学学术骨干等 17 人组成，学院党委书记吴忠道教授亲自带队。上海市免疫学研究所所长苏冰教授、副院长李斌教授及全体学术骨干参加了此次交流研讨。

和世界卫生组织框架下积极参与全球健康促进事业，为其他发展中国家提供力所能及援助的重要举措。8 月 26-30 日，中山大学中山医学院党委书记、寄生虫学教研室主任吴忠道教授到非洲的桑给巴尔岛访问，实地考察中国援助非洲的血吸虫病防治项目。

应肯尼亚阿迦汗大学邀请，我院寄生虫学教研室主任吕志跃教授以“全球健康丝路学者”身份于 11 月 3 日-17 日对肯尼亚城市与乡村医疗卫生系统及疟疾、艾滋病、血吸虫病等重大传染病流行与防治现状进行调研，并与阿迦汗大学、阿迦汗医院寄生虫病防治专家就双方建立长期合作关系达成共识，为中山大学-肯尼亚在重要热带病防治领域国际合作开启了新的篇章。

2018 年度承担国际合作项目：实验室本年度共承担国际（境外）合作项目 6 项，合同经费 548 万元。包括丙型肝炎病毒适应性图片和准种分布在体内外感染模型中的比较研究、非编码 RNA 在 HIV-1 潜伏感染的建立和维持过程中分子机理研究、细胞膜相关的长非编码 RNA 在肺癌发生发展中的生物学作用与调控机制、RNA 编辑酶 ADAR1 促寨卡

热带病防治研究教育部重点实验室建设研讨会

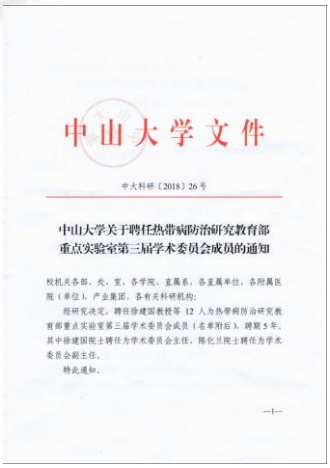
4 月 9 日，中山大学热带病防治研究教育部重点实验室 2018 年建设研讨会在北校园隆重召开。实验室 13 名学术带头人和青年骨干围绕“热带虫媒病毒的病原学研究与虫媒病生态防制”、“基于组学的重要螺传寄生虫的宿主适应性与致病机制”、“热带病原感染免疫与治疗新策略”、“临床细菌耐药与感染”及“新发及输入性热带病的主动监测与预警”等领域向近 200 名与会人员汇报了各团队近期取得的多项重大创新性研究成果。通过本次会议，为实验室未来的重点和亮点建设，包括国家重点实验室的申报策略、人才引进和培育的机制改革、研究方向整合和不可替代性的提高等提出切合实际、行之有效的建议，对推动实验室的发展，有着重要的指导作用。

病毒复制的分子机制研究、新型 Th17 细胞分化抑制剂的靶标特异性评价体系的建立、基于 RORγt 活性抑制的靶标特异性自免疫药物研发等。推动着在热带在等方面的研究有着重要的推动作用。

7. 运行管理与开放共享

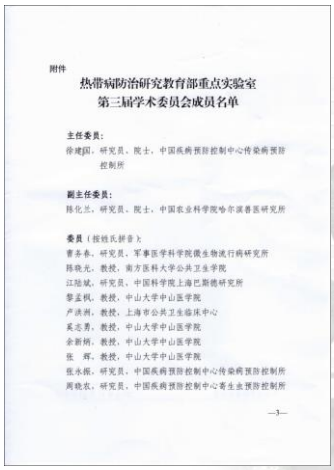
（1）运行管理与开放课题

热带病防治研究教育部重点实验室依据教育部重点实验室管理要求，实验室建立和健全了有关规章制度，制定了一系列管理办法并汇编成册。运行机制完善，科研氛围良好：本重点实验室实行主任协调领导下的 PI 制。定期召开学术委员会，学术委员会由徐建国研究员等 12 位国内外同领域高水平专家组成，在准确把握实验室发展方向和规划，提升学术研究水平和形成重大成果等方面发挥重要指导作用。实验室根据依托单位有关规定，对承担重大项目、发表高水平论文、获得授权发明专利及新药证书等实验室成员予以适当奖励。自立项创建以来，实验室科研氛围积极向上，学术氛围良好。


中山大学文件

中大科研〔2018〕26号

中山大学关于聘任热带病防治研究教育部重点实验室第三届学术委员会成员的通知


附件

热带病防治研究教育部重点实验室
第三届学术委员会成员名单

主任委员：
徐建国，研究员，院士，中国疾病预防控制中心传染病预防控制所

副主任委员：
陈化兰，研究员，院士，中国农业科学院哈尔滨兽医研究所

委员（按姓氏拼音）：
曹务春，研究员，军事医学科学院微生物流行病研究所
陈晓元，教授，南方医科大学公共卫生学院
江陆斌，研究员，中国科学院上海巴斯德研究所
黎孟枫，教授，中山大学中山医学院
卢洪洲，教授，上海市公共卫生临床中心
吴志勇，教授，中山大学中山医学院
余新炳，教授，中山大学中山医学院
张 辉，教授，中山大学中山医学院
张永振，研究员，中国疾病预防控制中心传染病预防控制所
周晓农，研究员，中国疾病预防控制中心寄生虫预防控制所

第三届学术委员会名单

实验室学术委员会与实验室成员合照

为了吸引、聚集资源环境领域国内外优秀学者来本平台开展高水平的基础性和应用基础性研究工作，遵照“开放、流动、联合、竞争”的运行机制，本平台面向国内外开放，设立开放基金，立项资助与本平台研究方向相关的具有创新思想的科研课题，并提供相应的科研条件，以促进新兴交叉学科的形成和发展。本年度设立开放课题共 8 项。

2018 年度实验室开放课题列表

序	课题名称	申请人	申请人单位	项目编号
1	河南新乡 CTX-M 型超广谱β内酰胺酶的分子流行病学研究	杨帆	新乡医学院	2018kfkt01
2	质粒介导多粘菌素耐药新机制 MCR-1 的分子流行病学	林琳	程度医学院	2018kfkt02
3	湖南和广东福寿螺肠道微生物群落结构和功能比较研究	王智	湖南师范大学生命科学学院	2018kfkt03
4	HIF-1α/Shh/CXCL12 通路在肿瘤相关成纤维细胞促肝癌复发的机制及其靶向调控的研究	李坚	中山大学附属第五医院	2018kfkt04
5	体外增强 HIV-1 特异性 CD8+ T 细胞功能小分子化合物的筛选及其体外作用研究	洪仲思	中山大学附属第五医院	2018kfkt05
6	结核感染中 Hb-CD163 信号轴的天然免疫功能与机制	沈洪波	同济大学附属上海市肺科医院	2018kfkt06
7	卡介苗（BCG） 抗结核纳米“胶囊”的构建、功能与机理	沈洪波	同济大学附属上海市肺科医院	2018kfkt07
8	阻断 AAK1 和 GAK 干预重症登革热的实验研究	肖非	中山大学附属第五医院	2018kfkt08

（2）科学传播

主办学术刊物。主办的《热带医学杂志》已成为国内具有影响力的专业杂志；主办的《分子诊断与治疗杂志》是我国第一份以分子诊断与治疗领域学术成果为主要刊载内容的专业学术期刊；目前正筹办《Journal of Tropical Diseases and Global Health Development (TDGHD/“Tropglob”)》，聘请香港中文大学冯明钊教授为杂志执行主编，邀请瑞士热带病与公共卫生研究所前所长 Marcel Tanner 教授为杂志主编，美国、欧洲、非洲和泰国等国家的热带病专家担任编委。

利用科研资源优势，积极开展科普活动。应邀与中央、地方电视台科技频道节目组联合录制多部热带病防治宣教片，并接待国内外 500 人次参观“蚊子工厂”，进行寄生虫病和蚊媒病防治科普宣讲。

医学标本馆定期向社会公众免费开放，普及医学知识。2013 年被评为广东省科学普及教育基地、广州市越秀区科普教育基地，普及生命、健康、医学相关知识教育。医学标本馆占地面积超过 5000 平方米 ，拥有含热带医学标本在内的各类医学标本近 15 万份。本年度获得 2 项广州市科普计划项目支持，维持标本馆的运行，合共 36 万元。

（3）医学实验支撑平台

医学实验支撑平台实现了仪器设备、场地和服务等的开放共享。平台基于“专管共用”和“共享使用”理念，购置先进仪器设备，创建现代化科研共享平台，并建立设施完善、符合国家标准的 BSL-III 实验室、BSL-II 实验室、SPF 级动物实验室、疾病模式动物实验室、斑马鱼实验室及动物分子影像实验室等专项技术实验室，以此构建了科研仪器共享平台和生物安全实验平台。

生物安全实验室第三个五年资质认可

生物安全三级实验室获得了第三个五年资质认可，实验室资格证书有效期至 2023 年 8 月 26 日。新的认可证书对我校生物安全三级实验室以及高致病性病原微生物科学研究的发展有着重要意义，我校生物安全三级实验室将继续秉承“安全无小事、完全无止境”的管理理念，保障实验室安全有序运行，做好高致病性病原微生物科学研究支撑，助力我校“双一流”大学的建设工作。

四、附件

附件 1、实验室固定人员名单

姓名	性别	学位	职称	专业
Dmitry Isaak Gabrilovich	男	博士	教授	免疫学
曹开源	男	博士	教授	免疫学
曾谷城	男	博士	教授	免疫学
邓凯	男	博士	教授	病毒感染与免疫治疗
丁涛	男	博士	教授	免疫学
董俊超	男	博士	教授	免疫学
高国全	男	博士	教授	分子生物学
高志良	男	博士	教授	免疫学
郭德银	男	博士	教授	致病机制与免疫调控
郭学敏	女	博士	教授	病原生物学
郝元涛	男	博士	教授	流行病学
何蕴韶	男	博士	教授	病原诊断技术
黄俊琪	女	博士	教授	抗感染免疫学
黄曦	男	博士	教授	免疫学
江丽芳	女	硕士	教授	病原生物学
蒋玮莹	女	博士	教授	遗传学
况二胜	男	博士	教授	病毒药物筛选
赖小敏	男	硕士	教授	免疫学
黎孟枫	男	博士	教授	病原生物学
李博	男	博士	教授	分子病毒学
李隽	男	博士	教授	病原生物学
李淼新	男	博士	教授	生物信息学
李伟忠	男	博士	教授	生物信息学
李学荣	男	博士	教授	医学微生物学
李义平	男	博士	教授	分子病毒学
刘焕亮	男	博士	教授	病毒学
陆家海	男	博士	教授	流行病学
伦照荣	男	博士	教授	人体寄生虫学
吕芳丽	女	博士	教授	人体寄生虫学学
吕志跃	男	博士	教授	寄生虫学
舒跃龙	男	博士	教授	流行病学
王金凯	男	博士	教授	生物信息学
吴敏昊	女	博士	教授	免疫学
吴长有	男	博士	教授	免疫学
吴忠道	男	博士	教授	寄生虫学学
奚志勇	男	博士	教授	虫媒病学

席丽艳	女	博士	教授	真菌学
杨建荣	男	博士	教授	生物信息学
杨克礼	男	博士	教授	免疫学
余新炳	男	博士	教授	人体寄生虫学
袁岩	男	博士	教授	病毒学
张辉	男	博士	教授	病毒学
张萍	女	博士	教授	病原生物学
周洁	女	博士	教授	免疫学
周兴旺	男	博士	教授	分子寄生虫学
柏川	男	博士	副教授	免疫学
蔡俊超	男	博士	副教授	病原生物学
洪海	女	博士	副教授	免疫学
胡旭初	男	博士	副教授	寄生虫学
黄艳	女	博士	副教授	寄生虫学
刘超	男	博士	副教授	病毒学
孙希	女	博士	副教授	寄生虫学
陶海燕	女	博士	副教授	地理模拟与疾病监控
田国宝	男	博士	副教授	免疫学
吴瑜	女	硕士	副教授	分子生物学
袁洁	女	博士	副教授	病原生物学
郑小英	女	硕士	副教授	虫媒学
周毅	男	博士	副教授	免疫学
朱勋	男	博士	副教授	分子生物学
赖德华	男	博士	副教授	人体寄生虫学
何蔼	女	硕士	副教授	病原生物免疫
黄朝峰	男	博士	副教授	抗病毒免疫
徐劲	男	硕士	副教授	人体寄生虫学
周俊梅	女	博士	副教授	医学微生物学
孙九峰	男	博士	副研究员	病原生物学
晏辉钧	男	硕士	高级讲师	医学微生物学
袁广卿	女	中专	高级实验师	生物安全
吴珏珩	女	博士	高级实验师	设备管理
元冬娟	女	博士	特聘研究员	寄生虫学
潘婷	女	博士	特聘研究员	病毒学
蓝秀健	女	硕士	高级实验师	公共设备维护与实验技术
罗海华	女	硕士	实验师	病毒学
张选红	女	硕士	实验师	公共设备维护与实验技术
陈琼珠	女	硕士	助理研究员	行政管理
关苑君	女	硕士	助理实验师	实验室管理
彭毅	女	本科	助理实验师	生物安全实验技术

附件 2、申请和授权专利

申请专利			
序	**专利名称**	**发明人**	**专利号**
1	辅酶 Q10 在抑制血小板活化和粘附中的应用	杨燕、凌文华、牙甫礼、 张佩雯、许晓虹	201810576415.1
2	RBMS3 作为肿瘤耐药检测、治疗及预后分子靶点的应用	李隽、宋立兵、吴阁艳、 朱金容、胡雅梦、谭展瑶、曹丽雪	201810142969.0
3	NKX2-8 在肿瘤耐药检测中的应用及 FAO 抑制剂在 NKX2-8 缺失型肿瘤中的应用	李隽、宋立兵、朱金容 吴阁艳、李梓文、曹丽雪、谭展瑶	201810142442.8
4	一种 MCR-1 抑制剂及其在制备抑制 MCR-1 阳性耐药菌药物中的应用	田国宝、柏川、冯思源、 沈聪	201810494825.1
5	氢化喹诺林类化合物在增强细菌对多粘菌素敏感性中的应用	柏川、田国宝、劳楚瑜、钟兰兰、温馨	201810494214.7
6	一种 7,8-取代-3-甲基黄嘌呤类化合物及其制备方法和应用	罗海彬、李进轩、李哲、 吴德燕	201810157714.1
7	一种以卤甲基化合物为原料制备氘代醛的方法	罗海彬、盛春泉、李祥民、武善超、陈树强、吴德燕	201810146057.0
8	一种草鱼出血病口服型疫苗及其制备与用途	余新炳、姜红烨、林志鹏、周心怡、边青	201810949894.7
9	一种 E-2-苯乙烯基苯并咪唑类化合物在制备抗乙肝病毒药物中的应用	潘婷、张辉	201810659020.8
10	一种 2-（2-甲基苯并噻唑）乙醇类化合物在制备抗乙肝病毒药物中的应用	潘婷、张辉	201810657853.0
11	一种 6，8-二羟基嘌呤类化合物在制备抗乙肝病毒药物中的应用	潘婷、张辉	201810657855.X
12	一种具有抗乙肝病毒活性和抗菌活性的苯并咪唑类化合物及其合成方法和应用	鲁桂、尤义鹏、黄功彬、 张辉、潘婷、张革、翟珮宏、鲁家琪、林桐、陈晓娜、温婷	201810715690.7
13	β-actin 蛋白作为日本血吸虫病肝纤维化发生血清学诊断标志物	张蓓蓓、吴忠道、吴晓瑛、元冬娟、刘嘉华、宋秋月	201810450282.3

	的应用		
14	基于磁富集电化学发光的外泌体核酸检测技术	黄曦、廖玉辉、樊志金、肖铿	201810657985.3
15	肺癌诊断分子标记物 lncRNA LINC00516 和试剂盒及其应用	黎孟枫、管洪宇、刘湜桦、刘帮洞、刘蕾、朱勋、吴珏珩、朱婷、吴姗姗、于暕辰	201810982670.6
16	一种肺癌早期转移诊断标志物及其试剂盒和应用	黎孟枫、管洪宇、吴姗姗、刘蕾、向涛、朱勋、吴珏珩、刘湜桦、朱婷、刘帮洞、于暕辰、张乐	201810983160.0
17	一种用于诊断肺癌转移的 lncRNA 检测试剂盒及其应用	黎孟枫、管洪宇、刘蕾、朱婷、朱勋、吴珏珩、于暕辰、刘湜桦、吴姗姗、刘帮洞	201810983180.8
18	检测 H7N9 禽流感病毒的试剂盒及其方法	马铈委、陆家海、原丽红	201810734289.8
19	基因 DESI2 在三阴乳腺癌诊断、预后评估及治疗中的应用	宋立兵、李隽、林楚勇、叶丽平、刘清华、汪梦	201810824478.4
20	基因 HES2 在食管鳞癌辅助诊断、预后判断和治疗中的应用	宋立兵、李隽、林楚勇、叶丽平、李悦	201810824526.X
21	氢化喹诺林类化合物在增强细菌对多粘菌素敏感性中的应用	柏川、田国宝、劳楚瑜、钟兰兰、温馨	201810494214.7

授权专利

序	专利名称	发明人	专利号
1	两性霉素 B 对中央记忆性 T 细胞体外扩增中的应用	张辉、张译文	201510228577.2
2	单宁酸作为 HIV-1 潜伏感染激活剂的应用	张辉、陈灿灿、刘超	201510745224.X
3	替考拉宁在制备抗中东呼吸综合征冠状病毒药物中的	潘婷、周南、张辉	201510343520.7
4	一种寄生虫虫卵的便携式检测装置	吕志跃、邬燕琪、徐一月、吴忠道、胡玥、 张梦颖	201720785468.5
5	α-生育酚在制备治疗血吸虫病药物中的应用	吕志跃、吴忠道、张丽梅、杨帆、王晓莹、潘彤、刘记、李浩、李梓雄、孙希	201510630548.9

6	一种生物样本的磁分离装置	邬燕琪、吕志跃、徐一月、吴忠道、胡玥 张梦颖	201720785491.4
7	POU5F1B 在肿瘤诊断、治疗、预后和预测复发中的应用	宋立兵、李隽、张鑫、谭展瑶、吴淑	201510112706.1
8	miR-425 在肿瘤的诊断、治疗及预后中的应用	宋立兵、李隽、林楚勇、周心怡、刘爱斌、吴淑	201510117211.8
9	BRCA2 的 3′非翻译区在制备肿瘤诊断、治疗和预后试剂中的应用	李隽、宋立兵、张鑫、 叶丽萍、吴淑 、刘爱斌、朱金容、吴阁艳	201510112642.5
10	夫西地酸或其药用盐在制备抗手足口病药物中的应用	曾施暖、郭学敏	201610008433
11	大环内酯类抗生素或其药用盐在制备抗手足口病药物中的应用	郭学敏、曾施暖、孟小斌、黄清苑、雷南风、曾令斌	201511030722.2
12	一种基于组织支架的三维视杯来源神经样细胞的钠离子通道检测方法	葛坚、顾怀宇、钟秀风、李康雳、杨斯婧	201510952749
13	苯骈 α-吡喃酮类化合物的应用及其制备方法	尹胜、罗海彬、林婷婷、黄仪有	201310416245.8
14	一种经皮穿刺口防漏固定器	谢婵、王培培、彭亮、 高志良	201720720691.1
15	混源萜类化合物 D1399 在制备抗乳腺癌药物中的应用	黎孟枫、袁洁、黄益、于暕辰、许佳怡、陈彬、蒋思萍、李静、刘岚、高晓霞	201610144721.9
16	利用手机轨迹追踪传染源和预测传染病流行趋势的方法	陆家海、刘荣飞、杜依蔓、宋征、张珂艺、李泽纯	201610060508.X

附件 3、2018 年发表论文列表和部分摘要

序	论文题目	全部作者	发表期刊
1	A Cellular MicroRNA Facilitates Regulatory T Lymphocyte Development by Targeting the FOXP3 Promoter TATA-Box Motif.	Zhang Y, Liu W, Chen Y, Liu J, Wu K, Su L, Zhang W, Jiang Y, Zhang X, Zhang Y, Liu C, Tao L, Liu B, Zhang H.	J Immunol. 2018 Feb 1;200(3):1053-1063.
2	A novel antigenic cathepsin B protease induces protective immunity in Trichinella-infected mice.	Yang Z, Li W, Yang Z, Pan A, Liao W, Zhou X.	Vaccine. 2018 Jan 4;36(2):248-255.
3	A Novel Hypothesis on Excessive Activation of Residual B Lymphocytes in Common Variable Immunodeficiency Concurrent with Aseptic, Erosive Polyarthritis.	Mo YQ, Zhang YN, Jing J, Ma JD, Chen YL, Wu CY, Dai L.	Med Sci Monit. 2018 Jul 16;24:4952-4960.
4	A powerful approach reveals numerous expression quantitative trait haplotypes in multiple tissues.	Ying D, Li MJ, Sham PC, Li M.	Bioinformatics. 2018 Apr 26.
5	A powerful approach reveals numerous expression quantitative trait haplotypes in multiple tissues.	Ying D, Li MJ, Sham PC, Li M.	Bioinformatics. 2018 Sep 15;34(18):3145-3150.
6	A powerful conditional gene-based association approach implicated functionally important genes for schizophrenia.	Li M, Jiang L, Mak TSH, Kwan JSH, Xue C, Chen P, Leung HC, Cui L, Li T, Sham PC.	Bioinformatics. 2018 Aug 7.
7	A Spatio-Temporal Model of Macrophage-Mediated Drug Resistance in Glioma Immunotherapy.	Zheng Y, Bao J, Zhao Q, Zhou T, Sun X.	Mol Cancer Ther. 2018 Apr;17(4):814-824.
8	Activation and Regulation of Blood Vδ2 T Cells Are Amplified by TREM-1\r +\r during Active Pulmonary Tuberculosis.	Wu Y, Fang YM, Ding L, Liu X, Francisco NM, Wen J, Liao C, Ma Z, Li Z, Li M, Ming S, Liu T, Zhang M, Wu M, Jacobs M, Gong S, Huang X.	J Immunol. 2018 Mar 1;200(5):1627-1638.

9	Adaptive mutation F772S-enhanced p7-NS4A cooperation facilitates the assembly and release of hepatitis C virus and is associated with lipid droplet enlargement.	Duan X, Anwar MI, Xu Z, Ma L, Yuan G, Chen Y, Liu X, Xia J, Zhou Y, Li YP.	Emerg Microbes Infect. 2018 Aug 8;7(1):143.
10	Adoptive Transfer of Interleukin-21-stimulated Human CD8+ T Memory Stem Cells Efficiently Inhibits Tumor Growth.	Chen Y, Yu F, Jiang Y, Chen J, Wu K, Chen X, Lin Y, Zhang H, Li L, Zhang Y.	J Immunother. 2018 May 1.
11	Antibodies against Schistosoma japonicum lactate dehydrogenase B enhance enzyme active.	Li Y, Gan W, Zhan W, Feng P, Chen H, Zheng Y, Hu X.	Mol Biochem Parasitol. 2018 Aug 21. pii: S0166-6851(18)30139-7.
12	Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis.	Lam NS, Long X, Su XZ, Lu F.	Pharmacol Res. 2018 Jul;133:77-100.
13	Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis.	Lam NS, Long X, Su XZ, Lu F.	Pharmacol Res. 2018 May 1;133:77-100.
14	Bacillus subtilis spore with surface display of paramyosin from Clonorchis sinensis potentializes a promising oral vaccine candidate.	Sun H, Lin Z, Zhao L, Chen T, Shang M, Jiang H, Tang Z, Zhou X, Shi M, Zhou L, Ren P, Qu H, Lin J, Li X, Xu J, Huang Y, Yu X.	Parasit Vectors. 2018 Mar 7;11(1):156.
15	Bayesian spatiotemporal analysis for association of environmental factors with hand, foot, and mouth disease in Guangdong, China.	Du Z, Lawrence WR, Zhang W, Zhang D, Yu S, Hao Y.	Sci Rep. 2018 Oct 11;8(1):15147.
16	Cascaded Electrochemiluminescence Signal Amplifier for the Detection of Telomerase Activity from Tumor Cells and Tissues.	Zhao Z, Tan Q, Zhan X, Lin J, Fan Z, Xiao K, Li B, Liao Y, Huang X.	Theranostics. 2018 Nov 9;8(20):5625-5633.
17	CD10(+)GPR77(+) Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness.	Su S, Chen J, Yao H, Liu J, Yu S, Lao L, Wang M, Luo M, Xing Y, Chen F, Huang D, Zhao J, Yang L, Liao D, Su F, Li M, Liu Q, Song E.	Cell. 2018 Feb 8;172(4):841-856.e16.
18	Chi3l3: a potential key orchestrator of eosinophil recruitment in meningitis induced by Angiostrongylus cantonensis.	Wan S, Sun X, Wu F, Yu Z, Wang L, Lin D, Li Z, Wu Z, Sun X.	J Neuroinflammation. 2018 Feb 2;15(1):31.

19	CK1 alpha suppresses lung tumour growth by stabilizing PTEN and inducing autophagy.	Cai J, Li R, Xu X, Zhang L, Lian R, Fang L, Huang Y, Feng X, Liu X, Li X, Zhu X, Zhang H, Wu J, Zeng M, Song E, He Y, Yin Y, Li J, Li M.	Nat Cell Biol. 2018 Apr;20(4):465-478.
20	Clonorchis sinensis adult-derived proteins elicit Th2 immune responses by regulating dendritic cells via mannose receptor.	Zhao L, Shi M, Zhou L, Sun H, Zhang X, He L, Tang Z, Wang C, Wu Y, Chen T, Shang M, Zhou X, Lin Z, Li X, Yu X, Huang Y.	PLOS Neglected Tropical Diseases, 2018, 12(3):e0006251-.
21	Clonorchis sinensis cyclophilin A immunization protected mice from CLP-induced sepsis.	Jiang J, Yin H, Sun Y, Huang H, Hu X.	Int Immunopharmacol. 2018 Jun;59:347-353.
22	Co-production of MCR-1 and NDM-5 in Escherichia coli isolated from a colonization case of inpatient.	Feng S, Shen C, Chen H, Zheng X, Xia Y, Zhong LL, Huang X, Wu X, Tian GB.	Infect Drug Resist. 2018 Aug 14;11:1157-1161.
23	Correction: Deficiency of pigment epithelium-derived factor in nasopharyngeal carcinoma cells triggers the epithelial-mesenchymal transition and metastasis.	Zhang T, Yin P, Zhang Z, Xu B, Di Che, Dai Z, Dong C, Jiang P, Hong H, Yang Z, Zhou T, Shao J, Xu Z, Yang X, Gao G.	Cell Death Dis. 2018 Jul 16;9(8):784.
24	Current treatment of ocular toxoplasmosis in immunocompetent patients: a network meta-analysis.	Zhang Y, Lin X, Lu F.	Acta Trop. 2018 Apr 25;185:52-62.
25	Current treatment of ocular toxoplasmosis in immunocompetent patients: a network meta-analysis.	Zhang Y, Lin X, Lu F.	Acta Trop. 2018 Sep;185:52-62.
26	Design, synthesis, and biological evaluation of novel 7-deazapurine nucleoside derivatives as potential anti-dengue virus agents.	Lin C, Yu J, Hussain M, Zhou Y, Duan A, Pan W, Yuan J, Zhang J.	Antiviral Res. 2018 Jan;149:95-105.
27	Development of an Infectious Cell Culture System for Hepatitis C Virus Genotype 6a Clinical Isolate Using a Novel Strategy and Its Sensitivity to Direct-Acting Antivirals.	Chen M, Zheng F, Yuan G, Duan X, Rong L, Liu J, Feng S, Wang Z, Wang M, Feng Y, Zhou Q, Li J, Deng K, Li C, Xia J, Rao G, Zhou Y, Fu Y, Li YP.	Front Microbiol. 2018 Dec 4;9:2950.

28	Disodium cromoglycate may act as a novel adjuvant for UV-attenuated Toxoplasma gondii vaccine in mouse model.	Li X, Wu Y, Huang S, Lu F.	Parasitol Int. 2018 Jun;67(3):351-356.
29	Diversity and Compatibility of Human Schistosomes and Their Intermediate Snail Hosts.	Sanogo B, Yuan D, Zeng X, Zhang Y, Wu Z.	Trends Parasitol. 2018 Jun;34(6):493-510.
30	Diversity and Compatibility of Human Schistosomes and Their Intermediate Snail Hosts.	Sanogo B, Yuan D, Zeng X, Zhang Y, Wu Z.	Trends Parasitol. 2018 Jun;34(6):493-510.
31	Dynamic spatiotemporal analysis of indigenous dengue fever at street-level in Guangzhou city, China.	Liu K, Zhu Y, Xia Y, Zhang Y, Huang X, Huang J, Nie E, Jing Q, Wang G, Yang Z, Hu W, Lu J.	PLoS Negl Trop Dis. 2018 Mar 21;12(3):e0006318.
32	Effects of Glycogen Synthase Kinase-3 Inhibitor TWS119 on Proliferation and Cytokine Production of TILs From Human Lung Cancer.	Tang YY, Sheng SY, Lu CG, Zhang YQ, Zou JY, Lei YY, Gu Y, Hong H.	J Immunother. 2018 Sep;41(7):319-328.
33	EGF-induced nuclear localization of SHCBP1 activates β-catenin signaling and promotes cancer progression.	Liu L, Yang Y, Liu S, Tao T, Cai J, Wu J, Guan H, Zhu X, He Z, Li J, Song E, Zeng M, Li M.	Oncogene. 2018 Sep 3.
34	Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010-2015 in Guangzhou.	Zhang SF, Tuo JL, Huang XB, Zhu X, Zhang DM, Zhou K, Yuan L, Luo HJ, Zheng BJ, Yuen KY, Li MF, Cao KY, Xu L.	PLoS One. 2018 Jan 29;13(1):e0191789.
35	Establishment of a medium-scale mosquito facility: tests on mass production cages for Aedes albopictus (Diptera: Culicidae).	Zhang D, Li Y, Sun Q, Zheng X, Gilles JRL, Yamada H, Wu Z, Xi Z, Wu Y.	Parasit Vectors. 2018 Mar 19;11(1):189.
36	Evidence for Kaposi Sarcoma Originating from Mesenchymal Stem Cell through KSHV-induced Mesenchymal-to-Endothelial Transition.	Li Y, Zhong C, Liu D, Yu W, Chen W, Wang Y, Shi S, Yuan Y.	Cancer Res. 2018 Jan 1;78(1):230-245.
37	Field evaluation of two commercial RT-rtPCR assays for porcine reproductive and respiratory syndrome virus detection using sera from ill and healthy pigs, China.	Zhang YT, Guo XQ, Callahan JD, Yuan GL, Zhang GH, Chen Y, Zhang HB, Pulscher LA, Lu JH, Gray GC.	J Vet Diagn Invest. 2018 Sep 21:1040638718800357.
38	Galectin-3 and Galectin-9 May Differently Regulate the Expressions of	Liu J, Huang S, Lu F.	Front Immunol. 2018 Jul 31;9:1648.

	Microglial M1/M2 Markers and T Helper 1/Th2 Cytokines in the Brains of Genetically Susceptible C57BL/6 and Resistant BALB/c Mice Following Peroral Infection With Toxoplasma gondii.		
39	ICAM-1 controls development and function of ILC2.	Lei AH, Xiao Q, Liu GY, Shi K, Yang Q, Li X, Liu YF, Wang HK, Cai WP, Guan YJ, Gabrilovich DI, Zhou J.	J Exp Med. 2018 Aug 6;215(8):2157-2174.
40	ICAM-1 Deficiency in the Bone Marrow Niche Impairs Quiescence and Repopulation of Hematopoietic Stem Cells.	Liu YF, Zhang SY, Chen YY, Shi K, Zou B, Liu J, Yang Q, Jiang H, Wei L, Li CZ, Zhao M, Gabrilovich DI, Zhang H, Zhou J.	Stem Cell Reports. 2018 Jul 10;11(1):258-273.
41	Identification of a novel compound targeting the nuclear export of influenza A virus nucleoprotein.	Huang F, Chen J, Zhang J, Tan L, Lu G, Luo Y, Pan T, Liang J, Li Q, Luo B, Zhang H, Lu G.	J Cell Mol Med. 2018 Mar;22(3):1826-1839.
42	Identification of long noncoding RNAs in Schistosoma mansoni and Schistosoma japonicum.	Liao Q, Zhang Y, Zhu Y, Chen J, Dong C, Tao Y, He A, Liu J, Wu Z.	Exp Parasitol. 2018 Aug;191:82-87.
43	Identification of nucleotides in the 5'UTR and amino acids substitutions that are essential for the infectivity of 5'UTR-NS5A recombinant of hepatitis C virus genotype 1b (strain Con1).	Li J, Feng S, Liu X, Guo M, Chen M, Chen Y, Rong L, Xia J, Zhou Y, Zhong J, Li YP.	Virology. 2018 May;518:253-263.
44	Imported parasitic diseases in mainland China: current status and perspectives for better control and prevention.	Song LG, Zeng XD, Li YX, Zhang BB, Wu XY, Yuan DJ, He A, Wu ZD.	Infect Dis Poverty. 2018 Aug 3;7(1):78.
45	Increased CCR7(lo)PD-1(hi)CXCR5(+)CD4(+) T Cells in Peripheral Blood Mononuclear Cells Are Correlated with Immune Activation in Patients with Chronic HBV Infection.	Huang YX, Zhao QY, Wu LL, Xie DY, Gao ZL, Deng H.	Can J Gastroenterol Hepatol. 2018 Oct 8;2018:1020925.
46	Increased IL-17-producing CD8(+) T cell frequency predicts short-term mortality in patients with hepatitis B virus-related acute-on-chronic liver	Zhang GL, Zhang T, Zhao QY, Xie C, Lin CS, Gao ZL.	Ther Clin Risk Manag. 2018 Oct 30;14:2127-2136.

	failure.		
47	Increased IL-27/IL-27R expression in association with the immunopathology of murine ocular toxoplasmosis.	Tong X, Chen S, Zheng H, Huang S, Lu F.	Parasitol Res. 2018 Jul;117(7):2255-2263.
48	Infection by the nematode Angiostrongylus cantonensis induces differential expression of miRNAs in mouse brain.	Mo ZX, Guo JQ, She D, Zhang X, Puthiyakunnon S, Chen XG, Wu ZD, Shin JW, Cui LW, Li H.	J Microbiol Immunol Infect. 2018 Feb;51(1):94-102.
49	Investigation into the genetic diversity in toll-like receptors 2 and 4 in the European badger Meles meles.	Whiteoak AM, Ideozu J, Alkathiry H, Tomlinson AJ, Delahay RJ, Cowen S, Mullineaux E, Gormley E, Birtles RJ, Lun ZR, Hide G.	Res Vet Sci. 2018 Aug;119:228-231.
50	Kallistatin inhibits lymphangiogenesis and lymphatic metastasis of gastric cancer by downregulating VEGF-C expression and secretion.	Ma C, Luo C, Yin H, Zhang Y, Xiong W, Zhang T, Gao T, Wang X, Che D, Fang Z, Li L, Xie J, Huang M, Zhu L, Jiang P, Qi W, Zhou T, Yang Z, Wang W, Ma J, Gao G, Yang X.	Gastric Cancer. 2018 Jul;21(4):617-631.
51	Kaposi's Sarcoma-Associated Herpesvirus K8 Is an RNA Binding Protein That Regulates Viral DNA Replication in Coordination with a Noncoding RNA.	Liu D, Wang Y, Yuan Y.	J Virol. 2018 Jan 10. pii: JVI.02177-17.
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A Novel Hypothesis on Excessive Activation of Residual B Lymphocytes in Common Variable Immunodeficiency Concurrent with Aseptic, Erosive Polyarthritis

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Background: The aim of this study was to report aseptic, erosive polyarthritis in a patient with common variable immunodeficiency (CVID), which is quite different from the vastly more common nonerosive form.

Material/Methods: Peripheral blood mononuclear cells of the patient were isolated. Flow cytometry was used to analyze the proportion and function of lymphocytes. A Parker-Pearson needle biopsy was performed on the right knee. Four of her unaffected family members were enrolled as controls.

Results: A 21-year-old woman was admitted for recurrent polyarthritis of 3-year duration. The right knee, hip, wrist, proximal interphalangeal joints, and left elbow were involved, with progressive joint destruction. She was diagnosed as having CVID based on her recurrent infections, poor response to vaccines, and marked hypogammaglobulinemia. No bacterium or mycobacterium was detected in synovium or synovial fluid. The synovium was infiltrated by lymphocytes rather than neutrophils. Polyarthritis did not resolve by adequate intravenous immunoglobulin substitution and empirical antibiotic treatment, but resolved gradually after treatment with methylprednisolone and tacrolimus, supporting the diagnosis of aseptic polyarthritis. Further analyses showed that although only 0.5% of residual B lymphocytes were existent in peripheral blood of the patient, expressions of activation marker CD69 and production of IL-1β, IL-6, and TNF-α were high. Marked infiltration with CD19+B lymphocytes (as well as CD4+ or CD8+ T lymphocytes) was detected in the synovium. The proportion of $IL21^{+}CD4^{+}$Th cells from peripheral blood of the patient was high. $CD4^{+}$ Th cells from the patient secreted nearly 3 times more IL-21 than the same cell type analyzed from unaffected family members, perhaps due to excessive compensation to assist the function of residual B lymphocytes.

Conclusions: A novel hypothesis in CVID concurrent with aseptic, erosive polyarthritis is that excessive activation of residual B lymphocytes infiltrate into the synovium of the involved joints and lead to polyarthritis and joint destruction.

MeSH Keywords: Arthritis • B-Lymphocytes • Common Variable Immunodeficiency

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Original paper

A powerful approach reveals numerous expression quantitative trait haplotypes in multiple tissues

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Abstract

Motivation: Recently many studies showed single nucleotide polymorphisms (SNPs) affect gene expression and contribute to development of complex traits/diseases in a tissue context-dependent manner. However, little is known about haplotype's influence on gene expression and complex traits, which reflects the interaction effect between SNPs.

Results: In the present study, we firstly proposed a regulatory region guided eQTL haplotype association analysis approach, and then systematically investigate the expression quantitative trait loci (eQTL) haplotypes in 20 different tissues by the approach. The approach has a powerful design of reducing computational burden by the utilization of regulatory predictions for candidate SNP selection and multiple testing corrections on non-independent haplotypes. The application results in multiple tissues showed that haplotype-based eQTLs not only increased the number of eQTL genes in a tissue specific manner, but were also enriched in loci that associated with complex traits in a tissue-matched manner. In addition, we found that tag SNPs of eQTL haplotypes from whole blood were selectively enriched in certain combination of regulatory elements (e.g. promoters and enhancers) according to predicted chromatin states. In summary, this eQTL haplotype detection approach, together with the application results, shed insights into synergistic effect of sequence variants on gene expression and their susceptibility to complex diseases.

Availability: The executable application "eHaplo" is implemented in Java and is publicly available at http://grass.cgs.hku.hk/limx/ehaplo/.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

The development of high throughput technologies has stimulated comprehensive surveys on genome-wide expression and DNA variation for disentangling the genetic architecture of human diseases. The genetics of transcript abundance has been extensively investigated through genome-wide expression studies (Ahuja et al. 2016; Edwards et al. 2013). These studies demonstrated that, for a large fraction of genes, gene expression is influenced by single nucleotide polymorphisms (SNPs) located in the vicinity of the regulated loci, named as expression quantitative trait loci (eQTLs), generally referred as *cis* eSNPs (Garnier et al. 2013). The importance of *cis* eSNPs would be enhanced if they were also associated with a disease, as such data would indicate that the associated gene is a candidate for the disease (Nica and Dermitzakis 2008). Recent eQTL studies have extended the focus from SNPs to other type of variations, including bi-allelic indels, copy number variations (CNVs), and short tandem repeats as determinants of gene expression (E. P. Consortium 2012; Grundberg et al. 2012; Gymrek et al. 2016; Lappalainen et al. 2013; Montgomery et al. 2013; Stranger et al. 2007). Meanwhile, many eQTL studies showed significant contribution of tissue specific eQTLs to common disease heritability (G. T. Consortium 2015; Torres et al. 2014). An eQTL study between blood and brain also found some of the tissue specific eQTLs were associated with related traits (Hernandez et al. 2012). These studies showed the promise of tissue specific eQTLs for the characterizing functional sequencing variation and for interpreting statistic associations of genome-wide association studies.

Haplotype, which refers to certain combination of multiple SNP alleles, is often used to explore synergistic or non-additive effects among multiple SNPs. Although methods based on individual SNPs have led to many

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Genetics and Population Analysis

A powerful conditional gene-based association approach implicated functionally important genes for schizophrenia

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Abstract

Motivation: It remains challenging to unravel new susceptibility genes of complex diseases and the mechanisms in genome-wide association studies. There are at least two difficulties, isolation of the genuine susceptibility genes from many indirectly associated genes and functional validation of these genes.

Results: We first proposed a novel conditional gene-based association test which can use only summary statistics to isolate independent association genes of a disease. Applying this method, we detected 185 genes of independent association with schizophrenia. We then designed an *in-silico* experiment based on expression/co-expression to systematically validate pathogenic potential of these genes. We found that genes of independent association with schizophrenia had more co-expression pairs in normal postnatal but not prenatal human brain regions than expected. Interestingly, no co-expression enrichment was found in the brain regions of schizophrenia patients. The genes with independent association also had more significant p-values for differential expression between schizophrenia patients and controls in the brain regions. In contrast, indirectly associated genes or associated genes by other widely-used gene-based tests had no such differential expression and co-expression patterns. In summary, this conditional gene-based association test is effective for isolating directly associated genes from indirectly associated genes, and the results insightfully suggest that common variants might contribute to schizophrenia largely by distorting expression and co-expression in post-natal brains.

Availability: The conditional gene-based association test has been implemented in a platform "KGG" in Java and is publicly available at http://grass.cgs.hku.hk/limx/kgg/.

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1 Introduction

Strategies for assessing the overall association of multiple variants in a biological function unit, such as a gene, have been widely used to identify new genetic factors of complex diseases/traits. Many statistical tests were proposed for evaluating overall association of multiple variants by using either individual-level genotypes (Ionita-Laza, et al., 2013) or summary statistics (Li, et al., 2011; Liu, et al., 2010; Moskvina, et al., 2011). There have been many successful examples of gene-based and pathway-based association tests for complex diseases/traits (Padhukasahasram, et al., 2014; Stein, et al., 2012), as evidenced in the

A Spatio-temporal Model of Macrophage-mediated Drug Resistance in Glioma Immunotherapy

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Running title: Modeling Macrophage-mediated Drug Resistance in Gliomas

Keywords: Tumor microenvironment; Drug resistance; Glioma; Immunotherapy; mathematical model

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Activation and Regulation of Blood Vδ2 T Cells Are Amplified by TREM-1$^+$ during Active Pulmonary Tuberculosis

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Triggering receptor expressed on myeloid cells 1 (TREM-1) is a receptor mainly expressed on myeloid cells, and it plays an important role in modulating immune response against infectious agents. The function of TREM-1 on nonmyeloid cells such as Vδ2 T cells has not been characterized, and their role in pulmonary tuberculosis (TB) remains unclear. To assess the expression of TREM-1 on blood Vδ2 T cells from pulmonary TB patients and investigate its mechanism of induction, we exploited flow cytometry analysis to study the expression of TREM-1 on Vδ2 T cells from active pulmonary TB patients and control subjects. In this study we demonstrate that TREM-1 (TREM-1$^+$) is highly expressed on Vδ2 T cells of patients with active pulmonary TB. Unlike TREM-1$^-$–expressing Vδ2 T cells, TREM-1$^+$–producing Vδ2 T cells display APC-like phenotypes. Surprisingly, TREM-1$^+$ signaling promotes the Ag-presenting capability of Vδ2 T cells to induce the CD4$^+$ T cell response. TREM-1$^+$Vδ2 T cells induced the proliferation and differentiation of naive CD4$^+$ T cells, as well as the elimination of intracellular mycobacteria. We identified TREM-1$^+$ (but not TREM-1$^-$) as an Ag-presentation amplifier on human blood Vδ2 T cells, and data shed new light on the regulation of Vδ2 T cells in the phase of innate and adaptive immune responses against *Mycobacterium tuberculosis* infection. Targeting TREM-1$^+$Vδ2 T cells may be a promising approach for TB therapy. *The Journal of Immunology*, 2018, 200: 000–000.

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacteria tuberculosis*. In its 2016 global TB report, the World Health Organization estimated that in 2015 there were 10.4 million new TB cases and 1.4 million people died of the disease (1). TB was thus declared as the leading cause of death from infectious diseases, and a great challenge to public health. Although *M. tuberculosis* infects approximately one third of the global population, only 10% of individuals develop active TB, demonstrating a crucial role of host immunity in the control of *M. tuberculosis* infection. The containment of *M. tuberculosis* infection largely depends on host cellular immunity mediated by both APCs and T cells. The inhaled infectious bacilli are phagocytized by APCs, which act as the first line of host defense against infection. APCs not only recognize microbial products of invading pathogen via germ-line encoding pattern-recognition receptors (PRRs) to trigger innate immune response, but more importantly, process Ags of ingested *M. tuberculosis* and present its peptides to T cells, leading to the induction of adaptive antimycobacterial immune response. Upon activation by the APCs, naive CD4$^+$ Th cells differentiate into distinct effector subsets depending on the microenvironmental cytokines present during activation (2, 3). Adaptive immunity to *M. tuberculosis* infection is characterized by the generation of Ag-specific CD4$^+$ Th1 cells (4). Effector Th1 cells recruited to the primary site of infection secrete IFN-γ, which in turn activates macrophages to kill intracellular mycobacteria (5). Although the process of Ag presentation is crucial for CD4$^+$ T cell activation and proliferation, little is known about the mechanisms controlling Ag presentation.

Macrophage and dendritic cells (DCs) are essential for Ag presentation during TB infection and have been considered professional APCs. In addition, during infection or inflammation, other cells also display an APC function, which are usually called

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Abbreviations used in this article: BCG, bacillus Calmette-Guérin; BFA, brefeldin A; CQ, chloroquine; DC, dendritic cell; MFI, mean fluorescence intensity; MHC-II, MHC class II; MOI, multiplicity of infection; PPD, purified protein derivative; PRR, pattern-recognition receptor; TB, tuberculosis; TREM-1, triggering receptor expressed on myeloid cells 1.

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ARTICLE Open Access

Adaptive mutation F772S-enhanced p7-NS4A cooperation facilitates the assembly and release of hepatitis C virus and is associated with lipid droplet enlargement

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Abstract

Hepatitis C virus (HCV) infection is a major cause of chronic hepatitis and liver cancer worldwide. Adaptive mutations play important roles in the development of the HCV replicon and its infectious clones. We and others have previously identified the p7 mutation F772S and the co-presence of NS4A mutations in infectious HCV full-length clones and chimeric recombinants. However, the underlying mechanism of F772S function remains incompletely understood. Here, we investigated the functional role of F772S using an efficient JFH1-based reporter virus with Core-NS2 from genotype 2a strain J6, and we designated J6-p7/JFH1-4A according to the strain origin of the p7 and NS4A sequences. We found that replacing JFH1-4A with J6-4A (wild-type or mutated NS4A) or genotype 2b J8-4A severely attenuated the viability of J6-p7/JFH1-4A. However, passage-recovered viruses that contained J6-p7 all acquired F772S. Introduction of F772S efficiently rescued the viral spread and infectivity titers of J6-p7/J6-4A, which reached the levels of the original J6-p7/JFH1-4A and led to a concomitant increase in RNA replication, assembly and release of viruses with J6-specific p7 and NS4A. These data suggest that an isolate-specific cooperation existed between p7 and NS4A. NS4A exchange- or substitution-mediated viral attenuation was attributed to the RNA sequence, and no p7-NS4A protein interaction was detected. Moreover, we found that F772S-enhanced p7-NS4A cooperation was associated with the enlargement of intracellular lipid droplets. This study therefore provides new insights into the mechanisms of adaptive mutations and facilitates studies on the HCV life cycle and virus–host interaction.

Introduction

Hepatitis C virus (HCV) chronically infects 71 million people worldwide according to the estimation of World Health Organization[1]. HCV infection can lead to chronic hepatitis C, which increases the risk of developing liver fibrosis, cirrhosis, and hepatocellular carcinoma[2,3]. To date, no HCV vaccine is available. Recently, the use of direct-acting antiviral agents (DAAs) has revolutionized HCV therapy and cured ≥ 90% of patients[4]. However, pegylated interferon-α in combination with ribavirin (Peg-IFN/RBV) is still the standard of care for hepatitis C in many countries and/or regions[5], which has unfavorable adverse effects and only cures ~50% of patients[6]. Thus, challenges for hepatitis C treatment remain

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Adoptive Transfer of Interleukin-21-stimulated Human CD8+ T Memory Stem Cells Efficiently Inhibits Tumor Growth

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Summary: Memory stem T (T_{SCM}) cells, a new subset of memory T cells with self-renewal and multipotent capacities, are considered as a promising candidates for adoptive cellular therapy. However, the low proportion of human T_{SCM} cells in total $CD8^+$ T cells limits their utility. Here, we aimed to induce human $CD8^+$ T_{SCM} cells by stimulating naive precursors with interleukin-21 (IL-21). We found that IL-21 promoted the generation of T_{SCM} cells, described as $CD45RA^+CD45RO^-CD62L^+CCR7^+CD122^+CD95^+$ cells, with a higher efficiency than that observed with other common γ-chain cytokines. Upon adoptive transfer into an A375 melanoma mouse model, these lymphocytes mediated much stronger antitumor responses. Further mechanistic analysis revealed that IL-21 activated the Janus kinase signal transducer and activator of transcription 3 pathway by upregulating signal transducer and activator of transcription 3 phosphorylation and consequently promoting the expression of T-bet and suppressor of cytokine signaling 1, but decreasing the expression of eomesodermin and GATA binding protein 3. Our findings provide novel insights into the generation of human $CD8^+$ T_{SCM} cells and reveal a novel potential clinical application of IL-21.

Key Words: memory stem T cell, adoptive transfer, interleukin-21, STAT3

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Efforts towards understanding T-lymphocyte memory have revealed the extraordinary potential of adaptive immunity. In infection and cancer, T lymphocytes expand and differentiate into effector cells for clearing the pathogen and into memory cells, which can survive for a long time and ensure protection against pathogens upon antigen rechallenge. Human T lymphocytes are commonly subdivided into naive precursor (T_N) cells, central memory (T_{CM}) cells, effector memory (T_{EM}) cells, and effector cells. The progressive differentiation of T lymphocytes leads to a gradual loss of functional and therapeutic potential. Recent work has revealed the existence of a newly reported T-cell subset, T memory stem (T_{SCM}) cells, in a graft-versus-host disease mouse model[1] and subsequently in human and nonhuman primates.[2,3] This T-cell population is phenotypically defined as $CD45RA^+CD62L^+$, and is distinguishable from T_N cells by the expression of the memory markers CD95 and CD122 in humans. Functionally, T_{SCM} cells can rapidly differentiate into memory and effector cells upon encountering antigens, which proves that they share the abilities of multipotency and self-renewal with T_N cells.[2] Moreover, with higher antitumor activity and survival, T_{SCM} cells have been proved to prolong lifespan in mouse tumor models and human hematopoietic stem cell transplantation (HSCT) patients.[2,4] In light of these appealing characteristics, T_{SCM} cells hold great promise for overcoming the current limitations of T-cell-based immunotherapies. However, the low proportion of T_{SCM} cells in the peripheral blood limits their utility in immunotherapy.[2] Although a potent Wnt-catenin signaling activator, TWS119,[5] and the γ-chain cytokines IL-7 and IL-15[6] have been reported to be effective for T_{SCM}-cell induction, for T_{SCM}-based immunotherapies to be clinically practicable, large-scale and well-functional ex vivo T_{SCM} expansion is required.

Interleukin-21 (IL-21), the youngest member in the common γ-chain cytokine family, is mainly produced by $CD4^+$ T cells and has a pleiotropic effect on both humoral and cell-mediated immune responses by regulating B cell, dendritic cell, natural killer (NK) cell, and $CD4^+$ T-cell function.[7] The effects of IL-21 in the development of innate immunity and CD4 T helper cell responses are well characterized, but its role in the priming of the $CD8^+$ T-cell response, particularly in humans, has not been fully explored. IL-21, similar to IL-2, enhances antigen activation and clonal expansion of $CD8^+$ T cells. However, in contrast to IL-2, IL-21 does not induce the effector cells undergoing activation-induced cell death (AICD) after long-term exposure.[8] In addition, IL-21 tends to retain $CD8^+$ T cells in a state of higher developmental plasticity by inhibiting the antigen-induced expression of differentiation-related transcriptional factors (TFs) and by preventing exhaustion of $CD8^+$ T cells.[9] For $CD8^+$ memory T cells, IL-21 maintains the expression of the costimulation receptor CD28 and functions as a key regulator to switch the proliferation between aged and fresh memory human $CD8^+$ T cells.[10,11] Moreover, IL-21 strongly synergizes with either IL-7 or IL-15 to improve the killing ability of $CD8^+$ T cells by promoting cell proliferation and interferon-γ (IFN-γ) production. These distinctive effects of IL-21 on $CD8^+$ T cells make it an antitumor cytokine with therapeutic potential. Therefore, whether IL-21 can enhance the homeostasis of all types of functional memory $CD8^+$ T cells merits further investigation.

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Review

Artemisinin and its derivatives in treating helminthic infections beyond schistosomiasis

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ABSTRACT

The World Health Organization estimated that more than 1.5 billion people are infected with soil-transmitted helminths globally, and foodborne trematodiases in humans cause ~2 million life-years lost to disability and death worldwide every year. Investment in prevention, treatment, and awareness of helminth infections and discovery of new, safe, effective, and affordable anti-helminth drugs are urgently needed. Artemisinin (ART) and its derivatives have been widely used to treat malaria and other protozoan infections; they also possess activities against helminths. So far, many papers on ART and its derivatives against schistosomal infections have been reported and reviewed. This review attempts to summarize recent advances in the uses of ART and its derivatives to treat infections of helminth parasites other than *Schistosoma* spp. in both humans and animals, including nematodes (*Toxocara canis*, *Trichinella spiralis, Haemonchus contortus*, *Meloidogyne* spp., *Globodera rostochiensis*, and *Xiphinema index*), cestodes (*Echinococcus* spp. and *Taenia crassiceps*), trematodes (*Echinostoma* spp., *Fasciola* spp., *Clonorchis sinensis, Opisthorchis viverrini*, *Paragonimus westermani*, *Heterophyes heterophyes*, and *Paramphistomum microbothrium*), and monogenea parasites (*Dactylogyrus* and *Gyrodactylus*). We concluded that ART and its derivatives are potentially effective drugs for treating various helminthic diseases of public health significance.

1. Introduction

Helminth infections lead to considerable morbidity, accentuate the morbidity of malaria and HIV/AIDS, and impair vaccine efficacy [1]. Discovery of effective therapeutic drugs is the key to improving health in regions where helminthic infections usually occur. Artemisinin (ART) and its derivatives have been used successfully to treat malaria and have been tested for treating other parasitic protozoan infections [2]. ART and its derivatives have also been reported to possess activities against many parasitic helminths. Therapeutic action of ART to *Schistosoma* spp. is due to either heme-initiated formation of free radicals [3] or abrogation of redox homeostasis by ART interacting with reduced flavin cofactors of flavin disulfide reductases [4]. ART derivatives [5] and synthetic peroxides such as ozonides and trioxolanes may be used as alternative or complementary drugs against schistosomes [6,7]. In addition, ART-based therapies have been shown to have great efficacy against *Fasciola* spp., *Opisthorchis* spp., and *Clonorchis sinensis* [8–11]. For example, both artemether and artesunate were found to be effective against the liver flukes *Fasciola hepatica* and *C. sinensis* [12,13]. Studies with artesunate and artemether for treating *Fasciola* infections have progressed to clinical trials or exploratory phase-2 trials in *Fasciola*-infected patients [14]. ART treatment has significant impact on egg production of triclabendazole-resistant Sligo isolate of *F. hepatica* fluke by disrupting parasite vitelline cells *in vivo* [15]. In addition, ART and its derivatives also have activities against nematodes [16] and cestodes [17].

In this paper, we summarized recent progress in the use of ART and its derivatives in treating helminth infections through extensive

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RESEARCH Open Access

Bacillus subtilis spore with surface display of paramyosin from *Clonorchis sinensis* potentializes a promising oral vaccine candidate

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Abstract

Background: Clonorchiasis caused by *Clonorchis sinensis* has become increasingly prevalent in recent years. Effective prevention strategies are urgently needed to control this food-borne infectious disease. Previous studies indicated that paramyosin of *C. sinensis* (CsPmy) is a potential vaccine candidate.

Methods: We constructed a recombinant plasmid of PEB03-CotC-CsPmy, transformed it into *Bacillus subtilis* WB600 strain (*B.s*-CotC-*Cs*Pmy), and confirmed CsPmy expression on the spore surface by SDS-PAGE, Western blotting and immunofluorescence assay. The immune response and protective efficacy of the recombinant spore were investigated in BALB/c mice after intragastrical or intraperitoneal immunization. Additionally, biochemical enzyme activities in sera, the intestinal histopathology and gut microflora of spore-treated mice were investigated.

Results: CsPmy was successfully expressed on the spore surface and the fusion protein on the spore surface with thermostability. Specific IgG in sera and intestinal mucus were increased after intraperitoneal and intragastrical immunization. The sIgA level in intestinal mucus, feces and bile of *B.s*-CotC-*Cs*Pmy orally treated mice were also significantly raised. Furthermore, numerous IgA-secreting cells were detected in intestinal mucosa of intragastrically immunized mice. No inflammatory injury was observed in the intestinal tissues and there was no significant difference in levels of enzyme-indicated liver function among the groups. Additionally, the diversity and abundance of gut microbiota were not changed after oral immunization. Intragastric and intraperitoneal immunization of *B.s*-CotC-CsPmy spores in mice resulted in egg reduction rates of 48.3 and 51.2% after challenge infection, respectively. Liver fibrosis degree in *B.s*-CotC-CsPmy spores treated groups was also significantly reduced.

Conclusions: CsPmy expressed on the spore surface maintained its immunogenicity. Both intragastrical and intraperitoneal immunization with *B.s*-CotC-CsPmy spores induced systemic and local mucosal immune response in mice. Although both intragastric and intraperitoneal immunization elicited a similar protective effect, intragastric immunization induced stronger mucosal immune response without side effects to the liver, intestine and gut microbiota, compared with intraperitoneal immunization. Oral immunization with *B. subtilis* spore expressing CsPmy on the surface was a promising, safe and needle-free vaccination strategy against clonorchiasis.

Keywords: *Clonorchis sinensis*, *Bacillus subtilis*, Spore, Paramyosin, Oral vaccine

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Bayesian spatiotemporal analysis for association of environmental factors with hand, foot, and mouth disease in Guangdong, China

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Hand, foot, and mouth disease (HFMD) remains a significant public health and economic burden in parts of China, particularly Guangdong Province. Although the association between meteorological factors and HFMD has been well documented, significant gaps remain in our understanding of the potential impact of environmental factors. Using county-level monthly HFMD data from China CDC and environmental data from multiple sources, we used spatiotemporal Bayesian models to evaluate the association between HFMD and environmental factors including vegetation index, proportion of artificial surface, road capacity, temperature and humidity, and assessed the spatial and temporal dynamic of the association. Statistically significant correlation coefficients from −0.056 to 0.36 (all $P < 0.05$) were found between HFMD incidence and all environmental factors. The contributions of these factors for HFMD incidence were estimated to be 16.32%, 12.31%, 14.61%, 13.53%, and 2.63%. All environmental factors including vegetation index (Relative Risk: 0.889; Credible Interval: 0.883–0.895), artificial surface (1.028; 1.022–1.034), road capacity (1.033; 1.028–1.038), temperature (1.039; 1.028–1.05), and relative humidity (1.015; 1.01–1.021) were statistically retained in the final spatiotemporal model. More comprehensive environmental factors were identified as associating with HFMD incidence. Taking these environmental factors into consideration for prevention and control strategy might be of great practical significance.

Hand, foot, and mouth disease (HFMD) remains a major public health concern in China, where over two million children are affected annually[1]. Guangdong is one of the most affected provinces in China where the incidence of HFMD exceeds 30 cases per 10,000 annually, and in recent years accounted for approximately 15% of total cases in China[2]. Even though vaccines have entered the market substantially reducing Enterovirus 71 (EV71), which is one of the major causative pathogens of HFMD, in certain areas of China the epidemic remains. Pathogens other than EV71 have been confirmed to be causative for HFMD, such as Coxsackievirus A16 (CVA16) and CVA6[3]. HFMD caused by these pathogens have become increasingly dominant. While pathogen characteristics such as the activity and type of pathogens at the point of infection are more likely directly related to HFMD onsets, environmental factors are potentially associated with HFMD infections[4].

Among various environmental factors, weather variables are investigated more for their effect on HFMD hazards. A nationwide study in China suggested that the seasonal patterns of HFMD were associated with precipitations, sunshine, temperature, and air pressure[5]. However, previous climatic variables do not explain the complexity of HFMD seasonality across China[5]. Zhao *et al.*[6] and Gou *et al.*[7] reported that high temperature could increase the risk of HFMD in Huainan and Gansu, China. In our previous study, we observed a higher risk of HFMD when temperatures were greater than 24.85 °C and relative humidity within 80.59–82.55%[8].

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Beta-Defensin 2 and 3 Promote Bacterial Clearance of *Pseudomonas aeruginosa* by Inhibiting Macrophage Autophagy through Downregulation of Early Growth Response Gene-1 and c-FOS

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Beta-defensins 2 and 3 (BD2 and BD3) are inducible peptides present at the sites of infection, and they are well characterized for their antimicrobial activities and immune-regulatory functions. However, no study has thoroughly investigated their immunomodulatory effects on macrophage-mediated immune responses against *Pseudomonas aeruginosa* (PA). Here, we use THP-1 and RAW264.7 cell lines and demonstrate that BD2 and BD3 suppressed macrophage autophagy but enhanced the engulfment of PA and Zymosan bioparticles as well as the formation of phagolysosomes, using immunofluorescence staining and confocal microscopy. Plate count assay showed that macrophage-mediated phagocytosis and intracellular killing of PA were promoted by BD2 and BD3. Furthermore, microarray and real-time PCR showed that the expression of two genes, early growth response gene-1 (EGR1) and c-FOS, was attenuated by BD2 and BD3. Western blot revealed that BD2 and BD3 inhibited the expression and nuclear translocation of EGR1 and c-FOS. Knockdown of EGR1 and c-FOS by siRNA transfection suppressed macrophage autophagy before and after PA infection; while overexpression of these two transcription factors enhanced autophagy but reversed the role of BD2 and BD3 on macrophage-mediated PA eradication. Together, these results demonstrate a novel immune defense activity of BD2 and BD3, which promotes clearance of PA by inhibiting macrophage autophagy through downregulation of EGR1 and c-FOS.

Keywords: beta-defensins, *Pseudomonas aeruginosa*, macrophages, autophagy, bacterial eradication

Abbreviations: PA, *Pseudomonas aeruginosa*; BD2, beta-defensins 2; BD3, beta-defensins 3; AMPs, antimicrobial peptides; LPS, lipopolysaccharide; TLRs, toll-like receptors; ATG, autophagy-related gene; ROS, reactive oxygen species; RNS, reactive nitrogen species; EGR1, early growth response gene-1; c-FOS, fos proto-oncogene; CCR6, C–C motif chemokine receptor 6; IL-6, interleukin 6; TNF, tumor necrosis factor; LC3, microtubule associated protein 1 light chain 3; MR, mannose receptor; SR, scavenger receptor; ERK, extracellular regulated MAP kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; AMPK, AMP-activated protein kinase; Bcl-2, B-cell leukemia/lymphoma-2; mTOR, mammalian target of rapamycin; TAB, TGF-beta activated kinase 1/MAP3K7 binding protein; PRRs, pattern recognition receptors; NLRs, nucleotide oligomerization domain (NOD)-like receptors; PAMPs, pathogen associated molecular pattern; CFTR, cystic fibrosis transmembrane conductance regulator; AnxA2, cell membrane protein Annexin A2; CR, complement receptors; FcγR, Fc receptors for IgG; CFU, colony forming units.

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Research Paper

Cascaded Electrochemiluminescence Signal Amplifier for the Detection of Telomerase Activity from Tumor Cells and Tissues

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Abstract

Telomerase is closely linked to the physiological transformation of tumor cells and is commonly overexpressed in most types of tumor cells. Therefore, telomerase has become a potential biomarker for the process of tumorigenesis, progression, prognosis and metastasis. Thus, it is important to develop a simple, accurate and reliable method for detecting telomerase activity. As a high signal-to-noise ratio mode, electrochemiluminescence (ECL) has been widely applied in the field of biomedical analysis. Here, our objective was to construct an improved ECL signal amplifier for the detection of telomerase activity.

Methods: A cascaded ECL signal amplifier was constructed to detect telomerase activity with high selectivity via controllable construction of a lysine-based dendric $Ru(bpy)_3^{2+}$ polymer (DRP). The sensitivity, specificity and performance index were simultaneously evaluated by standard substance and cell and tissue samples.

Results: With this cascaded ECL signal amplifier, high sensitivities of 100, 50, and 100 cells for three tumor cell lines (A549, MCF7 and HepG2 cell lines) were simultaneously achieved, and desirable specificity was also obtained. Furthermore, the excellent performance of this platform was also demonstrated in the detection of telomerase in tumor cells and tissues.

Conclusion: This cascaded ECL signal amplifier has the potential to be a technological innovation in the field of telomerase activity detection.

Key words: signal amplifier, telomerase activity, tumor cell, tumor tissue

Introduction

A unique hat-like structure is located at the end of the eukaryotic chromosome, and this structure is the biological complex known as a telomere [1-3]. Telomeres are composed of $(TTAGGG)_n$ repeats [4, 5] generally containing thousands of base pairs [6, 7], and they protect chromosomes from degradation [8, 9]. In eukaryotes, the length of the telomere is maintained by telomerase [10, 11], an essential

Cell

CD10$^+$GPR77$^+$ Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness

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SUMMARY

Carcinoma-associated fibroblasts (CAFs) are abundant and heterogeneous stromal cells in tumor microenvironment that are critically involved in cancer progression. Here, we demonstrate that two cell-surface molecules, CD10 and GPR77, specifically define a CAF subset correlated with chemoresistance and poor survival in multiple cohorts of breast and lung cancer patients. CD10$^+$GPR77$^+$ CAFs promote tumor formation and chemoresistance by providing a survival niche for cancer stem cells (CSCs). Mechanistically, CD10$^+$GPR77$^+$ CAFs are driven by persistent NF-κB activation via p65 phosphorylation and acetylation, which is maintained by complement signaling via GPR77, a C5a receptor. Furthermore, CD10$^+$GPR77$^+$ CAFs promote successful engraftment of patient-derived xenografts (PDXs), and targeting these CAFs with a neutralizing anti-GPR77 antibody abolishes tumor formation and restores tumor chemosensitivity. Our study reveals a functional CAF subset that can be defined and isolated by specific cell-surface markers and suggests that targeting the CD10$^+$GPR77$^+$ CAF subset could be an effective therapeutic strategy against CSC-driven solid tumors.

INTRODUCTION

Carcinoma-associated fibroblasts (CAFs) are activated fibroblasts (Orimo and Weinberg, 2006) constituting the major stromal components in many types of malignancies (Kalluri, 2016). Accumulating evidence suggests that CAFs play a crucial role in tumor development and are potential therapeutic targets for cancer. However, recent studies suggest that CAFs are heterogeneous and contain different subpopulations with distinct phenotypes and functions, which hinders their application in diagnosis and targeted therapy. Different CAF populations that secrete distinct profiles of cytokines have been identified in a variety of cancers (Öhlund et al., 2017; Sugimoto et al., 2006). Although significant prognostic impacts of CAFs have been studied in various tumors, including breast and lung cancers, whether CAFs are associated with good or poor prognosis is contradictory in different studies (Paulsson and Micke, 2014). More importantly, although it is generally thought that CAFs promote tumor progression, targeting CAFs leads to disease exacerbation in a cohort of pancreatic cancer patients (Amakye et al., 2013) and in a mouse model of pancreatic cancer (Özdemir et al., 2014; Rhim et al., 2014), suggesting that different fibroblast subsets may exert opposite functions in cancer progression. Therefore, to precisely target the cancer-promoting CAF subsets, it is necessary to identify specific markers to define these subpopulations and understand their functions and mechanisms. Although intracellular cytokine expression has been reported to characterize CAF subsets (Öhlund et al., 2017), the lack of specific cell-surface markers greatly impedes live-cell sorting for CAF subpopulations to investigate their functional heterogeneity and hampers the development of effective targeting therapy against cancer-promoting CAF subsets.

It has been shown that cancer stem cells (CSCs) are a key population of tumor cells that are highly tumorigenic and chemoresistant in many cancer types (Korkaya et al., 2012; Oskarsson et al., 2014; Yu et al., 2007). However, CSC markers are nonspecific or even unclear, which poses a great challenge to target

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RESEARCH Open Access

Chi3l3: a potential key orchestrator of eosinophil recruitment in meningitis induced by *Angiostrongylus cantonensis*

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Abstract

Background: *Angiostrongylus cantonensis*, an important foodborne parasite, can induce serious eosinophilic meningitis in non-permissive hosts, such as mouse and human. However, the characteristics and mechanisms of the infection are still poorly understood. This study sought to determine the key molecules and its underlying mechanism in inducing brain eosinophilic infiltration caused by *Angiostrongylus cantonensis*.

Methods: Mathematical models were established for prediction of significantly changing genes and the functional associated protein with RNA-seq data in *Angiostrongylus cantonensis* infection. The expression level of Chi3l3, the predicted key molecule, was verified using Western blotting and real-time quantitative PCR. Critical cell source of Chi3l3 and its relationship with eosinophils were identified with flow cytometry, immunohistochemistry, and further verified by macrophage depletion using liposomal clodronate. The role of soluble antigens of *Angiostrongylus cantonensis* in eosinophilic response was identified with mice airway allergy model by intranasal administration of *Alternaria alternate*. The relationship between Chi3l3 and IL-13 was identified with flow cytometry, Western blotting, and Seahorse Bioscience extracellular flux analyzer.

Results: We analyzed the skewed cytokine pattern in brains of *Angiostrongylus cantonensis*-infected mice and found Chi3l3 to be an important molecule, which increased sharply during the infection. The percentage of inflammatory macrophages, the main source of Chi3l3, also increased, in line with eosinophils percentage in the brain. Network analysis and mathematical modeling predirect a functional association between Chi3l3 and IL-13. Further experiments verified that the soluble antigen of *Angiostrongylus cantonensis* induce brain eosinophilic meningitis via aggravating a positive feedback loop between IL-13 and Chi3l3.

Conclusions: We present evidences in favor of a key role for macrophave-derived Chi3l3 molecule in the infection of *Angiostrongylus cantonensis*, which aggravates eosinophilic meningitis induced by *Angiostrongylus cantonensis* via a IL-13-mediated positive feedback loop. These reported results constitute a starting point for future research of angiostrongyliasis pathogenesis and imply that targeting chitinases and chitinase-like-proteins may be clinically beneficial in *Angiostrongylus cantonensis*-induced eosinophilic meningitis.

Keywords: Brain, Eosinophilic infiltration, Macrophage, Polarization, Soluble antigens of *A. cantonensis* larvae (L4) (sAg), Chi3l3-IL-13

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ARTICLES

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CK1α suppresses lung tumour growth by stabilizing PTEN and inducing autophagy

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The contribution of autophagy to cancer development remains controversial, largely owing to the fact that autophagy can be tumour suppressive or oncogenic in different biological contexts. Here, we show that in non-small-cell lung cancer (NSCLC), casein kinase 1 alpha 1 (CK1α) suppresses tumour growth by functioning as an autophagy inducer to activate an autophagy-regulating, tumour-suppressive PTEN/AKT/FOXO3a/Atg7 axis. Specifically, CK1α bound the C-terminal tail of PTEN and enhanced both PTEN stability and activity by competitively antagonizing NEDD4-1-induced PTEN polyubiquitination and abrogating PTEN phosphorylation, thereby inhibiting AKT activity and activating FOXO3a-induced transcription of Atg7. Notably, blocking CK1α-induced Atg7-dependent autophagy cooperates with oncogenic HRas^{V12} to initiate tumorigenesis of lung epithelial cells. An association of a CK1α-modulated autophagic program with the anti-neoplastic activities of the CK1α/PTEN/FOXO3a/Atg7 axis was demonstrated in xenografted tumour models and human NSCLC specimens. This provides insights into the biological and potentially clinical significance of autophagy in NSCLC.

Autophagy is a programmed degradation mechanism whereby damaged, long-lived or toxic proteins and organelles are engulfed and digested in response to environmental challenges[1]. The biological and clinical significance of autophagy in cancer, however, can be complex and can even display opposite effects, depending on cancer types and genetic contexts[2–4]. Aside from the notion that tumour cells can use autophagy to obtain nutrients as a pro-survival mechanism under adverse conditions, autophagy can also mediate tumour-suppressive mechanisms, and loss of autophagy may contribute to malignant transformation[4–6]. Understanding the biological effects of autophagy in a particular type of cancer should help in understanding the initiation and development of the cancer type.

Once initiated, autophagy begins with sequential formation of autophagosomes and autolysosomes, where the engulfed constituents are degraded[7,8]. Autophagosome formation requires sequential actions of Atg proteins, a distinguished set of autophagy mediator proteins, generating two ubiquitin-like conjugation systems: the Atg5-Atg12-Atg16 conjugation system and the LC3 conjugation system, which involves conversion of its cytosolic form (LC3-I) to its lipidated form (LC3-II), and incorporation of LC3-II into the autophagosomal membranes[9]. Notably, the E1 enzyme Atg7 is indispensable in conjugating both systems and thereby is essential for the conventional autophagy pathway[10,11]. Nevertheless, the role of Atg7 in cancer appears to be scenario-dependent. For example, Atg7 deficiency initially accelerates lung tumour development but suppresses tumour progression at later stages in the same mouse model[12]. Thus, clarifying the regulatory mechanism of Atg7 expression may facilitate understanding of its roles in cancer development.

The PI(3)K/AKT pathway and its downstream effector, the mTOR complex, have been well characterized as major inhibitory regulators of autophagy[13]. Indeed, AKT-mediated phosphorylation of Beclin1 inhibits autophagy and promotes tumourigenesis[14]. Moreover, AKT signaling contributes to cancer development and progression through multiple downstream effectors, such as FOXO transcription factors[15], and it has been reported that cytosolic FOXO1 induces autophagy to exert its tumour-suppressive effect[16]. Nonetheless, whether and how nuclear FOXOs mediate autophagy activity remains poorly understood.

The tumour suppressor PTEN, a natural antagonist of the PI(3)K/AKT pathway, has been found to positively regulate autophagy[17,18]. An abundance of PTEN is required for both normal lung morphogenesis and the prevention of lung carcinogenesis[19]. Of note, unlike frequently observed genomic alterations in other cancer types, the loss of PTEN in lung cancer is more likely due to post-transcriptional and post-translational modifications[20,21]. Particularly, ubiquitin-mediated proteasomal degradation of PTEN represents an important post-translational mechanism to maintain an optimal level of PTEN in physiological conditions[22]. So far, NEDD4-1 and WWP2 are the only two well-characterized

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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Clonorchis sinensis adult-derived proteins elicit Th2 immune responses by regulating dendritic cells via mannose receptor

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Abstract

Background

Clonorchis sinensis (*C. sinensis*) is the most widespread human liver fluke in East Asia including China and Korea. Clonorchiasis as a neglected tropical zoonosis, leads to serious economic and public health burden in China. There are considerable evidences for an etiological relation between chronic clonorchiasis and liver fibrosis in human beings. Liver fibrosis is a highly conserved and over-protected response to hepatic tissue injury. Immune cells including $CD4^+$ T cell as well as dendritic cell (DC), and pro-fibrogenic cytokines like interleukin 4 (IL-4), IL-13 have been identified as vital manipulators in liver fibrogenesis. Our previous studies had a mere glimpse of T helper type 2 (Th2) dominant immune responses as key players in liver fibrosis induced by *C. sinensis* infection, but little is known about the involved mechanisms in this pathological process.

Methodology/Principal findings

By flow cytometry (FACS), adult-derived total proteins of *C. sinensis* (*Cs*TPs) down-regulated the expression of surface markers CD80, CD86 and major histocompatibility complex class II (MHC-II) on lipopolysaccharide (LPS) induced DC. ELISA results demonstrated that *Cs*TPs inhibited IL-12p70 release from LPS-treated bone marrow-derived dendritic cells (BMDC). IL-10 level increased in a time-dependent manner in LPS-treated BMDCs after incubation with *Cs*TPs. $CD4^+$ T cells incubated with LPS-treated BMDCs plus *Cs*TPs could significantly elevate IL-4 level by ELISA. Meanwhile, elevated expression of pro-fibrogenic mediators including IL-13 and IL-4 were detected in a co-culture system of LPS-activated BMDCs and naive T cells containing *Cs*TPs. *In vivo*, *Cs*TPs-immunized mice enhanced

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Clonorchis sinensis cyclophilin A immunization protected mice from CLP-induced sepsis

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ABSTRACT

Cyclophilin A (CyPA), ubiquitously existing in cytoplasm of all eukaryotes, can be secreted in response to inflammatory stimuli. Extracellular CyPA plays a prominent role in the pathological processes of inflammatory diseases, acting as a proinflammatory mediator, exerting chemotactic effects, promoting apoptosis of endothelial cells and amplifying ROS generation, thus being considered as a potential treatment target of sepsis, a systemic inflammatory response syndrome. Our previous study found that antibodies against cyclophilin A of *Clonorchis sinensis* (CsCyPA) could neutralize mouse cyclophilin A (MuCyPA). In this study, we explored whether CsCyPA immunization could prevent or ameliorate mice sepsis induced by cecum ligation puncture (CLP). The results showed that CsCyPA immunization could improve the 72 h survival rate of mice after CLP. Moreover, the protective effect presented in a titer-dependent manner. The levels of cytokine IL-1β, IL-6, TNF-α, MCP-1 and AST in serum were remarkably decreased compared to CLP control group mice. Pathological damages of liver, lung and kidney were ameliorated accompanied by less inflammatory cell infiltration. CFU per whole peripheral blood at 12 h and 24 h after CLP surgery was significantly lower than that of CLP control group. In vitro, intracellular ROS generation and cytokine mRNA expression in peritoneal macrophages stimulated by LPS were reduced obviously with anti-CsCyPA antibodies (anti-CsCyPAs) preincubation. All these results demonstrated that CsCyPA immunization protected mice from CLP induced sepsis.

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. It remains high mortality in intensive care units, especially in the case of multiple-resistant bacterial infection [2]. New antibiotics development falls behind drug-resistance development, and human will face a drug unavailable circumstance [3,4]. Thus, prevention sepsis instead of prevention infection may be a new way to deal with sepsis caused by various unpredictable objects. The real direct life-threatening elements are the uncontrollable inflammatory responses, severe oxidative stress and circulatory disturbance [5–7]. Targeting to the key pathological factors released by host during infection probably blocks the progress of sepsis. Therefore, identification of the key pathological molecule of host which plays an important role in oxidative stress, inflammatory response and circulatory disturbance is the focus of new strategy against sepsis.

Inspecting pathophysiological process of sepsis, an unattractive protein cyclophilin A interests us as it is an important player taking part in almost all stages of sepsis. Cyclophilin A (CyPA), a highly conversed and ubiquitously expressed cytosolic protein, was first identified as the main target for cyclosporine in 1984 [8–10]. As the most abundant cyclophilin, CyPA is a multifunctional molecule possessing peptidyl prolyl isomerase activity (PPIase activity) and endonuclease activity [11,12]. Intracellularly, it catalyzes the cis-trans isomerization of peptidyl-prolyl bonds of certain proteins and facilitates proteins folding into functional conformation [12]. Besides, CyPA also participates in a range of cell functions, including intracellular trafficking, signal transduction and transcriptional regulation [13,14]. However, CyPA can be secreted into extracellular space spontaneously by various cell types due to inflammatory stimuli, hypoxia, infection, and oxidative stress or released in cell death [15,16]. Secreted CyPA is closely associated with the development and progression of many acute or chronic inflammatory diseases, such as viral infection, periodontitis, and atherosclerosis, tumor, diabetes et al. [17]. During sepsis development,

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Infection and Drug Resistance

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RAPID COMMUNICATION

Co-production of MCR-1 and NDM-5 in *Escherichia coli* isolated from a colonization case of inpatient

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Abstract: Colistin is increasingly used as an antibiotic of last resort for treating carbapenem-resistant Enterobacteriaceae. Mobile colistin resistance gene *mcr-1* has been increasingly reported in Enterobacteriaceae around the world. Of particular concern is the spread of *mcr-1* into carbapenemase-producing Enterobacteriaceae, which results in highly drug-resistant strains that are potentially untreatable. Notably, such *mcr-1*-carrying isolates harboring carbapenemase genes have been reported in animals and patients with infection. Here, we report an *Escherichia coli* strain carrying co-transferable *mcr-1*-harboring IncX4 and bla_{NDM-5}-harboring IncX3 plasmids, which was recovered in the context of fecal colonization.

Keywords: *Escherichia coli*, MCR-1, NDM-5, co-production

Introduction

Colistin is increasingly used as an antibiotic of last resort for treating multidrug-resistant Gram-negative bacteria, especially carbapenem-resistant Enterobacteriaceae. In December 2015, transmissible colistin resistance gene *mcr-1*, encoding phosphoethanolamine transferase, was reported from China. The gene *mcr-1* has since been increasingly reported in Enterobacteriaceae around the world.[1,2] Of particular concern is spread of *mcr-1* into carbapenemase-producing Enterobacteriaceae, which results in highly drug-resistant strains that are potentially untreatable.

Methods and results

A total of 349 non-duplicate *Escherichia coli* clinical isolates were collected from serial fecal specimens in a hospital with capacity of 3,000 beds in Guangzhou, China in 2016 for the purpose of routine drug resistance monitoring. All isolates were characterized by API 20E system (BioMerieux, Marcy l'Etoile, France) and 16S rDNA sequencing. The *mcr-1* gene was detected using polymerase chain reaction (PCR) and sequencing.[2] As a result, 88 (25.2%) isolates were positive for *mcr-1*. This *mcr-1* positivity was higher than found in our previous study (11.3%),[2] indicating that the prevalence of *mcr-1* in *E. coli* is still increasing in this area. Susceptibility testing was performed for routine resistance observation; the results showed that one of the strains, *E. coli* GB788, was resistant to both colistin and carbapenem (Table 1). PCR and sequencing confirmed that *E. coli* GB788 carried both *mcr-1* and bla_{NDM-5} genes. *E. coli* GB788 was then subjected to phylogenetic typing and multilocus sequence typing for molecular epidemiology.[2] As a result, *E. coli* GB788 was classified as phylogenetic group A and sequence type 46 which has been sporadically identified among drug-resistant *E. coli* strains.[3]

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Cell Death & Disease

CORRECTION Open Access

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

Ting Zhang[1,2,3], Ping Yin[2], Zichen Zhang[4], Banglao Xu[3], Di Che[1,2], Zhiyu Dai[2], Chang Dong[2], Ping Jiang[2], Honghai Hong[2,5], Zhonghan Yang[2], Ti Zhou[2], Jianyong Shao[4], Zumin Xu[2,6], Xia Yang[1,2,7] and Guoquan Gao[1,2,8]

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Current treatment of ocular toxoplasmosis in immunocompetent patients: a network meta-analysis

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ABSTRACT

Ocular toxoplasmosis (OT) is the most frequent form of infectious posterior uveitis caused by the protozoan parasite *Toxoplasma gondii*. To evaluate the available evidence in peer-reviewed publications about the most effective therapy for OT in immunocompetent patients, herein a systematic literature search was conducted using Embase, PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) database from January 1987 to October 2017, with search terms "OT", "retinochoroiditis", "treatment", and "immunocompetent"; search filters "controlled clinical trial", "randomized clinical trial", and "clinical trial". The included studies were performed to evaluate the various treatment modalities of OT. Different treatment regimens were compared with regard to the improvement of visual acuity, the resolution of vitreous inflammation, recurrence, and side-effects. We independently extracted data and assessed eligibility and risk of bias using the preferred reporting items for systematic reviews and meta-analysis, and resolved any disagreement through discussion. A Bayesian network meta-analysis model was used to evaluate the interesting outcomes of all the interventions. Total 10 trials of treatments for OT were found to meet the inclusion criteria. Six trials of treatments including clindamycin, azithromycin, and trimethoprim-sulfamethoxazole (TMP-SMX) were compared with conventional therapy (the combination of pyrimethamine, sulfadiazine, and corticosteroids) for evaluation of the effect on visual acuity, vitreous inflammation, recurrence of OT, and side-effects. Two trials were compared TMP-SMX with placebo. One trial was compared azithromycin with TMP-SMX. And another trial was compared among treatments with clindamycin, P-S, TMP-SMX, and placebo. Based on our network meta-analysis, therapy with TMP-SMX seems to be an alternative treatment of OT in immunocompetent patients.

1. Introduction

Toxoplasma gondii infects up to one third of the world's population (Montoya and Liesenfeld, 2004). Ocular toxoplasmosis (OT), caused by infection with *T. gondii*, is one of the main causes of posterior uveitis around the world (Glasner et al., 1992). It has been estimated that approximately 2% of individuals experiencing toxoplasmosis will develop ocular manifestation (Gilbert and Stanford, 2000). Evidences suggest that postnatally acquired *T. gondii* infection is responsible for the majority of OT (Arantes et al., 2015; Gilbert and Stanford, 2000; Holland, 2003). In Brazil, the prevalence of toxoplasmic retinochoroiditis is approximately 27% among patients with eye diseases (Ferreira et al., 2014). In addition, OT can happen in both immuocompromised and immunocompetent patients (Butler et al., 2013). Toxoplasmic retinochoroiditis in immunocompromised patients needs immediate treatment (Maenz et al., 2014). Appropriate treatment is very important to protect the newborns and to prevent impaired vision of toxoplasmic retinochoroiditis in mothers during pregnancy (Turkcu et al., 2017). In immunocompetent patient, acute retinal necrosis has a poor visual prognosis if not promptly treated (Ramsay et al., 2000). Currently, no definitive treatment has been established for OT (Borkowski et al., 2016). In the early 1950s, it was demonstrated that the synergistic action of pyrimethamine and sulfonamides (P-S) can interfere with *T. gondii* parasite replication (Eyles and Coleman, 1953; Eyles and Coleman, 1960). From then on, the combination of pyrimethamine, sulfadiazine, and corticosteroids has been used as the "conventional triple therapy" for the treatment of OT (Flegr et al., 2014; Zamora et al., 2015). However, this standard treatment may not be available in some areas. In addition, it may have major adverse side-effects such as skin rash, kidney stones, and Stevens-Johnson syndrome (Soheilian et al.,

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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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Development of an Infectious Cell Culture System for Hepatitis C Virus Genotype 6a Clinical Isolate Using a Novel Strategy and Its Sensitivity to Direct-Acting Antivirals

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Hepatitis C virus (HCV) is classified into seven major genotypes, and genotype 6 is commonly prevalent in Asia, thus reverse genetic system representing genotype 6 isolates in prevalence is required. Here, we developed an infectious clone for a Chinese HCV 6a isolate (CH6a) using a novel strategy. We determined CH6a consensus sequence from patient serum and assembled a CH6a full-length (CH6aFL) cDNA using overlapped PCR product-derived clones that shared the highest homology with the consensus. CH6aFL was non-infectious in hepatoma Huh7.5 cells. Next, we constructed recombinants containing Core-NS5A or 5′UTR-NS5A from CH6a and the remaining sequences from JFH1 (genotype 2a), and both were engineered with 7 mutations identified previously. However, they replicated inefficiently without virus spread in Huh7.5 cells. Addition of adaptive mutations from CH6a Core-NS2 recombinant, with JFH1 5′UTR and NS3-3′UTR, enhanced the viability of Core-NS5A recombinant and acquired replication-enhancing mutations. Combination of 22 mutations in CH6a recombinant with JFH1 5′UTR and 3′UTR (CH6aORF) enabled virus replication and recovered additional four mutations. Adding these four mutations, we generated two efficient recombinants containing 26 mutations (26m), CH6aORF_26m and CH6aFL_26m (designated "CH6acc"), releasing HCV of $10^{4.3}$–$10^{4.5}$ focus-forming units (FFU)/ml in Huh7.5.1-VISI-mCherry and Huh7.5 cells. Seven newly identified mutations were important for HCV replication, assembly, and release. The CH6aORF_26m virus was inhibited in a dose- and genotype-dependent manner by direct-acting-antivirals targeting NS3/4A, NS5A, and NS5B. The CH6acc enriches the toolbox of HCV culture systems, and the strategy and mutations applied here will facilitate the culture development of other HCV isolates and related viruses.

Keywords: hepatitis C virus, genotype, cell culture system, adaptive mutation, consensus sequence, direct-acting antiviral agents

Review

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Diagnosis, Monitoring, and Control of Schistosomiasis—An Update

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Schistosomiasis is a neglected disease of tropics and subtropics, which has been associated with illness and death of millions of people, especially children. Although, excessive use of anthelmintic drugs and improvement of sanitation procedures have been in practice, yet timely detection, and diagnosis of low-intensity infections, are of utmost importance for reducing morbidity and final elimination of the disease. The diagnosis methods, currently being used for schistosomiasis, have several limitations, hence warrant further investigations for development of novel detection methods with higher rapidity, reliability, and convenience. Nanoparticles have widely been used in bioassays, because of their low-cost, high sensitivity and rapidity. Nano-diagnosis of schistosomiasis is a potential prospect, so this review described the application of nanotechnology for detection of antigen, antibody and the nucleic acid of *Schistosoma*. Furthermore, the techniques described in this review included magnetic affinity enzyme-linked immunoassay, colloidal gold, nanotechnology-based screen-printed biosensors, and electrochemical genosensors, etc. Moreover, the prospects and obstacles in the development of nanoparticle-based sensors for diagnosis of schistosomiasis were discussed. Finally, this study will provide the basis for nanoparticle-based detection and control of schistosomiasis, thus helping the improvement of public health.

KEYWORDS: *Schistosomiasis, Nanotechnology, Nano-Diagnosis, MEIA, Colloidal Gold.*

CONTENTS

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INTRODUCTION

Schistosomiasis is a widely prevalent but highly neglected parasitic disease. It is caused by penetration of larvae of blood flukes through skin upon exposure to infested water. It is common in tropical and subtropical regions, especially in poverty affected areas, where health and food security measures are limited or poorly implemented. Over 240 million people of 78 countries have been affected by it, while about 800 million people are at the risk of infection.[1–3] People who are affected exhibit the symptoms of abdominal pain, anemia, hematuresis, fibrosis of liver and urinary bladder.[4] Since anthelmintic drugs are extensively being used, schistosomiasis is under control in most of the areas;[5] however, in order to implement the goals of reducing morbidity and final elimination,[6,7] surveillance and early diagnosis of schistosomiasis is the focus of current strategies. Therefore, novel inexpensive and convenient diagnosis methods, with higher sensitivity and specificity, need to be developed for early diagnose, as well as to monitor the prevalence of schistosomiasis, especially in poverty affected areas.

Trends in Parasitology

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Review

Diversity and Compatibility of Human Schistosomes and Their Intermediate Snail Hosts

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Human schistosomiasis is a major neglected tropical disease that remains endemic in numerous countries of the tropics and subtropics. Controlling the transmission of schistosomes in their intermediate snail hosts remains a key challenge in the fight against schistosomiasis. Divergence in species, biogeography, and genotype in schistosomes and their intermediate hosts has resulted in diverse parasite–host interactions. This review focuses on recent insights in the biogeography and diversity of schistosome species and their snail hosts, and the molecular basis of compatibility polymorphism between them.

Highlights

Globalization has expanded the range of *Schistosoma* species and their intermediate freshwater snail hosts. This has resulted in the occurrence of schistosomiasis in previously nonendemic regions.

There is a high degree of variation in the susceptibility of snail host populations to *Schistosoma* species, and compatibility polymorphism is a well known feature of this host–parasite system.

The emergence and expansion of viable hybrid offspring from two *Schistosoma* species are creating shifts in compatibility with snail hosts.

These recent developments call for an upgrade in the surveillance of *Schistosoma* species and their intermediate snail hosts to help to control the spread of schistosomiasis.

Human *Schistosoma* Species

Schistosomiasis (see Glossary) is an important human helminthic disease and is ranked secondary to malaria in causing long-term chronic human morbidity [1–3]. The disease results from infection with parasitic trematode worms of the genus *Schistosoma* and occurs in 78 countries across South America, Asia, and Africa. It decreases both the growth and intellectual development of children and the production and working capacity of adults [3]. The World Health Organization estimates that almost 240 million people are affected worldwide, and 700 million people are living in endemic areas [1–3]. Schistosomiasis can become especially severe in socioeconomically underdeveloped countries due to factors that include poor public health education, low water quality, poor sanitation, and natural disasters (such as flooding, which can spread infected snail hosts) [1–4]. In addition, globalization exchanges between endemic and nonendemic countries increases the risk of transmitting schistosomes to nonendemic countries. For example, the rapid growth of China-supported projects and labor services in Africa has resulted in an increase in imported cases of *Schistosoma haematobium* and *Schistosoma mansoni* schistosomiasis in travelers and workers returning to China from Africa [5,6].

The predominant species of *Schistosoma* infecting humans are, in chronological order of detection, *S. haematobium* (1852), *S. japonicum* (1904), *S. mansoni* (1907), *S. intercalatum* (1934), and *S. mekongi* (1978) [1,2]. *Schistosoma malayensis* (1988) has also been found and described in Malaysia, while its public health significance is still undetermined [7]. *Schistosoma guineensis* was taxonomically separated from *S. intercalatum* in 2003 [8]. Three of these seven species, *S. haematobium*, *S. japonicum*, and *S. mansoni,* are the main pathogens of human schistosomiasis. Other *Schistosoma* species must be considered as well – *Schistosoma mattheei*, a parasite of baboons and bovids in Zambia, also has the potential to infect humans [9]. The emergence of natural hybrids of *S. haematobium–S. guineensis* [10] and *S. haematobium–S. intercalatum* in Cameroon [11,12], and *S. haematobium* and the cattle schistosome *S. bovis* [13,14] clearly indicate that we also need to pay attention to the risk of other hybrids that could potentially infect humans.

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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Dynamic spatiotemporal analysis of indigenous dengue fever at street-level in Guangzhou city, China

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Abstract

Background

This study aimed to investigate the spatiotemporal clustering and socio-environmental factors associated with dengue fever (DF) incidence rates at street level in Guangzhou city, China.

Methods

Spatiotemporal scan technique was applied to identify the high risk region of DF. Multiple regression model was used to identify the socio-environmental factors associated with DF infection. A Poisson regression model was employed to examine the spatiotemporal patterns in the spread of DF.

Results

Spatial clusters of DF were primarily concentrated at the southwest part of Guangzhou city. Age group (65+ years) (Odd Ratio (OR) = 1.49, 95% Confidence Interval (CI) = 1.13 to 2.03), floating population (OR = 1.09, 95% CI = 1.05 to 1.15), low-education (OR = 1.08, 95% CI = 1.01 to 1.16) and non-agriculture (OR = 1.07, 95% CI = 1.03 to 1.11) were associated with DF transmission. Poisson regression results indicated that changes in DF incidence rates were significantly associated with longitude (β = -5.08, P<0.01) and latitude (β = -1.99, P<0.01).

OPEN

Effects of Glycogen Synthase Kinase-3β Inhibitor TWS119 on Proliferation and Cytokine Production of TILs From Human Lung Cancer

Ying Ying Tang, Si Yuan Sheng,† Chuan Gang Lu,‡ Yu Qing Zhang,§ Jian Yong Zou,‖ Yi Yan Lei,‖ Yong Gu,‖ and Hai Hong**

Summary: The canonical Wnt-β-catenin signaling pathway arrests the differentiation of T cells and plays an important role in phenotypic maintenance of naive T cells and stem cell-like memory T cells in human peripheral blood, but its effect on tumor-infiltrating lymphocytes (TILs) from non–small cell lung cancer is little known. In this study, we showed that glycogen synthase kinase-3β inhibitor TWS119 has different effects on $CD4^+$ and $CD8^+$ T cells in TILs. TWS119 preserved the expansion of naive T cell and $CD8^+$ stem cell-like memory T cells, and induced $CD8^+$ effector T-cell proliferation in TILs. To further determine whether TWS119 impaired the effector function of TILs, TILs were stimulated with polyclonal stimulation, IL-2 and IFN-γ production were detected. Our data showed that TWS119 does not affect the production of IFN-γ in TILs compared with the control group; whereas TWS119 inhibited IFN-γ secretion of T cells from healthy donor. IL-2 production in $CD4^+$ central memory T cells and $CD4^+$ effector memory T cells from TILs was significantly increased with the TWS119 treatment; TWS119 also promoted the secretion of IL-2 in all cell subsets of $CD8^+$ TILs. These findings reveal that TWS119 has a distinct effect on the proliferation and cytokine production of TILs, and provide new insights into the clinical application of TILs with TWS119 treatment for the adoptive immunotherapy.

Key Words: glycogen synthase kinase-3β inhibitor, TILs, lung cancer, naive T cells, stem cell-like memory T cells

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The canonical Wnt-β-catenin signaling pathway plays an essential role in human thymocyte and peripheral T-cell development.[1–3] Wnt pathway preserves the naive T-cell (Tn) phenotype, maintains the "stemness" in mature memory $CD8^+$ T cells, arrests effector T-cell (Teff)-differentiation in human peripheral blood and cord blood-derived T lymphocytes.[4,5] As the downstream transcription factors of the Wnt-β-catenin signaling pathway, T-cell-specific transcription factors-1 (TCF-1) and lymphoid enhancer binding factor-1 (LEF-1) are required for normal thymic T-cell development; high expression of TCF-1 in Tn cells and stem cell-like memory T cell (Tscm cells),[6] TCF-1 expression decreased when the Tn cells differentiate into Teff cells. The 4, 6-disubstituted pyrrolopyrimidine TWS119 is a potent inhibitor of serine-threonine kinase glycogen synthase kinase-3β (Gsk-3β)[7]; by facilitating the β-catenin accumulation in cytoplasm and translocate into nucleus, TWS119 promotes the expression of TCF-1 and LEF-1 in the nucleus by binding to β-catenin.[8–10] Cultured with TWS119, the majority of T cells retained a characteristic of Tn cells phenotype; while in the absence of the TWS119 treatment, native T-cell activation increased, TCF-1 and LEF-1 down-regulation. Research observed that TWS119 maintain the phenotype of Tn cells by promoting the expression of TCF-1 and blocked $CD8^+$ T-cell differentiation, and inhibited the production of IFN-γ.[4,11,12]

Tumor-infiltrating lymphocyte (TILs) can be expanded from tumor. TILs are heterogeneous cell group, the major population is T cells.[13] Our research illuminated that Tscm cells was found in TILs from non–small cell lung cancer (NSCLC) except Tn cells, Teff, central memory T cells (Tcm), effector memory T cells (Tem),[14,15] the frequency and function of Tscm cells and other subset of T cell from TILs is distinct from that of other lymphoid organ.[16] Tscm cells was first identified in human peripheral blood; Tscm cells share the phenotype of Tn cells while possess the function of memory T cells; in addition, Tscm cells have a strong antitumor function; Tscm cells also own stem cell-like features and have ability to self-renewal and differentiation.[17] Because of these characteristics, Tscm cells are considered to be one of the optimal cell type for adoptive cell transfer (ACT) of cancer immunotherapy.[18,19] Tscm cells in TILs expressed $CD3^+CD4^+/CD8^+CD45RA^+CD45RO^-CCR7^+CD62L^+CD122^+CD95^+$, which was different from the phenotype of Tscm cells from the peripheral blood mononuclear cells (PBMCs) and lymph node.[15] We also observed that Tn cells in TILs possess robust capacity to produce IFN-γ, which varies from the Tn cells from the peripheral blood and lymph node (unpublished data). Whether TWS119 can affect the phenotype and function of Tscm and Tn cells in TILs remain limited. In this study, we analyzed the proliferation and cytokine production of T-cell subsets in TILs from NSCLC with the treatment of TWS119. In terms of proliferation capacity of T-cell subsets, the reactivity to TWS119 was significantly different between TILs from lung cancer and PBMC from healthy donor, and

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ARTICLE

EGF-induced nuclear localization of SHCBP1 activates β-catenin signaling and promotes cancer progression

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Abstract

Aberrant activation of EGFR represents a common event in non-small cell lung carcinoma (NSCLC) and activates various downstream signaling pathways. While EGFR activation of β-catenin signaling was previously reported, the mediating mechanism remains unclear. Our current study found that EGFR activation in NSCLC cells releases SHC-binging protein 1 (SHCBP1) from SHC adaptor protein 1 (SHC1), which subsequently translocates into the nucleus and directly promotes the transactivating activity of β-catenin, consequently resulting in development of NSCLC cell stemness and malignant progression. Furthermore, SHCBP1 promotes β-catenin activity through enhancing the CBP/β-catenin interaction, and most interestingly, a candidate drug that blocks the CBP/β-catenin binding effectively abrogates the aforementioned biological effects of SHCBP1. Clinically, SHCBP1 level in NSCLC tumors was found to inversely correlate with patient survival. Together, our study establishes a novel convergence between EGFR and β-catenin pathways and highlights a potential significance of SHCBP1 as a prognostic biomarker and a therapeutic target.

Introduction

Lung cancer is the most commonly diagnosed cancer type and a leading cause of cancer death globally. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases. Despite the availability of surgical therapy, radiotherapy, and chemotherapy, prognosis of NSCLC is still poor with overall five-year survival rate being as low as 15%, mainly due to development of resistance to chemo- and radiotherapy, postoperative recurrence and early metastasis [1–6]. Even though molecular targeted therapeutic drugs, e.g. EGFR tyrosine kinase inhibitors (TKIs), have shown encouraging efficacies on NSCLC patients in recent years, the vast majority of NSCLC patients who are initially sensitive to TKIs acquire TKI

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BMC Public Health

RESEARCH ARTICLE Open Access

Epidemiological trends and risk factors associated with dengue disease in Pakistan (1980–2014): a systematic literature search and analysis

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Abstract

Background: Dengue is becoming more common in Pakistan with its alarming spreading rate. A historical review needs to be carried out to find the root causes of dengue dynamics, the factors responsible for its spread and lastly to formulate future strategies for its control.

Methods: We searched (January, 2015) all the published literature between 1980 and 2014 to determine spread/burden of dengue disease in Pakistan.

Results: A total of 81 reports were identified, showing high numbers of dengue cases in 2010, 2011, and 2013. The tendency of dengue to occur in younger than in older age groups was evident throughout the survey period and all four serotypes were recorded, with DENV1 the least common. Most dengue hemorrhagic fever (DHF) cases fell in the 20–45 years age range. High frequencies tended to be observed first in the Southern coastal region characterized by mild winters and humid warm summers and then the disease progressed towards the lowland areas of the Indus plain with cool winters, hot summers and monsoon rainfall. Based on this survey, new risk maps and infection estimates were identified reflecting public health burden imposed by dengue at the national level.

Conclusions: Our study showed that dengue is common in the three provinces of Pakistan, i.e., Khyber Pakhtunkhwa (KP), Punjab and Sindh. Based on the literature review as well as on our study analysis the current expansion of dengue seems multifactorial and may include climate change, virus evolution, and societal factors such as rapid urbanization, population growth and development, socioeconomic factors, as well as global travel and trade. Due to inadequate remedial strategies, effective vector control measures are essential to target the dengue vector mosquito where high levels of human-vector contact occur. The known social, economic, and disease burden of dengue is alarming globally and it is evident that the wider impact of this disease is grossly underestimated. An international multi-sectoral response, outlined in the WHO Global Strategy for Dengue Prevention and Control, 2012–2020, is now essential to reduce the significant influence of this disease in Dengue endemic areas. Overall gaps were identified in knowledge around seroprevalence, dengue incidence, vector control, genotype evolution and age-stratified serotype circulation.

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PLOS ONE

RESEARCH ARTICLE

Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010-2015 in Guangzhou

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Abstract

Human coronavirus (HCoV) is one of the most common causes of respiratory tract infection throughout the world. To investigate the epidemiological and genetic variation of HCoV in Guangzhou, south China, we collected totally 13048 throat and nasal swab specimens from adults and children with fever and acute upper respiratory infection symptoms in Gunazhou, south China between July 2010 and June 2015, and the epidemiological features of HCoV and its species were studied. Specimens were screened for HCoV by real-time RT-PCR, and 7 other common respiratory viruses were tested simultaneously by PCR or real-time PCR. HCoV was detected in 294 cases (2.25%) of the 13048 samples, with most of them inpatients (251 cases, 85.4% of HCoV positive cases) and young children not in nursery (53.06%, 156 out of 294 HCoV positive cases). Four HCoVs, as OC43, 229E, NL63 and HKU1 were detected prevalent during 2010–2015 in Guangzhou, and among the HCoV positive cases, 60.20% were OC43, 16.67% were 229E, 14.97% were NL63 and 7.82% were HKU1. The month distribution showed that totally HCoV was prevalent in winter, but differences existed in different species. The 5 year distribution of HCoV showed a peak-valley distribution trend, with the detection rate higher in 2011 and 2013 whereas lower in 2010, 2012 and 2014. The age distribution revealed that children (especially those <3 years old) and old people (>50 years) were both high risk groups to be infected by HCoV. Of the 294 HCoV positive patients, 34.69% (101 cases) were co-infected by other common respiratory viruses, and influenza virus was the most common co-infecting virus (30/101, 29.70%). Fifteen HCoV-OC43 positive samples of 2013–2014 were selected for S gene sequencing

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Parasites & Vectors

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Establishment of a medium-scale mosquito facility: tests on mass production cages for *Aedes albopictus* (Diptera: Culicidae)

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Abstract

Background: Mass egg production is an important component of *Aedes albopictus* mosquito control programs, such as the sterile insect technique and incompatible insect technique, which requires the releases of large number of sterile males. Developing standard operating procedures and optimized cages for adult maintenance of *Ae. albopictus* can improve the mass rearing efficiency.

Methods: Three different sex ratios of females to males with a total number of 4,000 mosquitoes were tested by evaluating the insemination rate, egg production (total number of eggs per cage), female fecundity and egg hatch rate in small cage (30 × 30 × 30 cm). Blood meals with adenosine triphosphate (ATP, 0.05 g/ml), cage structures (Big cage A: 90 × 30 × 30 cm; Big cage B: 90 × 30 × 50 cm or 90 × 50 × 30 cm) and rearing densities (12,000, 16,000 and 20,000 mosquitoes, corresponding to 0.9 cm^2/mosquito, 0.675 cm^2/mosquito and 0.54 cm^2/mosquito, respectively) were also tested and evaluated on the basis of egg production, female fecundity and egg hatch rate. An adult rearing unit holding 15 of Big cage A with optimal egg production was designed to produce 10 million eggs per rearing cycle in a 1.8 m^2 space.

Results: Female to male ratios at 3:1 in small cages resulted in higher egg production but did not affect insemination rate, female fecundity and egg hatch rate. A concentration of 0.05 g/ml of ATP added to blood meals improved the blood-feeding frequency and thus increased the overall egg production per cage. Cage structures affected the egg production per cage, but not egg hatch rate. A medium rearing density at 0.675 cm^2/mosquito (16,000 mosquitoes) resulted in higher egg production compared to both low and high densities. An adult rearing unit for *Ae. albopictus* on the basis of Big cage A has been developed with the capacity of producing 10 million eggs within 15 days.

Conclusions: Our results have indicated that the adult rearing methods and adult maintenance unit are recommended for *Ae. albopictus* mass rearing in support of the establishment of a medium-sized mosquito factory.

Keywords: Mosquito factory, Adult mass-reared methods, Mass production cage, *Aedes albopictus*

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Field evaluation of two commercial RT-rtPCR assays for porcine reproductive and respiratory syndrome virus detection using sera from ill and healthy pigs, China

Ying-Tao Zhang, Xiao-Qin Guo, Johnny D. Callahan, Gui-Li Yuan, Gui-Hong Zhang, Yao Chen, Hai-Bing Zhang, Laura A. Pulscher, Jia-Hai Lu, Gregory C. Gray[1]

Abstract. Porcine reproductive and respiratory syndrome virus (PRRSV) is a highly contagious respiratory virus causing severe morbidity in pigs worldwide. Control strategies for PRRSV often rely on detecting PRRSV, culling or isolating sick pigs, disinfecting pig barns, vaccination, and monitoring for virus spread. Given the high economic impact of PRRSV on pig farms, there is a great need for rapid and reliable PRRSV detection assays. We compared the performance of 2 commercial reverse-transcription real-time PCR (RT-rtPCR) assays, the VetMAX PRRSV NA and EU reagents (ABI assay) and the PRRSV general RT-rtPCR kit (Anheal assay), for the molecular detection of PRRSV in sera collected from pigs in China. Between June and September 2015, sera were collected from 219 healthy and 104 suspected PRRSV-infected pigs on 4 farms in China. Employing blinding, the 2 assays were run by 2 laboratories (Guangzhou Animal Health Inspection Institute [GAHII] and Sun Yat-sen University [SYSU] laboratories) and compared. Although both assays detected PRRSV with 100% specificity at both laboratories, the sensitivity (95% vs. 78% at GAHII; 94% vs. 72% at SYSU Laboratory) and the reproducibility (kappa value 0.933 vs. 0.931) were slightly better for the ABI assay compared to the Anheal assay.

Key words: China; detection; porcine reproductive and respiratory syndrome; test evaluation.

Introduction

The worldwide demand for pork has dramatically increased in the past 2 decades, with China emerging as the world's largest pork consumer. As of 2016, China was home to ~46% of the world's pigs (~456 M; http://www.fao.org/faostat/en/#data/QA, using filters: China, World + (Total); Stocks; Pigs; 2016). As the demand for pork has increased, the trend in pork production has moved from many small farms to large industrial farming in China. Although industrial farming techniques have been embraced throughout China, increasing the productivity of swine farming, not all farms have embraced high levels of biosecurity. Large farms with dense populations of pigs have much opportunity for sustained respiratory virus transmission within herds. In particular, influenza A viruses, porcine reproductive and respiratory syndrome virus (PRRSV), and porcine circoviruses are often found in farms in China.[10]

Porcine reproductive and respiratory syndrome (PRRS) is one of the most economically important and devastating viral diseases impacting pig production worldwide. Financial losses are chiefly the result of increased mortality and morbidity (e.g., poor reproductive performance) and increased use of vaccines, medications, and detection assays. Secondary respiratory complications following a PRRS outbreak on a farm can lead to additional costs. Comprehensive PRRS control strategies must include detection assays and herd monitoring after detection of PRRSV in a herd.

The high economic impact of PRRSV necessitates rapid and accurate detection so that herd management practices can achieve their highest impact.[1] The rapid evolution, genetic variability,[3] and high mutation rate of PRRSV strains confound the development of long-term, reliable detection assays, and mutations in PCR target areas may quickly render

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frontiers in Immunology

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Galectin-3 and Galectin-9 May Differently Regulate the Expressions of Microglial M1/M2 Markers and T Helper 1/Th2 Cytokines in the Brains of Genetically Susceptible C57BL/6 and Resistant BALB/c Mice Following Peroral Infection With *Toxoplasma gondii*

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Toxoplasmic encephalitis (TE), an opportunistic infection, is a severe health problem in immunocompromised patients. Previous studies have revealed that C57BL/6 mice are susceptible and BALB/c mice are resistant to TE. To investigate the mechanisms involved in the immunopathogenesis of TE in susceptible C57BL/6 and resistant BALB/c mice, both strains of mice were perorally infected with the Prugniuad (Pru) strain of *Toxoplasma gondii*. Our results showed that compared with BALB/c mice, C57BL/6 mice infected with *T. gondii* Pru strain had more severe brain histopathological damage, and higher mRNA expression levels of tachyzoite-specific surface antigen 1, bradyzoite-specific antigen 1, interferon gamma (IFNγ), interleukin (IL)-10, arginase1 (Arg1) (M2 marker), galectin (Gal)-3, Gal-9, *T. gondii* microneme protein 1 (TgMIC1), TgMIC4, and TgMIC6 during the course of infection by using quantitative real-time reverse transcription-polymerase chain reaction. Further analysis displayed that BALB/c mice showed higher numbers of microglial cells and higher levels of IL-1β, inducible nitric oxide synthase (iNOS) (M1 marker), and chitinase-3-like protein 3 (Ym1) (M2 marker) in the early infective stage [at day 14 or 35 post infection (p.i.)] compared with C57BL/6 mice, whereas C57BL/6 mice showed higher numbers of microglial cells and higher levels of IL-10, iNOS (M1 marker), and Ym1 (M2 marker) at days 35, 50, or 70 p.i. compared with BALB/c mice. Correlation analysis showed that significant positive correlations existed between Gal-3 and IL-4/IL-10/iNOS/Ym1 and between Gal-9 and IL-4/Ym1 in C57BL/6 mice; between Gal-3 and IFNγ/Arg1 and between Gal-9 and IFNγ/Arg1 in BALB/c mice. Together, our data demonstrated that different Gal-3 and Gal-9 expressions as well as different positive correlations were found between Gal-3 and T helper 1 (Th1)/Th2/M1/M2 cytokines or between Gal-9 and Th1/Th2/M2 cytokines in the brains of *T. gondii* Pru strain-infected C57BL/6 and BALB/c mice.

Keywords: toxoplasmic encephalitis, galectins, microglial M1/M2 markers, *T. gondii* microneme proteins, mice

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ARTICLE

ICAM-1 controls development and function of ILC2

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Group 2 innate lymphoid cells (ILC2s) are emerging as key players in the pathogenesis of allergic airway inflammation. The mechanisms regulating ILC2, however, are not fully understood. Here, we found that ICAM-1 is required for the development and function of ILC2. ICAM-1–deficient (*ICAM-1*$^{-/-}$) mice displayed significantly lower levels of ILC2s in the bone marrow and peripheral tissues than wild-type controls. CLP transfer and in vitro culture assays revealed that the regulation of ILC2 by ICAM-1 is cell intrinsic. Furthermore, ILC2s from *ICAM-1*$^{-/-}$ mice were functionally impaired, as indicated by the diminished production of type-2 cytokines in response to IL-33 challenge. The reduction in lung ILC2s caused a clear remission of airway inflammation in *ICAM-1*$^{-/-}$ mice after administration of papain or *Alternaria alternata*. We further demonstrate that ILC2 defects caused by ICAM-1 deficiency are due to ERK signaling-dependent down-regulation of GATA3 protein. Collectively, these observations identify ICAM-1 as a novel regulator of ILC2.

Introduction

Group 2 innate lymphoid cells (ILC2s) do not express antigen-specific receptors. However, similar to CD4 T cells, they produce type-2 cytokines, including IL-5 and IL-13, when exposed to epithelium-derived cytokines such as IL-33, IL-25, and thymic stromal lymphopoietin (Halim et al., 2012a; Walker et al., 2013; Martinez-Gonzalez et al., 2015; Klose and Artis, 2016). In adult mice, ILC2s develop from common lymphoid progenitors (CLPs) in the bone marrow (BM), followed by $\alpha_4\beta_7^+$ lymphoid progenitors (α-LP), common helper-like ILC progenitors (ChILP), and finally differentiate into ILC2 precursors (ILC2P; Serafini et al., 2015; Zook and Kee, 2016). ILC2s have been found in mucous tissues (lung and intestine), nonlymphoid organs (liver, kidney, and visceral adipose tissue), lymphoid tissues (spleen, BM, and mesenteric lymph node [mLN]), and blood (Walker et al., 2013; Brestoff et al., 2015; Serafini et al., 2015; Riedel et al., 2017; Karta et al., 2018). ILC2s have been shown to be important in inflammation, tissue remodeling, metabolism, and thermal homeostasis; however, their function depends on the tissue they reside and the pathological conditions (McKenzie et al., 2014; Artis and Spits, 2015; Lee et al., 2015). Notably, lung ILC2s play a crucial role in promoting allergic airway inflammation during innate immune responses (Halim et al., 2014; Martinez-Gonzalez et al., 2015).

In recent years, the transcriptional programs and signaling molecules that control the development, homeostasis, and function of ILC2s have been extensively studied (Ebbo et al., 2017; Zhong and Zhu, 2017). GATA3 is a key regulator of ILC2s (Hoyler et al., 2012; Mjösberg et al., 2012). Other transcription factors such as RORα (Halim et al., 2012b; Wong et al., 2012), TCF-1 (Yang et al., 2013), Gfi1 (Spooner et al., 2013), G9a (Antignano et al., 2016), and Ets1 (Zook et al., 2016) also contribute to the regulation of ILC2 development and/or function. Very recently, it was reported that ILC2s express certain costimulation molecules such as ICOS and PD-1, which regulate ILC2 function through STAT5 signaling (Maazi et al., 2015; Taylor et al., 2017). These results suggest a potential role of costimulation molecules in ILC2 function.

Intercellular cell adhesion molecule-1 (ICAM-1 or CD54), which primarily interacts with leukocyte function-associated molecule (LFA)–1, is a transmembrane glycoprotein receptor of the immunoglobulin superfamily (Stanciu and Djukanovic, 1998; Hogg et al., 2011). It is broadly expressed in many cell types, including T cells, B cells, neutrophils, endothelial cells, and epithelial cells (Stanciu and Djukanovic, 1998). Apart from its role in mediating the adhesion of inflammatory cells to the vascular endothelium, epithelium, and extracellular matrix, ICAM-1 also functions as a costimulation molecule to assist tight

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Stem Cell Reports
Article

OPEN ACCESS

ICAM-1 Deficiency in the Bone Marrow Niche Impairs Quiescence and Repopulation of Hematopoietic Stem Cells

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SUMMARY

The bone marrow niche plays a critical role in controlling the fate of hematopoietic stem cells (HSCs) by integrating intrinsic and extrinsic signals. However, the molecular events in the HSC niche remain to be investigated. Here, we report that intercellular adhesion molecule-1 (ICAM-1) maintains HSC quiescence and repopulation capacity in the niche. ICAM-1-deficient mice (ICAM-$1^{-/-}$) displayed significant expansion of phenotypic long-term HSCs with impaired quiescence, as well as favoring myeloid cell expansion. ICAM-1-deficient HSCs presented normal reconstitution capacity during serial transplantation; however, reciprocal transplantation experiments showed that ICAM-1 deficiency in the niche impaired HSC quiescence and repopulation capacity. In addition, ICAM-1 deletion caused failure to retain HSCs in the bone marrow and changed the expression profile of stroma cell-derived factors, possibly representing the mechanism for defective HSCs in ICAM-$1^{-/-}$ mice. Collectively, these observations identify ICAM-1 as a regulator in the bone marrow niche.

INTRODUCTION

Hematopoiesis is the process whereby the pool of all mature blood cells is replenished throughout an organism's life time (Doulatov et al., 2012; Sawai et al., 2016). Hematopoietic stem cells (HSCs) have the capability of both self-renewal and differentiation, which ensures their homeostasis and maintains the hematopoietic system (Orford and Scadden, 2008). Under steady-state conditions, HSCs reside in a dormant state characterized by slow cell cycling, such as quiescence or G0 phase (Pietras et al., 2011). In response to stress, injury, or infections, HSCs exit the G0 phase and proliferate to generate hematopoietic progenitor cells, which will subsequently differentiate and reconstitute the blood and immune lineages (Nakamura-Ishizu et al., 2014; Wilson et al., 2008, 2009). The bone marrow microenvironment, which is known as the niche, has been shown to play a major role in the precise equilibrium between quiescence, self-renewal, and differentiation of HSCs (Crane et al., 2017; Schofield, 1978). The bone marrow niche contains a variety of stroma cells types that help maintain HSC function by providing extracellular matrix proteins, cytokines, chemokines, and growth factors (Mendelson and Frenette, 2014). Stroma cells can interplay with HSCs in the niche, either by secreting certain factors or via direct cell-cell communication through signaling molecules expressed on the cell surface; in this way, they are uniquely adapted to support HSCs (Blaser et al., 2017; Greenbaum et al., 2013; Suda et al., 2005).

The cellular and molecular mechanisms regulating the interplay between HSCs and the bone marrow niche have been extensively investigated (Arai et al., 2004; Goncalves et al., 2016). Among these, adhesion molecules play an important role not only in terms of anchoring hematopoietic cells to the bone marrow niche but also by regulating their functional status (Chen et al., 2013; Jeannet et al., 2013; Simmons et al., 1997). HSCs express diverse adhesion receptors, such as P selectin glycoprotein ligand-1 (PSGL-1), integrins α4β1 and α5β1, and very late antigen-4 (VLA-4), which interact with extracellular matrix proteins and cell adhesion molecules expressed by niche cells (Prosper and Verfaillie, 2001; Winkler et al., 2012). In addition to retaining HSCs in the proper bone marrow niche, the interaction

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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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Identification of long noncoding RNAs in *Schistosoma mansoni* and *Schistosoma japonicum*

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ABSTRACT

Schistosomiasis is a major parasitic disease caused by 3 principal species of schistosome. Studies of schistosome transcriptomes have focused on protein-coding transcripts and although miRNAs are attracting increased attention, few reports have concerned the long noncoding RNAs (lncRNAs). These have been shown to play key roles in the regulation of gene expression through interactions with mRNAs, proteins and miRNAs. In this study, we first identified lncRNAs from RNA-seq data in *Schistosoma mansoni* and *Schistosoma japonicum*: 3247 and 3033 potential lncRNAs were found in these two species respectively. ChIP-seq analysis to determine H3K4me3 profiles along the gene regions corresponding to lncRNAs showed that in 12% of cases this mark was enriched in regions proximal to the transcription start sites, supporting their validity as actively transcribed genes. Besides, the sequence conservation of lncRNAs between schistosome species was much lower than that of mRNAs, but higher than that of the randomly selected genomic sequences, which is consistent with that in mammals. Our results demonstrate that lncRNAs form a significant part of the schistosome transcriptome and suggest that they play an important role in the biology of the parasite.

1. Introduction

Schistosomiasis, caused by the genus *Schistosoma,* is among one of the most serious parasitic diseases in human. It had been reported that more than 258 million individuals in 78 countries were affected and around 200 thousand deaths were annually caused by schistosomiasis worldwide (WHO, 2016). The genus *Schistosoma* infecting human beings is mainly divided into three species: *Schistosoma haematobium* (*S.haematobium*), *Schistosoma mansoni* (*S.mansoni*) and *Schistosoma japonicum* (*S.japonicum*) (King et al., 2005). *S.haematobium*, endemic to the eastern Mediterranean and Africa, results in urinary schistosomiasis. *S.mansoni* occurs in Africa and South America and causes intestinal schistosomiasis. *S.japonicum*, distinct from above two species, is the Asian schistosome, which occurs in oriental countries and causes intestinal schistosomiasis. Despite such differences between these three species, the pathogenesis is similar. In general, adult schistosome worms can colonize human blood vessels and excrete hundreds or even thousands of eggs into the host. These eggs are either trapped in nearby tissues or excreted from body. The immune response of the host to the trapped eggs results in granulomatous reaction and the further schistosomiasis. Therefore, available evidence always indicated that the trapped eggs, not the adult worms, should be responsible for the morbidity through immune-mediated granulomatous response (Chabasse et al., 1985; Doenhoff et al., 2008; Doenhoff et al., 1991). However, the potential genetic mechanisms hidden behind the host-parasite interaction activities remain partially clear. Understanding the mechanisms in genome or transcriptome layers is crucial for us to identify the key effectors that may be a promising biomarker or therapeutic target. Previous studies mainly focused on the protein-coding portion of *Schistosoma* genome and transcriptome, which include the transcriptome databases for *S.mansoni* (Verjovski-Almeida et al., 2003) and *S.japonicum* (Hu et al., 2003), characterization of promoters (Copeland et al., 2007), expression analysis (Verjovski-Almeida et al., 2007), mapping and annotation of protein-coding genes (Brejova et al., 2009) and so on.

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Identification of nucleotides in the 5'UTR and amino acids substitutions that are essential for the infectivity of 5'UTR-NS5A recombinant of hepatitis C virus genotype 1b (strain Con1)

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ABSTRACT

Genotype 1b strain Con1 represents an important reference in the study of hepatitis C virus (HCV). Here, we aimed to develop an advanced infectious Con1 recombinant. We found that previously identified mutations A1226G/F1464L/A1672S/Q1773H permitted culture adaption of Con1 Core-NS5A (C-5A) recombinant containing 5'UTR and NS5B-3'UTR from JFH1 (genotype 2a), thus acquired additional mutations L725H/F886L/D2415G. C-5A containing all seven mutations (C-5A_7m) replicated efficiently in Huh7.5 and Huh7.5.1 cells and had an increased infectivity in SEC14L2-expressing Huh7.5.1 cells. Incorporation of Con1 NS5B was deleterious to C-5A_7m, however Con1 5'UTR was permissive but attenuated the virus. Nucleotides G1, A4, and G35 primarily accounted for the viral attenuation without affecting RNA translation. C-5A_7m was inhibited dose-dependently by simeprevir and daclatasvir, and substitutions at A4, A29, A34, and G35 conferred resistance to miR-122 antagonism. The novel Con1 5'UTR-NS5A recombinant, adaptive mutations, and critical nucleotides described here will facilitate future studies of HCV culture systems and virus-host interaction.

1. 1. Introduction

Worldwide, over 150 million people are infected with hepatitis C virus (HCV), and more than 350,000 annual deaths are associated with HCV-related liver diseases, such as cirrhosis, liver failure, and hepatocellular carcinoma (Mohd Hanafiah et al., 2013; Perz et al., 2006). HCV is a small enveloped, positive-sense single-stranded RNA virus belonging to the genus *Hepacivirus* of the family *Flaviviridae*. The RNA genome is approximately 9.6 kb consisting of a single open reading frame (ORF) flanked by highly structured 5' and 3' untranslated regions (UTRs). The ORF is translated into a polyprotein precursor, which is processed into viral structural proteins (Core, E1, and E2) and non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) (Moradpour et al., 2007). The 5'UTR could be divided into four structured domains (I, II, III, and IV) essential for HCV RNA replication and translation (Fricke et al., 2015). Domains I and II are essential for viral RNA replication (Friebe et al., 2001; Kim et al., 2002), and domains II, III, and IV, together with the partial coding sequence of the Core, constitute an internal ribosomal entry site (IRES) that is responsible for RNA translation (Honda et al., 1996). Domain I includes a stem-loop structure (SLI, nucleotides 5–20), of which the RNA structure other than nucleotide sequence is found to be critical for RNA replication and virus production (Li et al., 2011a; Luo et al., 2003). Deletions of nucleotides 1–4 or 1–20 eliminate virus production (Friebe et al., 2001; Li et al., 2016). The positions of nucleotide and amino acids are referenced to strain H77 (GenBank accession no. AF009606) in this manuscript. Besides, cellular factors that bind to the 5'UTR, such as miR-122, poly(C)-binding protein 2 (PCBP2), hnRNP L, and NF90, also regulate the replication and translation of HCV RNA (Jopling et al., 2005; Li et al., 2014a; Wang et al., 2011).

HCV is classified into seven major genotypes and numerous subtypes (denoted a, b, etc.). The differences between major genotypes and subtypes are ~33% and ~25%, respectively, at the nucleotide and amino acids levels. Genotypes 1 and 3 are the most prevalent and

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Infectious Diseases of Poverty

SCOPING REVIEW Open Access

Imported parasitic diseases in mainland China: current status and perspectives for better control and prevention

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Abstract

Background: The high prevalence of parasitic diseases leads to millions of deaths and disabilities each year in developing countries. China has also been greatly affected by parasitic infections, including filariasis, leishmaniasis, malaria, schistosomiasis, and soil-transmitted nematodosis. However, the situation in China improved dramatically after comprehensive parasitic disease control efforts were strengthened, leading to the elimination of filariasis in 2006 and to significant control over other diseases. However, imported parasitic disease cases are inevitable, and such cases have increasingly been reported as a result of enhanced globalization and international or regional cooperation. These imported diseases represent a major obstacle to the elimination of several parasitoses, such as malaria.

Main text: This paper reviews imported cases of parasitic diseases in mainland China, particularly malaria and schistosomiasis, based on data reported separately by the Chinese annual reports and from other published papers. We summarize the new challenges that face parasitic disease control efforts in mainland China and perspectives regarding better control. We argue that both the provision of professional education and updated training for medical care personnel and the management and surveillance of people entering China are essential. We recommend that Chinese migrant workers should be considered a priority group for health education and that public awareness of imported diseases should be emphasized. Furthermore, we underscore the importance of investigating the distribution of introduced/potential vectors, parasite susceptibility, and improvements in diagnostic techniques and drug stocks.

Conclusions: Imported cases have become the main challenge to the elimination of several parasitoses, such as malaria and schistosomiasis, in mainland China. China should act to meet these challenges, which are closely associated with national biological safety.

Keywords: Parasitic diseases, Imported disease, China

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Research Article

Increased CCR7^{lo}PD-1^{hi}CXCR5^{+}CD4^{+} T Cells in Peripheral Blood Mononuclear Cells Are Correlated with Immune Activation in Patients with Chronic HBV Infection

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T follicular helper cells (Tfh cells) affect essential immune pathogenesis in chronic hepatitis B virus (HBV) infection. The CCR7^{lo}PD-1^{hi} Tfh subset has a partial Tfh effector phenotype and is associated with active Tfh differentiation, whereas the CCR7^{hi}PD-1^{lo} Tfh subset is a resting phenotype. We recruited 20 healthy volunteers and 77 patients with chronic HBV infection, including those in the immune tolerant (IT) phase (n=19), immune clearance (IC) phase (n=20), low replicative (LR) phase (n=18), and reactivation (RA) phase (n=20). The expression of CD4, CXCR5, PD-1, and CCR7 was detected in T cells from peripheral blood by flow cytometry. The frequency of the CCR7^{lo}PD-1^{hi} T subset was significantly higher in the patients than in the healthy controls (14.92±4.87% vs 12.23±2.95%, p=0.018). The frequency of this Tfh subset in the IC group (18.42%±3.08) was increased compared with the IT group (11.94±2.87%, p=0.001) and LR group (13.65±4.93%, p=0.031) and was higher in the RA group than in the IT group (16.03±5.37% vs 11.94±2.87%, p=0.030). We observed a weak positive correlation between the CCR7^{lo}PD-1^{hi} Tfh subset population and the alanine transaminase (ALT) level (r=0.370, p=0.001). The CCR7^{lo}PD-1^{h} Tfh subset in the chronic HBV-infected patients was elevated to various degrees among the different immune phases. CCR7^{lo}PD-1^{hi}CXCR5^{+}CD4^{+} T cells are correlated with the immune status of chronic HBV infection patients and may be developed as a potential indicator for antiviral treatment.

1. Introduction

HBV infection remains among the most serious issues in global public health despite extensive vaccination and effective antiviral treatments. A total of 250 million people suffer from chronic hepatitis B virus (HBV) infection worldwide, most of whom live in Africa and Asia [1, 2]. HBV-associated diseases, such as liver failure, cirrhosis, and hepatocellular carcinoma, contribute to the deaths of 1 million people per year [3].

Our understanding of the natural history of HBV infection and the resultant disease is continuously improving. Complex interactions between the viral and host immune systems participate in disease progression, allowing for HBV penetration into host cells, formation of persistence, and chronization of HBV infection or complete elimination of the virus [4, 5]. Although various clinical and experimental investigations have helped diagnose, treat, and prevent hepatitis B, the exact mechanism underlying the host immune reactions remains unclear.

According to the complex interactions between the virus, hepatocytes, and the host immune system, the natural course of chronic HBV infection is usually stratified into 4 phases, the immune tolerant (IT) phase, the immune clearance (IC) phase, the low replicative (LR) phase, and the reactivation (RA) phase [6].

Proteins of partial HBV can modulate immunity and enable immune escape. In the course of the disease, a better prognosis can be achieved if HBeAg seroconversion occurs early. The prevalence of cirrhosis and hepatocellular

Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Increased IL-17-producing CD8+ T cell frequency predicts short-term mortality in patients with hepatitis B virus-related acute-on-chronic liver failure

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Therapeutics and Clinical Risk Management

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Background: IL-17-producing CD8+ T (Tc17) cells promote inflammation and have been identified in chronic hepatitis. However, the role of Tc17 cells in patients with hepatitis B virus (HBV)-related acute-on-chronic liver failure (HBV-ACLF) remains unclear.

Methods: The frequency of Tc17 cells in blood samples from 66 patients with HBV-ACLF was determined by flow cytometry. The levels of Tc17 cell-related cytokines were measured by FlowCytomix assays. The prognostic prediction accuracy was evaluated by the receiver operating characteristic (ROC) curve analysis. Survival was analyzed using Kaplan–Meier curves. Mortality predictors were determined by the Cox regression analysis.

Results: The frequency of Tc17 cells was markedly higher in patients with HBV-ACLF than in those with chronic hepatitis B and normal control subjects. Increased frequencies of Tc17 cells may indicate liver injury and were positively correlated with disease severity. The Tc17 cell frequency was significantly higher in non-surviving patients with HBV-ACLF than in surviving patients. The ROC curve analysis showed that Tc17 cell frequency accurately predicted 90-day survival in patients with HBV-ACLF, with an accuracy equivalent to those of the Model for End-Stage Liver Disease (MELD), MELD-Na, and Chronic Liver Failure Consortium ACLF scores. Kaplan–Meier analysis showed an association between the increase in circulating Tc17 cells and poor overall survival in patients with HBV-ACLF. Moreover, the multivariate Cox regression analysis showed that Tc17 cell frequency was an independent predictor of overall survival in patients with HBV-ACLF.

Conclusion: Tc17 cells may play a proinflammatory role in HBV-ACLF pathogenesis. Furthermore, the increased frequency of circulating Tc17 cells could be an independent prognostic biomarker in patients with HBV-ACLF.

Keywords: liver disease, inflammation, prognosis, T cells

Introduction

Acute-on-chronic liver failure (ACLF) is a severe clinical syndrome characterized by the acute deterioration of preexisting chronic liver diseases and is linked with substantial short-term mortality.[1] In China, HBV-related ACLF (HBV-ACLF) accounts for most patients because of the high prevalence of HBV infection.[2] The lack of knowledge on the mechanism underlying HBV-ACLF and the lack of effective treatment result in extremely high mortality.[3] Accumulating evidence has shown that systemic inflammation caused by excessive immune-mediated inflammation plays a central role in the mechanism underlying HBV-ACLF. Moreover, systemic inflammation has been

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ORIGINAL PAPER

Increased IL-27/IL-27R expression in association with the immunopathology of murine ocular toxoplasmosis

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Abstract
Interleukin 27 (IL-27) is a member of the IL-6/IL-12 family, and IL-27 receptor (IL-27R) consists of WSX-1 (the IL-27Rα subunit) and the signal-transducing subunit gp130. Human and mouse mast cells (MCs) express the IL-27R. To explore the expressions of IL-27/IL-27R subunits (WSX-1 and gp130) during acute ocular toxoplasmosis (OT), we established mouse model by intraocular injection of 500 *Toxoplasma gondii* RH strain tachyzoites. Histopathological changes were analyzed, MCs were counted by toluidine blue staining, and tryptase$^+$/IL-27$^+$ MCs were examined by immunofluorescence double-staining in the eyes and cervical lymph nodes (CLNs) of *T. gondii*-infected mice. The mRNA expressions of IL-27p28, WSX-1, gp130, and tachyzoite specific surface antigen 1 (SAG1) in the eyes and CLNs of *T. gondii*-infected mice, and the expressions of WSX-1 and gp130 in the murine mastocytoma cell line P815 infected with *T. gondii* tachyzoites in vitro were examined by using quantitative real-time reverse transcription-polymerase chain reaction. Our results showed that, after *T. gondii* infection, severe histopathological changes, increased numbers of total MCs and degranulated MCs, elevated expressions of IL-27p28, WSX-1, and gp130 were found in the eyes and CLNs, and significant correlations between the levels of IL-27 and SAG1 existed in the eyes and CLNs of *T. gondii*-infected mice. In addition, increased levels of WSX-1 and gp130 were examined in *T. gondii*-infected P815 cells. Our data suggested that IL-27/IL-27R expression induced by *T. gondii* infection may regulate MC-mediated immune response during acute OT in mouse model.

Keywords Ocular toxoplasmosis · IL-27p28 · WSX-1 · gp130 · Mast cell · Mice

Introduction

Ocular toxoplasmosis (OT) is a major cause of infectious uveitis and a potentially vision-threatening disease (Garweg 2016). The eye is a very complex organ, and factors leading to development of OT are poorly understood. In addition to their well-established role in allergy, mast cells (MCs) have been described as contributing to functional regulation of both innate and adaptive immune responses in host defense (Fang and Xiang 2015). It has been reported that a rodent (*Calomys callosus*) model inoculated either intraperitoneally or via the conjunctiva with *T. gondii* tachyzoites can induce an increase in MC numbers, suggesting that MCs play an important role in the host inflammatory response during *T. gondii* infection (Gil et al. 2002). So far, knowledge about the contribution of MCs to ocular toxoplasmic invasion is limited. One of the major factors limiting progress in understanding the immunopatholgical mechanisms of OT is the difficulty to obtain samples from patients with acute OT. Therefore, the establishment of

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Investigation into the genetic diversity in toll-like receptors 2 and 4 in the European badger *Meles meles*

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ABSTRACT

The Toll-like receptor (TLR) genes are a conserved family of genes central to the innate immune response to pathogen infection. They encode receptor proteins, recognise pathogen associated molecular patterns (PAMPs) and trigger initial immune responses. In some host-pathogen systems, it is reported that genetic differences, such as single nucleotide polymorphisms (SNPs), associate with disease resistance or susceptibility. Little is known about TLR gene diversity in the European badger (*Meles meles*). We collected DNA from UK badgers, carried out PCR amplification of the badger TLR2 gene and exon 3 of TLR4 and determined DNA sequences for individual badgers for TLR2 (n = 61) and TLR4 exon 3 (n = 59). No polymorphism was observed in TLR4. Three TLR2 amino acid haplotype variants were found. Ninety five percent of badgers were homozygous for one common haplotype (H1), the remaining three badgers had genotypes H1/H3, H1/H2 and H2/H2. By broad comparison with other species, diversity in TLR genes in badgers seems low. This could be due to a relatively localised sampling or inherent low genetic diversity. Further studies are required to assess the generality of the low observed diversity and the relevance to the immunological status of badgers.

Toll-like receptors (TLRs) are a family of proteins that target highly conserved molecules essential for parasite and pathogen survival (Takeda and Akira, 2005). Single nucleotide polymorphisms (SNP) in TLR genes have been linked to pathogen susceptibility in some host species. For example, there is a relationship between TLR variation and *Borrelia afzelii* susceptibility (Tschirren et al. (2013)) and TLR polymorphism and susceptibility to bovine tuberculosis (bTB) in both Chinese Holstein cattle (Sun et al., 2012) and water buffalo (Alfano et al., 2014). Other studies have shown links between TLR variation and risks of cancer (Gomaz et al., 2012), diabetes (Liu et al., 2012), asthma (Schwartz and Cook, 2005) and TB (Zhang et al., 2013) in humans.

TLR genes are conserved throughout evolution (Lu et al., 2008) and homologues are found across a wide range of species (Vasselon and Detmers, 2002). The proteins that they encode have two broad domains; an extracellular Leucine Rich Repeat (LRR) domain which recognises and binds certain pathogen associated molecular patterns (PAMPs) and an intracellular Toll-Interleukin receptor homology domain (TIR). The LRR displays variability which is thought to be driven by an evolutionary arms race with invading parasites and pathogens (Roach et al., 2005). The TIR domain is highly conserved and functions to deliver intracellular signals triggering an innate immune response. Studies on TLR variation have found a higher degree of variation within the LRR domains, some of which appears to be generated by positive selection on amino acid diversity (Jann et al., 2008; Werling et al., 2009). Polymorphisms in the LRR domain can be associated with enhanced susceptibility to disease. For example, the change from arginine to glutamine at position 753 in the human TLR2 gene increases susceptibility to staphylococcal infection (Lorenz et al., 2000), tuberculosis (Ogus et al., 2004), rheumatic fever (Berdeli et al., 2005) and urinary tract infection (Tabel et al., 2007).

TLR population studies are of increasing interest for analysis of broad host responses to disease. This is particularly the case in humans

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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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Clinical Infectious Diseases

MAJOR ARTICLE

Large-scale Artemisinin–Piperaquine Mass Drug Administration With or Without Primaquine Dramatically Reduces Malaria in a Highly Endemic Region of Africa

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Background. Mass drug administration (MDA), with or without low-dose primaquine (PMQ_{LD}), is being considered for malaria elimination programs. The potential of PMQ_{LD} to block malaria transmission by mosquitoes must be balanced against liabilities of its use.

Methods. Artemisinin–piperaquine (AP), with or without PMQ_{LD}, was administered in 3 monthly rounds across Anjouan Island, Union of Comoros. *Plasmodium falciparum* malaria rates, mortality, parasitemias, adverse events, and *PfK13* Kelch-propeller gene polymorphisms were evaluated.

Results. Coverage of 85 to 93% of the Anjouan population was achieved with AP plus PMQ_{LD} (AP+PMQ_{LD}) in 2 districts (population 97 164) and with AP alone in 5 districts (224 471). Between the months of April–September in both 2012 and 2013, average monthly malaria hospital rates per 100 000 people fell from 310.8 to 2.06 in the AP+PMQ_{LD} population (ratio 2.06/310.8 = 0.66%; 95% CI: 0.02%, 3.62%; $P = .00007$) and from 412.1 to 2.60 in the AP population (ratio 0.63%; 95% CI: 0.11%, 1.93%; $P < .00001$). Effectiveness of AP+PMQ_{LD} was 0.9908 (95% CI: 0.9053, 0.9991), while effectiveness of AP alone was 0.9913 (95% CI: 0.9657, 0.9978). Both regimens were well tolerated, without severe adverse events. Analysis of 52 malaria samples after MDA showed no evidence for selection of *PfK13* Kelch-propeller mutations.

Conclusions. Steep reductions of malaria cases were achieved by 3 monthly rounds of either AP+PMQ_{LD} or AP alone, suggesting potential for highly successful MDA without PMQ_{LD} in epidemiological settings such as those on Anjouan. A major challenge is to sustain and expand the public health benefits of malaria reductions by MDA.

Keywords. malaria control; *Plasmodium falciparum*; artemisinin-based combination therapy; *PfK13* Kelch-propeller gene; Comoros Islands.

Malaria infects ~210 million people and kills nearly 0.5 million people annually, with ~90% of malaria deaths in Africa [1]. In the Union of Comoros, *Plasmodium falciparum* infections have historically accounted for 15–30% of hospitalizations and 15–20% of registered deaths in the pediatric services [2]. To eliminate this burden, the Comoros National Health Development Plan for 2010–2014 aimed to reduce parasite carriage rates to <5% [3]. Objectives included access for all Comorians to long-lasting insecticide–treated nets, indoor residual spraying, intermittent presumptive treatment for pregnant women, medical care for malaria, and implementations of mass drug administration (MDA).

An important goal of MDA is the comprehensive treatment of asymptomatic parasite carriers who silently sustain transmission in endemic populations [4, 5]. MDA regimens have therefore included primaquine (PMQ) to kill the *P. falciparum* gametocytes that infect mosquitoes. A single dose of PMQ (0.25 mg base/ kg) may clear *P. falciparum* gametocytes without serious complications from G6PD deficiency [6]. In a modeling study, low-dose PMQ (PMQ_{LD}; 9 mg adult dose) was predicted to enhance the transmission blocking effect of MDA with artemisinin-based combination therapy (ACT) [7]. Indeed, MDA of artemisinin–piperaquine (AP; Artequick) plus PMQ_{LD} (AP +

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WILEY

ORIGINAL ARTICLE

LncRNA DUXAP9-206 directly binds with Cbl-b to augment EGFR signaling and promotes non-small cell lung cancer progression

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Abstract

Long noncoding RNAs (lncRNAs) are involved in the pathology of various tumours, including non-small cell lung cancer (NSCLC). However, the underlying molecular mechanisms of their specific association with NSCLC have not been fully elucidated. Here, we report that a cytoplasmic lncRNA, DUXAP9-206 is overexpressed in NSCLC cells and closely related to NSCLC clinical features and poor patient survival. We reveal that DUXAP9-206 induced NSCLC cell proliferation and metastasis by directly interacting with Cbl-b, an E3 ubiquitin ligase, and reducing the degradation of epidermal growth factor receptor (EGFR) and thereby augmenting EGFR signaling in NSCLC. Notably, correlations between DUXAP9-206 and activated EGFR signaling were also validated in NSCLC patient specimens. Collectively, our findings reveal the novel molecular mechanisms of DUXAP9-206 in mediating the progression of NSCLC and DUXAP9-206 may serve as a potential target for NSCLC therapy.

KEYWORDS
Cbl-b, DUXAP9-206, EGFR signaling, lncRNA, non-small cell lung cancer

1 | INTRODUCTION

Lung cancer is a leading cause of cancer-related mortality worldwide.[1,2] Non-small cell lung cancer (NSCLC), which includes several histological subtypes, such as lung adenocarcinoma, lung squamous cell carcinoma, large-cell lung carcinoma and several other histologic types accounts for over 85% of all lung cancer cases.[2] Although significant progress has been made in current therapeutic strategies, the overall 5-year survival rate is still only 15% with all stages and subtypes combined and the prognosis for majority of the patients

Ting Zhu and Shu An contributed equally to this work.

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Original Paper

MicroRNA-197 Promotes Metastasis of Hepatocellular Carcinoma by Activating Wnt/β-Catenin Signaling

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Key Words
Hepatocellular carcinoma • MicroRNA • EMT • Metastasis • Wnt/β-catenin

Abstract
Background/Aims: MicroRNA-197 (miR-197) has been shown to play roles in epithelial-mesenchymal transition (EMT) and metastasis. The Wnt/β-catenin pathway is associated with EMT, but whether miR-197 regulatesWnt/β-catenin remains unclear. This study was to demonstrate the role of miR-197 on the Wnt/β-catenin pathway in hepatocellular carcinoma (HCC). ***Methods:*** Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to detect the expression of miR-197 in 105 HCC specimens and 15 HCC cell lines. We tested the predicted target gene of miR-197 using a genetic report system. The role of miR-197 in HCC cell invasion and migration (wound healingand cell invasion and migrationby Transwell assays) and in an HCC xenograft modelwas analyzed. ***Results:*** Using a miRNA microarray analysis of HCC specimens and compared with non-metastatic HCC, miR-197 was identified as one of the most upregulated miRNAs in metastatic HCC. miR-197 expression was positively associated with the invasiveness of HCC cell lines. Metastatic HCC cells with high miR-197 expression had Wnt/β-catenin signaling activation. High levels of miR-197 expression also promoted EMT and invasionHCC cells *in vitro* and *in vivo*. miR-197 directly targeted Axin-2, Naked cuticle 1 (NKD1), and Dickkopf-related protein 2 (DKK2), leading to inhibition of Wnt/β-catenin signaling. High miR-197 expression was found in HCC specimens from patients with portal vein metastasis;high miR-197 expression correlated to the expression of Axin2, NKD1, and DKK2. ***Conclusion:*** miR-197 promotes HCC invasion and metastasis by activating Wnt/β-catenin signaling. miR-197 could possibly be used as a prognostic marker and therapeutic target for HCC.

Z. Hu, P. Wang and J. Lin contributed equally to this work.

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SCIENTIFIC REPORTS

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Mycobacterium tuberculosis peptide E7/HLA-DRB1 tetramers with different HLA-DR alleles bound CD4$^+$ T cells might share identical CDR3 region

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Human CD4$^+$ T cells play an important role in the immune response to *Mycobacterium tuberculosis* (MTB). However, little is known about the spectratyping characteristics of the CD4$^+$ T-cell receptor (TCR) α- and β-chains CDR3 region in tuberculosis (TB) patients. We sorted MTB peptide E7-bound CD4$^+$ T cells by using E7/HLA-DR tetramers constructed with different HLA-DRB1 alleles and extracted the CDR3 amino-acid sequences of TCR α- and β-chains. The results showed that the CDR3 sequences of E7-bound CD4$^+$ T cells were completely or partially identical in a single patient. The sequences of MTB peptide C5-bound CD4$^+$ T cells shared another, and non-peptide bound CD4$^+$ T cells, as well as unbound CD4$^+$ T cells with tetramers were different from each other. Specifically, diverse CDR3 sequences of E7-bound CD4$^+$ T cells displayed similar protein tertiary structure in one TB patient. In summary, the TCR α- and β-chains of CDR3 lineage of CD4$^+$ T cells in TB patients apparently drifted, and the predominant CDR3 sequences of TCR α- and β-chains that recognized the MTB antigen exhibited peptide specificity, and certain HLA-DR restriction was also established. This study elucidates the possible causes and mechanisms of peptide-specific CD4$^+$ T-cell-related presentation against MTB.

Tuberculosis (TB) is one of the most widespread chronic infectious diseases mainly presented as a respiratory infection caused by *Mycobacterium tuberculosis* (MTB). While the mechanisms leading to loss of immune defense and disease reactivation are yet unknown, it is well established that CD4$^+$ T cells are critical in controlling TB infection[1–5]. T cells recognize antigens by their T-cell receptors (TCRs), a process limited by the histocompatibility complex (MHC)[6]. CD4$^+$ T cells are activated by recognizing the antigen peptide/MHC class II complex and induce a series of immunological reactions[7]. The human leukocyte antigen (HLA) gene is a set of complicated complex components and structures, the most important feature of which is its high polymorphism. The HLA-II class loci are in the HLA-D region, which includes HLA-DQ, DP, and DR sub-regions. The complex of HLA-DR

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ARTICLE

MYEOV functions as an amplified competing endogenous RNA in promoting metastasis by activating TGF-β pathway in NSCLC

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Abstract

Non-small cell lung cancer (NSCLC) remains a major cause of death worldwide. As metastatic disease is primarily responsible for the poor clinical outcome of NSCLC, it is important to understand the process, and its underlying molecular mechanism as well, via which NSCLC cells disseminate. In this study, we identified a new competing endogenous RNA (ceRNA), namely, the MYEOV transcript, and found that it is upregulated in NSCLC and associated with a poor prognosis of the disease. We further uncovered that the MYEOV ceRNA plays a critical role in the invasion and metastasis of NSCLC cells. Intriguingly, the MYEOV ceRNA exerted its pro-metastatic function independent of its protein-coding capacity, but in a miR-30c-2-3p binding-dependent manner. Further experiments demonstrated that the MYEOV ceRNA sequestered miR-30c-2-3p from binding its targets TGFBR2 and USP15 mRNAs, which in turn leading to constitutive activation of TGF-β signaling and tumor progression in NSCLC. By identifying a new layer of regulatory modality for TGF-β signaling, our findings extend the current understanding on the molecular mechanism mediating NSCLC progression and highlight a potential role of MYEOV transcript to serve as the therapeutic target.

Introduction

Lung cancer remains a major cause of death worldwide, and non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung cancer cases diagnosed [1]. Despite the advances made over the past decades in the treatment of NSCLC, the overall 5-year survival rate of the disease remains lower than 15% for all stages combined [2]. Metastatic disease is primarily responsible for the generally low survival of NSCLC, and therefore, better understanding of the molecular mechanisms via which NSCLC disseminate is needed [3, 4]. Identifying novel molecules that can repress the invasiveness and metastasis of lung cancer will facilitate the development of new anti-lung cancer strategies.

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MAJOR ARTICLE

NLRP3 Inflammasome Activation Mediates Zika Virus–Associated Inflammation

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Zika virus (ZIKV) is a mosquito-borne virus that has been identified as a cause of several severe disease manifestations, including congenital microcephaly and Guillain-Barré syndrome, meningoencephalitis, and myelitis. Previous studies showed that ZIKV-infected patients exhibited elevated plasma levels of interleukin 1β (IL-1β), indicating that ZIKV may activate inflammasomes. However, the molecular basis for its viral pathogenesis remains poorly understood. In this current study, we found that ZIKV infection caused severe inflammatory pathological changes and promoted IL-1β production in vitro and in vivo. We here demonstrate that the maturation and secretion of IL-1β during ZIKV infection was mediated by NLRP3 inflammasome activation and that ZIKV nonstructural protein 5 (NS5) facilitated the assembly of the NLRP3 inflammasome complex, leading to IL-1β activation through interaction with NLRP3 and induction of reactive oxygen species production. Collectively, our data identify NLRP3 inflammasome–derived IL-1β production as a critical feature of inflammation during ZIKV infection. These findings offer new insights into inflammasome-mediated diseases and may provide new therapeutic options for ZIKV-associated diseases.

Keywords. Zika virus, NS5, NLRP3 inflammasome, interleukin-1 beta.

Zika virus (ZIKV) belongs to the family *Flaviviridae* (genus *Flavivirus*) and is transmitted by *Aedes* mosquitoes. Although symptomatic ZIKV infection in humans generally involves a mild, self-limited acute febrile illness associated with rash, arthralgia, and conjunctivitis, some patients develop more-severe neurological complications, such as congenital microcephaly and Guillain-Barré syndrome, meningoencephalitis, and myelitis [1–4]. Recent studies have revealed an increase in the levels of proinflammatory cytokines, such as interleukin 1β (IL-1β), interferon γ (IFN-γ), interleukin 6 (IL-6), and interleukin 8 (IL-8), in ZIKV-infected patients, compared with healthy people [5]. These observations indicate that the inflammatory response may contribute to the ZIKV-associated diseases. However, the mechanisms by which ZIKV stimulates inflammatory signaling are not defined.

The proinflammatory cytokine IL-1β is a central component of the cytokine milieu and plays an important role in fever, septic shock, and inflammatory diseases. The generation of mature active IL-1β requires cleavage of the precursor, pro–IL-1β, by the inflammasome [6]. The inflammasome is a large multiprotein complex that senses infection or danger stimuli in the cell and controls the maturation and secretion of IL-1β and IL-18 [6]. Several types of inflammasomes have been identified, of which the nucleotide and oligomerization domain, leucine-rich repeat-containing protein family, pyrin-containing domain 3 (NLRP3) inflammasome is the most studied and best characterized [7]. Upon activation and oligomerization, NLRP3 interacts with the caspase-recruitment domain (CARD) molecule known as adaptor molecule apoptosis-associated speck-like protein containing CARD (ASC). Clustered ASCs in turn recruit pro–caspase 1 via a CARD-CARD interaction and induce the autoproteolytic conversion of the proenzyme into active caspase 1 [8]. Activated caspase 1 leads to the cleavage and release of mature IL-1β and IL-18 [9]. Activation of the NLRP3 inflammasome and IL-1β release mediate host protection against pathogen invasions. However, hyperactivation of the NLRP3 inflammasome contributes to the pathogenesis of inflammatory diseases, such as viral encephalitis and viral fulminant hepatitis [10–12].

Activation of the NLRP3 inflammasome requires signals at both the transcriptional and posttranslational levels. The first signal leads to synthesis of pro–IL-1β and other components of the inflammasome, such as NLRP3, through the Toll-like receptor/nuclear factor κB pathway. The second signal is transduced by various pathogen-associated molecular patterns and damage-associated molecular patterns to activate the assembly of the NLRP3 inflammasome, caspase 1 activation, and IL-1β secretion [13]. Several molecular mechanisms have been indicated for NLRP3 activation to induce caspase 1 activation and IL-1β maturation. These include the generation of mitochondrial

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LETTER TO THE EDITOR

Non-coding RNA: a key regulator of the pathogenicity and immunity of Flaviviridae viruses infection

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Flaviviridae is a family of viruses that mainly spread through arthropod vectors, such as mosquitoes. Major members of the Flaviviridae family include dengue virus (DENV), yellow fever virus, Zika virus (ZIKV), West Nile virus and hepatitis C virus (HCV). As Flaviviridae viruses remain a major global public health threat, elucidation of the exact mechanisms of pathogenesis during infection is required for the successful control of these deadly viruses.

Recent evidence has shown that non-coding RNAs induced by viral infection might play a critical role in regulating the virus – host interaction during Flaviviridae infection. We recently showed that severe human DENV infection induced the downregulation of microRNA (miRNA)-378 in peripheral blood mononuclear cells, which might suppress the expression of Granzyme B (GrzB) (Figure 1), suggesting that the DENV – miRNA – 378 – GrzB interaction axis is actively involved in the virus – host interaction during Flaviviridae infection.[1] However, whether and how miRNA-378 regulates pro-viral immunopathogenesis or anti-viral immunity during DENV infection require further study. The importance of host non-coding RNA in mediating the virus – host interaction is further solidified by recent findings suggesting that the liver-specific tumor suppressor miRNA-122 contributes to enhanced HCV replication; viral RNA appears to suppress the normal host targets of miRNA-122 and to enhance the long-term oncogenic potential of HCV infection[2] (Figure 1). Moreover, it is thought that miRNA-15b acts as a positive regulator of the production of virus-induced inflammatory cytokines, such as interleukin (IL)-1b, IL-6 and CCL2, in HeLa cells during Japanese encephalitis virus infection.[3] Together, these findings suggest that miRNAs are a central mediator of immune networks or virus – host interaction processes during Flaviviridae virus infection.

In addition to miRNAs, other non-coding RNAs, such as long non-coding RNAs, circular RNAs and PIWI-interacting RNAs, may play critical roles in Flaviviridae virus infections.[4–9] Further studies are required to elucidate the expression profiles of non-coding RNAs and their roles (Figure 1). It is also worth mentioning that the expression levels of several miRNAs, including miRNA-378, are variable in severe cases of human DENV infection; it remains unclear how these miRNAs and other non-coding RNAs act to regulate T-cell, B-cell and monocyte function.

Flaviviridae viruses have genomic structures similar to positive-sense single-stranded RNA, containing one open reading frame flanked by 5′ and 3′ untranslated regions (UTRs). Recent evidence has shown, however, that 3′ UTRs of full-length genomic RNA contain subgenomic non-coding flavivirus RNA (sfRNA). Some human miRNAs are known to originate from viral genomes. Recent evidence suggests that the sfRNA of DENV is an important non-coding RNA, which is able to shape the epidemiological fitness of DENV by binding to TRIM25 (tripartite motif-containing protein 25), thereby inhibiting the anti-viral interferon response (Figure 1). It was recently reported that a complex fold structure, the multi-pseudoknot, is responsible for ZIKV sfRNA production (Figure 1), suggesting that sfRNA in the 3′ UTR may also participate in the pathogenicity of ZIKV.[10] However, the exact role and mechanisms of action of ZIKV sfRNA require further study. Taken together, these data suggest that the non-coding RNA found in the genomes of Flaviviridae viruses is a key regulator of the balance between pro-viral pathogenicity and anti-viral immunity and is thereby a critical determinant of infection outcome.

Collectively, non-coding RNAs, either from the host or from the viral genome, are of great importance in modulating

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Retrovirology

REVIEW Open Access

Non-coding RNAs and retroviruses

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Abstract

Retroviruses can cause severe diseases such as cancer and acquired immunodeficiency syndrome. A unique feature in the life cycle of retroviruses is that their RNA genome is reverse transcribed into double-stranded DNA, which then integrates into the host genome to exploit the host machinery for their benefits. The metazoan genome encodes numerous non-coding RNAs (ncRNA), which act as key regulators in essential cellular processes such as antiviral response. The development of next-generation sequencing technology has greatly accelerated the detection of ncRNAs from viruses and their hosts. ncRNAs have been shown to play important roles in the retroviral life cycle and virus–host interactions. Here, we review recent advances in ncRNA studies with special focus on those have changed our understanding of retroviruses or provided novel strategies to treat retrovirus-related diseases. Many ncRNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are involved in the late phase of the retroviral life cycle. However, their roles in the early phase of viral replication merit further investigations.

Keywords: Non-coding RNA, Retroviruses, Viral life cycle, Virus latency, MicroRNA, Long non-coding RNA

Background

The classification and life cycle of retroviruses

Retroviruses represent a large and diverse family of enveloped RNA viruses defined by common taxonomic denominators that include structure, composition, and replicative properties [1]. A key feature of the retroviral life cycle is that the RNA genome is reverse-transcribed to double-stranded DNA, which is subsequently integrated into the host genome and turns to a provirus. The viral genes are transcribed from the integrated proviral DNA to produce proteins and genomic RNA required to assemble the progeny viral particles. Retroviruses are further subdivided into seven groups (genus) defined by their evolutionary relatedness [2]. Retroviruses in five of these groups have oncogenic potential (formerly referred to as oncoviruses), and the other two groups are lentiviruses and spumaviruses. The representative of the lentivirus family is the human immunodeficiency virus type 1 (HIV-1), the causative agent of acquired immunodeficiency syndrome (AIDS). There are over 36 million people living with HIV-1 worldwide, with approximately 2.1 million new infections being reported in 2015. To date, there is no cure for AIDS because of the existence of the HIV reservoir. The latent reservoir is a group of HIV-infected cells (mainly resting $CD4^+$ T cells) that do not actively produce new HIV-1, but could produce virus again upon stimulation [3].

The life cycle of retroviruses can be simply divided into the early and late phases. The early phase refers to the steps from cell binding to integration of the viral cDNA in the host genome, whereas the late phase begins with the expression of viral genes and is followed by the assembly, release, and maturation of progeny virions [4]. For HIV-1, the lifecycle can be briefly divided into seven steps: (1) attachment and binding, (2) fusion and uncoating, (3) reverse transcription, (4) integration, (5) transcription, (6) assembly, and (7) budding (Fig. 1A–G). Steps 1–4 represent the early phase, and steps 5–7 represent the late phase of a typical retrovirus life cycle. In addition, there is a special state of the retrovirus life cycle called latent infection. Under such conditions, the proviral DNA is transcriptionally inactive without producing infectious viral particles. As the host $CD4^+$ T cells are activated, the phase of latent HIV infection can be reversed to productive infection [3, 5]. Numerous host factors are involved

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VACCINES AND ANTIVIRAL AGENTS

Nonsteroidal Anti-inflammatory Drugs Potently Inhibit the Replication of Zika Viruses by Inducing the Degradation of AXL

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ABSTRACT Zika virus (ZIKV) is genetically and biologically related to other *Flaviviridae* family members and has disseminated to many countries. It is associated with severe consequences, including the abnormal development of the neural system in fetuses and neurological diseases in adults. Therefore, the development of anti-ZIKV drugs is of paramount importance. Screening of generic drugs revealed that several nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, naproxen, acetaminophen, and lornoxicam, potently inhibited the entry of Zika virus Env/HIV-1-pseudotyped viruses. They also significantly inhibited the replication of wild-type ZIKV both in cell lines and in primary human fetal endothelial cells. Interestingly, the NSAIDs exerted this inhibitory effect by potently reducing the expression of AXL, the entry cofactor of ZIKV. Further studies showed that the NSAIDs downregulated the prostaglandin E_2/prostaglandin E receptor 2 (EP2)/cAMP/protein kinase A (PKA) signaling pathway and reduced PKA-dependent CDC37 phosphorylation and the interaction between CDC37 and HSP90, which subsequently facilitated CHIP/ubiquitination/proteasome-mediated AXL degradation. Taken together, our results highlight a new mechanism of action of antiviral agents which may assist in designing a convenient strategy for treating ZIKV-infected patients.

IMPORTANCE Zika virus (ZIKV) infection, which causes congenital malformations, including microcephaly and other neurological disorders, has attracted global attention. We observed that several NSAIDs significantly inhibited ZIKV infection. Based on our observations, we propose a novel mechanism of action of antiviral compounds which involves the blockade of virus entry via degradation of the entry cofactor. Furthermore, NSAIDs can be practically used for preventing ZIKV infection in pregnant women, as certain NSAIDs, including ibuprofen and acetaminophen, are considered clinically safe.

KEYWORDS AXL, NSAID, ZIKV, ubiquitination

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Novel genetically stable infectious clone for a Zika virus clinical isolate and identification of RNA elements essential for virus production

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ABSTRACT

Zika virus (ZIKV) is an *Aedes* mosquitoes-transmitted flavivirus, and its infection may cause severe neurological diseases. A genetically stable infectious clone is essential for ZIKV research, however the toxicity and instability of the viral cDNA in bacteria potentially due to its bacterial promoter activity are major challenges. Here, we constructed a full-length cDNA clone for isolate ZG01 by introducing non-coding changes T1865C/A1868G to reduce the bacterial promoter activity. Wild-type and recombinant ZG01 were highly attenuated in Vero cells, thus we serially passaged wild-type ZG01 through neonatal mice and Vero cells to generate high-titer virus, from which four mutations (4m, C2178T/G2913A/T4991C/T10561C) were identified. Addition of 4m greatly enhanced the infectivity, as ZG01_4m released ZIKV of $10^{7.0}$–$10^{7.5}$ plaque-forming unit (PFU)/ml in infected Vero and A549 cells. ZG01_4m resembled the infectivity of high-titer ZG01 *in vitro* and *in vivo*. Notably, ZG01_4m plasmid was genetically stable after multiple rounds of transformation-purification in bacteria. Using ZG01_4m, we identified a potential RNA-RNA interaction between 5′UTR and 3′UTR and demonstrated that the nucleotides involved were essential for ZIKV production. The genetically stable ZG01 cDNA clone provides a reliable tool for the study of this important virus, and the strategy used here is feasible for the development of reverse genetics systems for other ZIKV isolates and related flaviviruses.

1. Introduction

Zika virus (ZIKV) belongs to the *Flavivirus* genus of *Flaviviridae* family, and the flaviviruses are the most important arthropod-borne viruses (arboviruses) in the world posing a health burden to millions of individuals annually. ZIKV is closely related to other important members within the family causing human diseases globally, such as dengue virus (DENV), hepatitis C virus (HCV), West Nile virus (WNV), yellow fever virus (YFV), tick-borne encephalitis, and Japanese encephalitis virus (JEV) (Pierson and Diamond, 2013). ZIKV genome is a positive-sense single-stranded RNA of about 11,800 nucleotides (nts), consisting of a single open reading frame (ORF) and untranslated regions at 5′ and 3′ untranslated regions (5′UTR and 3′UTR). The ORF encodes a polyprotein precursor, which is cleaved by host and viral proteases into three structural proteins [C, capsid; prM, premembrane/membrane; and E, envelope) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3A, NS4A, NS4B, and NS5). Structural proteins form infectious virion, while nonstructural proteins are mainly involved in viral RNA translation and replication, assembly of virus particles, and interaction with host immune responses.

ZIKV was first isolated from a sentinel rhesus macaque in 1947 in the Zika Forest in Uganda (the original strain MR766) (Dick et al., 1952) and was first reported with human infection in 1954 (Macnamara, 1954). ZIKV is primarily transmitted by *Aedes* species mosquitoes. Recently, accumulating evidences have shown that ZIKV is able to transmit through the sex, blood transfusion, and organ transplantation (Joguet et al., 2017; Musso et al., 2014, 2015; Nogueira et al., 2017). Although ZIKV RNA has been reported in urine, saliva,

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Full length article

Oral delivery of *Bacillus subtilis* spores expressing grass carp reovirus VP4 protein produces protection against grass carp reovirus infection

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ABSTRACT

Grass carp (*Ctenopharyngodon idellus*) hemorrhagic disease (GCHD), caused by grass carp reovirus (GCRV), has given rise to an enormous loss in grass carp industry during the past years. Up to date, vaccination remained to be the most effective way to protect grass carp from GCHD. Oral vaccination is of major interest due to its advantages of noninvasive, time-saving, and easily-operated. The introduction of oral vaccination has profound impact on aquaculture industry because of its feasibility of extensive application for fish in various size and age. However, the main challenge in developing oral vaccine is that antigens are easily degraded and are easy to induce tolerance. *Bacillus subtilis* (*B. subtilis*) spores would be an ideal oral vaccine delivery system for their robust specialty, gene operability, safety and adjuvant property. VP4 protein is the major outer capsid protein encoded by GCRV segment 6 (S6), which plays an important role in viral invasion and replication. In this study, we used *B. subtilis* spores as the oral delivery system and successfully constructed the *B. subtilis* CotC-VP4 recombinant spores (CotC-VP4 spores) to evaluate its protective efficacy in grass carp. Grass carp orally immunized with CotC-VP4 spores showed a survival rate of 57% and the relative percent survival (RPS) of 47% after the viral challenge. Further, the specific IgM levels in serum and the specific IgZ levels in intestinal mucus were significantly higher in the CotC-VP4 group than those in the Naive group. The immune-related genes including three innate immune-related genes (IL-4/13A, IL-4/13B, CSF1R), four adaptive immune-related genes (BAFF, CD4L, MHC-II, CD8), three inflammation-related genes (IL-1β, TNF-α, TGF-β) and interferon type I (IFN-I) related signaling pathway genes were significantly up-regulated in the CotC-VP4 group. The study demonstrated that the CotC-VP4 spores produced protection in grass carp against GCRV infection, and triggered both innate and adaptive immunity post oral immunization. This work highlighted that *Bacillus subtilis* spores were powerful platforms for oral vaccine delivery, and the combination of *Bacillus subtilis* spores with GCRV VP4 protein was a promising oral vaccine.

1. Introduction

Grass carp (*Ctenopharyngodon idellus*) is an essential pisciculture species with an annual production of 6.1 million tons worldwide [1,2]. The aquaculture industry has faced enormous challenges of the grass carp hemorrhagic disease (GCHD) that, during the past years, economic impacts addressed the urgency to tackle this aquacultural illness [3]. GCHD, is a hemorrhagic disease caused by grass carp reovirus (GCRV). The epidemic of GCHD has yielded a mortality rate of up to 81.4% [4]. However, no effective antiviral therapeutics, to date, has been developed to treat the disconcerting disease, becoming an unsolved burden. To conquer GCRV and control the infection, vaccination prevails to be

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PEAK1, acting as a tumor promoter in colorectal cancer, is regulated by the EGFR/KRas signaling axis and miR-181d

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Abstract

PEAK1 is upregulated in multiple human malignancies and has been associated with tumor invasion and metastasis, but little is known about the role of PEAK1 in colorectal cancer (CRC) progression. We investigated the expression pattern, function and regulatory mechanisms of PEAK1 in CRC. Here, we found that PEAK1 is overexpressed in CRC tissues and that high PEAK1 expression predicts poor survival in colon cancer but not rectal cancer. Functionally, silencing PEAK1 inhibits cell proliferation, migration, and invasion in vitro and inhibits the growth of tumor xenografts in nude mice. Mechanistic studies revealed that PEAK1 is induced by epidermal growth factor receptor (EGFR) signaling and that PEAK1 is required for KRas-induced CRC cell growth and metastasis. Furthermore, we demonstrated that miR-181d directly targets PEAK1. Ectopic expression of miR-181d reduces the expression of PEAK1 and inhibits the growth and metastasis of CRC cells in vitro. Clinically, miR-181d is downregulated in CRC samples, and low miR-181d is correlated with poor patient survival. Our study demonstrates the importance of PEAK1 in CRC progression and suggests a potential mechanism by which increasing PEAK1 expression in CRC might be the result of EGFR/KRas signal activation and consequent miR-181d repression.

Introduction

Colorectal cancer (CRC) is the most common malignant tumor worldwide[1]. Distant metastasis is a major cause of death in CRC patients[2, 3]. Currently, the standard first-line treatments that have shown promising results for metastatic colorectal cancer (mCRC) are cytotoxic chemotherapy and/or targeted therapies[4]. The most commonly used target therapies for mCRC are the monoclonal antibodies cetuximab and panitumumab, both of which can inactivate the EGFR signaling pathway[5]. Unfortunately, primary and secondary resistance after anti-EGFR antibody therapy has emerged. Recent studies have identified mutations in downstream effectors of the EGFR signaling pathway, such as KRas[6–8] and other genes[9–11], as the primary cause of resistance. Therapeutic resistance to EGFR blockade could be overcome through combinatorial therapies targeting EGFR downstream genes[9]. Therefore, defining these genes can help guide treatment and improve clinical care.

Pseudopodium-enriched atypical kinase 1 (PEAK1), a non-receptor atypical tyrosine kinase family member KIAA2002 (sgk269), localizes to the actin cytoskeleton and focal adhesions (FAs) and regulates FA turnover[12, 13]. PEAK1 contains multiple tyrosine phosphorylation sites[12], and one of these, Y1188, can be phosphorylated by

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ORIGINAL ARTICLE

Pigment Epithelium-Derived Factor Plays a Role in Alzheimer's Disease by Negatively Regulating Aβ42

Mao Huang[1,2] · Weiwei Qi[1,2] · Shuhuan Fang[3] · Ping Jiang[2] · Cong Yang[3] · Yousheng Mo[3] · Chang Dong[2] · Yan Li[2] · Jun Zhong[1] · Weibin Cai[2] · Zhonghan Yang[2] · Ti Zhou[2] · Qi Wang[3] · Xia Yang[1,2,5] · Guoquan Gao[1,2,4,6]

Abstract

Alzheimer's disease (AD) is the most common cause of dementia. Pigment epithelium-derived factor (PEDF), a unique neurotrophic protein, decreases with aging. Previous reports have conflicted regarding whether the PEDF concentration is altered in AD patients. In addition, the effect of PEDF on AD has not been documented. Here, we tested serum samples of 31 AD patients and 271 normal controls. We found that compared to PEDF levels in young and middle-aged control subjects, PEDF levels were reduced in old-aged controls and even more so in AD patients. Furthermore, we verified that PEDF expression was much lower and amyloid β-protein (Aβ)42 expression was much higher in senescence-accelerated mouse prone 8 (SAMP8) strain mice than in senescence-accelerated mouse resistant 1 (SAMR1) control strain mice. Accordingly, high levels of Aβ42 were also observed in PEDF knockout (KO) mice. PEDF notably reduced cognitive impairment in the Morris water maze (MWM) and significantly downregulated Aβ42 in SAMP8 mice. Mechanistically, PEDF downregulated presenilin-1 (PS1) expression by inhibiting the c-Jun N-terminal kinase (JNK) pathway. Taken together, our findings demonstrate for the first time that PEDF negatively regulates Aβ42 and that PEDF deficiency with aging might play a crucial role in the development of AD.

Key Words Alzheimer's disease · Pigment epithelium-derived factor · Aβ42 · Presenilin-1

Introduction

Alzheimer's disease (AD) is the most common cause of dementia among the elderly, affecting up to 35.6 million people worldwide [1]. Unfortunately, a cure for AD has not been identified yet. Senile plaques (SPs) composed of ~4-kDa amyloid β-protein (Aβ) fibrils are generally considered as the upstream causative factor as well as a major therapeutic target of AD [2,

Mao Huang and Weiwei Qi contributed equally to this work.

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ORIGINAL ARTICLE

WILEY Cancer Science

Pigment epithelium-derived factor/vascular endothelial growth factor ratio plays a crucial role in the spontaneous regression of infant hemangioma and in the therapeutic effect of propranolol

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Infantile hemangioma (IH) is a benign tumor that is formed by aberrant angiogenesis and that undergoes spontaneous regression over time. Propranolol, the first-line therapy for IH, inhibits angiogenesis by downregulating activation of the vascular endothelial growth factor (VEGF) pathway, which is hyperactivated in IH. However, this treatment is reportedly ineffective for 10% of tumors, and 19% of patients relapse after propranolol treatment. Both pro-angiogenic and anti-angiogenic factors regulate angiogenesis, and pigment epithelium-derived factor (PEDF) is the most effective endogenous anti-angiogenic factor. PEDF/VEGF ratio controls many angiogenic processes, but its role in IH and the relationship between this ratio and propranolol remain unknown. Results of the present study showed that the PEDF/VEGF ratio increased during the involuting phase of IH compared with the proliferating phase. Similarly, in hemangioma-derived endothelial cells (HemEC), which were isolated with magnetic beads, increasing the PEDF/VEGF ratio inhibited proliferation, migration, and tube formation and promoted apoptosis. Mechanistically, the VEGF receptors (VEGFR1 and VEGFR2) and PEDF receptor (laminin receptor, LR) were highly expressed in both IH tissues and HemEC, and PEDF inhibited HemEC function by binding to LR. Interestingly, we found that propranolol increased the PEDF/VEGF ratio but did so by lowering VEGF expression rather than by upregulating PEDF as expected. Furthermore, the combination of PEDF and propranolol had a more suppressive effect on HemEC. Consequently, our results suggested that the PEDF/VEGF ratio played a pivotal role in the spontaneous regression of IH and that the combination of PEDF and propranolol might be a promising treatment strategy for propranolol-resistant IH.

Abbreviations: co-IP, co-immunoprecipitation; EC, endothelial cell; HemEC, hemangioma-derived endothelial cell; IH, infant hemangioma; LR, laminin receptor; MVD, microvessel density; non-HemEC, non-hemangioma-derived endothelial cell; PEDF, pigment epithelium-derived factor; VEGFR1, vascular endothelial growth factor receptor 1; VEGFR2, vascular endothelial growth factor receptor 2; VEGF, vascular endothelial growth factor; VM, venous malformation; α-SMA, alpha smooth muscle actin; β-AR, β-adrenergic receptor.

Liuqing Zhu, Jinye Xie, and Zhenyin Liu contributed equally to this work.

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Prediction of the potential global distribution for *Biomphalaria straminea*, an intermediate host for *Schistosoma mansoni*

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Abstract

Background

Schistosomiasis is a snail-borne parasitic disease and is endemic in many tropical and subtropical countries. *Biomphalaria straminea*, an intermediate host for *Schistosoma mansoni*, is native to the southeastern part of South America and has established in other regions of South America, Central America and southern China during the last decades. *S. mansoni* is endemic in Africa, the Middle East, South America and the Caribbean. Knowledge of the potential global distribution of this snail is essential for risk assessment, monitoring, disease prevention and control.

Methods and findings

A comprehensive database of cross-continental occurrence for *B. straminea* was compiled to construct ecological models. We used several approaches to investigate the distribution of *B. straminea*, including direct comparison of climatic conditions, principal component analysis and niche overlap analyses to detect niche shifts. We also investigated the impacts of bioclimatic and human factors, and then used the bioclimatic and footprint layers to predict the potential distribution of *B. straminea* at global scale. We detected niche shifts accompanying the invasions of *B. straminea* in the Americas and China. The introduced populations had enlarged its habitats to subtropical regions where annual mean temperature is relatively low. Annual mean temperature, isothermality and temperature seasonality were identified as most important climatic features for the occurrence of *B. straminea*. Additionally, human factors improved the model prediction ($P<0.001$). Our model showed that under current climate conditions the snail should mostly be confined to the tropic and subtropic regions, including South America, Central America, Sub-Saharan Africa and Southeast Asia.

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Infectious Diseases of Poverty

SCOPING REVIEW Open Access

Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods

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Abstract

Background: Snail-borne parasitic diseases, such as angiostrongyliasis, clonorchiasis, fascioliasis, fasciolopsiasis, opisthorchiasis, paragonimiasis and schistosomiasis, pose risks to human health and cause major socioeconomic problems in many tropical and sub-tropical countries. In this review we summarize the core roles of snails in the life cycles of the parasites they host, their clinical manifestations and disease distributions, as well as snail control methods.

Main body: Snails have four roles in the life cycles of the parasites they host: as an intermediate host infected by the first-stage larvae, as the only intermediate host infected by miracidia, as the first intermediate host that ingests the parasite eggs are ingested, and as the first intermediate host penetrated by miracidia with or without the second intermediate host being an aquatic animal. Snail-borne parasitic diseases target many organs, such as the lungs, liver, biliary tract, intestines, brain and kidneys, leading to overactive immune responses, cancers, organ failure, infertility and even death. Developing countries in Africa, Asia and Latin America have the highest incidences of these diseases, while some endemic parasites have developed into worldwide epidemics through the global spread of snails. Physical, chemical and biological methods have been introduced to control the host snail populations to prevent disease.

Conclusions: In this review, we summarize the roles of snails in the life cycles of the parasites they host, the worldwide distribution of parasite-transmitting snails, the epidemiology and pathogenesis of snail-transmitted parasitic diseases, and the existing snail control measures, which will contribute to further understanding the snail-parasite relationship and new strategies for controlling snail-borne parasitic diseases.

Keywords: Snail-borne parasitic diseases, Epidemiology, Pathogenesis, Snail control

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SCIENTIFIC REPORTS

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Spatial and Temporal Characteristics of 2014 Dengue Outbreak in Guangdong, China

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The record-breaking number of dengue cases reported in Guangdong, China in 2014 has been topic for many studies. However, the spatial and temporal characteristics of this unexpectedly explosive outbreak are still poorly understood. We adopt an integrated approach to ascertain the spatial-temporal progression of the outbreak in each city in Guangdong as well as in each district in Guangzhou, where the majority of cases occurred. We utilize the Richards model, which determines the waves of reported cases at each location and identifies the turning point for each wave, in combination with a spatial association analysis conducted by computing the standardized G* statistic that measures the degree of spatial autocorrelation of a set of geo-referenced data from a local perspective. We found that Yuexiu district in Guangzhou was the initial hot spot for the outbreak, subsequently spreading to its neighboring districts in Guangzhou and other cities in Guangdong province. Hospital isolation of cases during early stage of outbreak in neighboring Zhongshan (in effort to prevent disease transmission to the vectors) might have played an important role in the timely mitigation of the disease. Integration of modeling approach and spatial association analysis allows us to pinpoint waves that spread the disease to communities beyond the borders of the initially affected regions.

Dengue fever (DF) is an infectious disease, currently affecting most of the regions lying within the tropical and subtropical belts. It is caused by dengue virus, and is vectored by mosquitoes belonging to the genus *Aedes*, which thrive in hot and humid climates. Its worldwide quick spread in the last decades is unprecedented and worrisome, to the extent that World Health Organization has recently included DF in the list of the potential public health emergencies of international concern[1].

Currently, the highest-risk area for DF infection is the Asia-Pacific region, which is home to 75% of the world population exposed to dengue virus[2]. Located in this area, the southern region of China had more than 650,000 reported cases (with 610 fatalities) from 1978 to 2008. According to a recent study[3], this situation seems to forebode the transformation of DF from an imported to an endemic disease. No effective dengue virus vaccine is currently available in China. Hence the most widely used intervention measures are suppressing vector population and blocking chain of disease transmission (e.g. home isolation of mild cases), as implemented by Guangdong Provincial Health and Family Planning Commission[4].

In the last decades, the most severe outbreak was recorded in 2014, with 47,056 laboratory-confirmed infections[5], mostly reported in Guangdong province (>95%). Here, unlike in many other dengue risk regions, the dominant mosquito species is *Aedes albopictus*[6]. Moreover, in its capital city, Guangzhou, there is an intense flow of people to and from Southeast Asia[7], which increases the probability of imported cases. The 2014 record-breaking number of cases has drawn the attention of many researchers, leading to several (and quite different) explanations for such an unusual event. For examples, Cheng *et al.*[8] identifies the date of the first imported case and the abnormal rainfall in May and August as the main factors. Li *et al.*[9] suggests that there had been some

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Research Paper

Spread of MCR-3 Colistin Resistance in China: An Epidemiological, Genomic and Mechanistic Study

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ABSTRACT

Background: Mobilized resistance to colistin is evolving rapidly and its global dissemination poses a severe threat to human health and safety. Transferable colistin resistance gene, *mcr-3*, first identified in Shandong, China, has already been found in several countries in multidrug-resistant human infections. Here we track the spread of *mcr-3* within 13 provinces in China and provide a complete characterization of its evolution, structure and function.

Methods: A total of 6497 non-duplicate samples were collected from thirteen provinces in China, from 2016 to 2017 and then screened for the presence of *mcr-3* gene by PCR amplification. *mcr-3*-positive isolates were analyzed for antibiotic resistance and by southern blot hybridization, transfer analysis and plasmid typing. We then examined the molecular evolution of MCR-3 through phylogenetic analysis. Furthermore, we also characterized the structure and function of MCR-3 through circular dichroism analyses, inductively coupled plasma mass spectrometry (ICP-MS), liquid chromatography mass spectrometry (LC/MS), confocal microscopy and chemical rescue tests.

Findings: 49 samples (49/6497 = 0.75%) were *mcr-3* positive, comprising 40 samples (40/4144 = 0.97%) from 2017 and 9 samples (9/2353 = 0.38%) from 2016. Overall, *mcr-3*-positive isolates were distributed in animals and humans in 8 of the 13 provinces. Three *mcr-3*-positive IncP-type and one *mcr-1*-bearing IncHI2-like plasmids were identified and characterized. MCR-3 clusters with PEA transferases from *Aeromonas* and other bacteria and forms a phylogenetic entity that is distinct from the MCR-1/2/P(M) family, the largest group of transferable colistin resistance determinants. Despite that the two domains of MCR-3 not being exchangeable with their counterparts in MCR-1/2, structure-guided functional mapping of MCR-3 defines a conserved PE-lipid recognizing cavity prerequisite for its enzymatic catalysis and its resultant phenotypic resistance to colistin. We therefore propose that MCR-3 uses a possible "ping-pong" mechanism to transfer the moiety of PEA from its donor PE to the 1(or 4′)-phosphate of lipid A via an adduct of MCR-3-bound PEA. Additionally, the expression of MCR-3 in *E. coli* prevents the colistin-triggered formation of reactive oxygen species (ROS) and interferes bacterial growth and viability.

Interpretation: Our results provide an evolutionary, structural and functional definition of MCR-3 and its epidemiology in China, paving the way for smarter policies, better surveillance and effective treatments.

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ARTICLE

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Structure of Schlafen13 reveals a new class of tRNA/rRNA- targeting RNase engaged in translational control

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Cleavage of transfer (t)RNA and ribosomal (r)RNA are critical and conserved steps of translational control for cells to overcome varied environmental stresses. However, enzymes that are responsible for this event have not been fully identified in high eukaryotes. Here, we report a mammalian tRNA/rRNA-targeting endoribonuclease: SLFN13, a member of the Schlafen family. Structural study reveals a unique pseudo-dimeric U-pillow-shaped architecture of the SLFN13 N′-domain that may clamp base-paired RNAs. SLFN13 is able to digest tRNAs and rRNAs in vitro, and the endonucleolytic cleavage dissevers 11 nucleotides from the 3′-terminus of tRNA at the acceptor stem. The cytoplasmically localised SLFN13 inhibits protein synthesis in 293T cells. Moreover, SLFN13 restricts HIV replication in a nucleolytic activity-dependent manner. According to these observations, we term SLFN13 RNase S13. Our study provides insights into the modulation of translational machinery in high eukaryotes, and sheds light on the functional mechanisms of the Schlafen family.

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REVIEW

Th1 cytokines, true functional signatures for protective immunity against TB?

Gucheng Zeng[1], Guoliang Zhang[2] and Xinchun Chen[3]

The lack of an effective preventative vaccine against tuberculosis (TB) presents a great challenge to TB control. Since it takes an extremely long time to accurately determine the protective efficacy of TB vaccines, there is a great need to identify the surrogate signatures of protection to facilitate vaccine development. Unfortunately, antigen-specific Th1 cytokines that are currently used to evaluate the protective efficacy of the TB vaccine, do not align with the protection and failure of TB vaccine candidates in clinical trials. In this review, we discuss the limitation of current Th1 cytokines as surrogates of protection and address the potential elements that should be considered to finalize the true functional signatures of protective immunity against TB.
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Keywords: protective immunity; tuberculosis; vaccine

INTRODUCTION

In the past 50 years, accumulating evidence has demonstrated that T cells play critical roles in host defense against *Mycobacterium tuberculosis* (Mtb) infection. An insufficient T-cell response renders the host unable to clear Mtb and therefore results in the establishment of persistent Mtb infection. In both systematic and aerosol-challenged murine TB models, T cells were shown to be required for host protective immunity against TB.[1–3] While CD8+T cells play a critical role in mediating immune protection against TB, the protective role of T cells was initially shown to be mainly mediated by CD4 T cells (Figure 1).[4,5] Interestingly, CD4+ cells can act as innate-like cells to contain the very early extrapulmonary dissemination of Mtb and slow down the rapid progression of TB. Protective roles against TB can possibly be attributed to CD4+ cells' master helper function to sustain the systemic and pulmonary anti-TB responses of CD8+ T cells and CD3-non-T lymphocytes.[6] In agreement with these findings, clinical observations suggested that HIV-1-induced loss of CD4 T cells renders TB susceptibility and increases reactivation of latent Mtb infection, further highlighting the importance of T cells in defense against TB.[7,8]

After encountering the Mtb antigen presented by antigen-presenting cells (APCs), naive CD4 T cells differentiate into effector and/or memory cells. Depending on the specificity and affinity of TCR, availability of cognate Mtb antigens, co-stimulation signaling, and so on, naive CD4 T cells can be differentiated into various subsets, including at least Th1, Th2, Th17, Treg and T_{FH} cells. Among these subsets, IFN-γ-producing Th1 cells are accepted as the major population that mediates protective immunity against TB. Indeed, mice deficient in Th1 cytokines (for example, IFN-γ, IL-12p40) succumbed early to Mtb infection with high bacillus loads.[9–11] Furthermore, mice with defects in IFN-γ-dependent enzymes show a similar susceptible phenotype.[12–15] Rapid clonal expansion, pulmonary trafficking and the accumulation of many PPD Ag-specific IFN-γ+CD4+ and few CD8+ T effector cells in BCG-vaccinated macaques upon pulmonary Mtb challenge further highlighted the critical importance of Th1 cytokines in mediating protective immunity against TB infection.[16] In humans, individuals carrying genotypes (that is, IFNGR1, IL-12B, IL12RB1) with impaired Th1 immune response are associated with increased susceptibility to mycobacterial diseases.[17–19]

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Th17 cells over 5.9% at admission indicate poor prognosis in patients with HBV-related acute-on-chronic liver failure

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Abstract

Our previous study demonstrated that Th17 cells increased significantly in patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF). However, their prognostic role in HBV-ACLF patients remains unknown.

Sixty-eight consecutive HBV-ACLF patients were enrolled in this cohort study. Th17 cells were examined using flow cytometry. Disease severity scores were assessed. ROC curves were used to evaluate the value in predicting prognosis. Survival was analyzed using Kaplan–Meier curves. Predictors of mortality were determined by regression analysis.

Th17 cells were significantly higher in HBV-ACLF patients compared to patients with chronic hepatitis B and normal controls (both $P < .001$). Also, Th17 cells were higher in nonsurviving HBV-ACLF patients than in surviving patients ($P = .014$). Th17 cells were positively correlated with CLIF-Consortium ACLF (CLIF-C ACLF) score ($r = 0.240$, $P = .048$). ROC curves showed that the frequency of Th17 cells had accuracy in predicting 90-day prognosis equivalent to MELD, MELD-Na and CLIF-C ACLF scores in HBV-ACLF ($P = .34$, $P = .26$, and $P = .15$, respectively). More importantly, the area under the ROC curve (AUROC) increased when Th17 cells were combined with MELD, MELD-Na or CLIF-C ACLF score than using Th17 cells alone ($P = .021$, $P = .006$, and $P = .023$, respectively). Kaplan–Meier analysis revealed that higher Th17 cells (≥5.9%) were closely associated with poor overall survival in HBV-ACLF ($P = .0086$). Additionally, multivariate regression analysis showed that the frequency of Th17 cells over 5.9% was an independent predictor of mortality (OR = 0.154, $P = .025$).

Circulating Th17 cells positively correlated with disease severity in HBV-ACLF. The frequency of Th17 cells over 5.9% could serve as a prognostic biomarker for HBV-ACLF patients.

Abbreviations: 95% CI = 95% confidence interval, ACLF = acute-on-chronic liver failure, AUROC = area under the ROC curve, CHB = chronic hepatitis B, CLIF-C = Chronic Liver Failure Consortium, HBV = hepatitis B virus, MELD = model for end-stage liver disease, NC = normal control, PTA = prothrombin time activity, ROC curve = receiver operating characteristic curve, Tbil = total bilirubin.

Keywords: acute-on-chronic liver failure, biomarker, hepatitis B virus, prognosis, Th17 cells

1. Introduction

Acute-on-chronic liver failure (ACLF) is characterized by acute deterioration of pre-existing chronic liver diseases and is associated with substantial short-term mortality due to the development of multiple organ failure.[1] In China, HBV-related ACLF accounts for the majority of ACLF cases due to the high prevalence of HBV infection.[2] An unclear understanding of the pathogenesis of HBV-ACLF and a lack of effective therapy result in extremely high mortality.[3] There is growing evidence that immune-mediated response plays a core role in the mechanism of HBV-ACLF.[1,2]

Th17 cell is a relatively new discovered subset of $CD4^+$ T-helper cell characterized by the production of interleukin-17 (IL-17) and has received increasing attention. Several lines of evidence have shown that Th17 cells are involved in the pathogenesis of different types of liver diseases, including viral hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis and hepatocellular carcinoma (HCC).[4] It has been reported that circulating Th17 cells in chronic hepatitis B (CHB) patients positively correlate with disease severity and extent of hepatic injury. Therefore, it has been supposed that Th17 cells contribute to CHB progression.[5,6] Furthermore, our previous study and others' reports have demonstrated that Th17 cells increased significantly in HBV-ACLF patients compared to CHB patients and participated in the progression of HBV-ACLF.[7–9] Recently, Th17 cells were found to be associated with poor prognosis in HCC patients and colorectal cancer patients,[10,11] indicating that Th17 cells may act as a biomarker in predicting patients'

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Review

The roles of galectins in parasitic infections

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ABSTRACT

Galectins is a family of multifunctional lectins. Fifteen galectins have been identified from a variety of cells and tissues of vertebrates and invertebrates. Galectins have been shown to play pivotal roles in host–pathogen interaction such as adhesion of pathogens to host cells and activation of host innate and adaptive immunity. In recent years, the roles of galectins during parasite infections have gained increasing attention. Galectins produced by different hosts can act as pattern recognition receptors detecting conserved pathogen-associated molecular patterns of parasites, while galectins produced by parasites can modulate host responses. This review summarizes some recent studies on the roles of galectins produced by parasitic protozoa, nematodes, and trematodes and their hosts. Understanding the roles of galectins in host–parasite interactions may provide targets for immune intervention and therapies of parasitic infections.

1. Galectins, their expressions and functions

Galectins, a family of lectins that binds *N*-acetyllactosamine-containing glycans, have diverse roles in many cellular processes and are receiving increasing interest as therapeutic targets because of their roles in immune signaling pathways (Farhadi and Hudalla, 2016; Rabinovich and Toscano, 2009). Galectins are widely distributed in organisms from lower invertebrates to mammals. In mammals, galectin family consists of 15 proteins, galectin (Gal)-1 to -15, which can be divided into three groups (prototype, chimera type, and tandem-repeat type) based on their structures (Balan et al., 2010). The prototype group includes Gal-1, -2, -5, -7, -10, -11, -13, and -14, whereas the chimera type only contains Gal-3 that can form homodimers. Both the prototype and the chimera type galectins have a single carbohydrate recognition domain (CRD). The chimera type Gal-3 has an extended N-terminal peptide. The tandem-repeat type includes Gal-4, -6, -8, -9, and -12 and has two non-identical CRDs linked by a short peptide (Unajak et al., 2015). Gal-15, also known as OVGAL11, is a member of the galectin family of secreted beta-galactoside lectins containing a conserved carbohydrate recognition domain and a putative integrin binding domain. It was originally found to be induced in gastrointestinal tissue and secreted into the intestinal lumen in response to infection of a nematode parasite *Haemonchus contortus* in sheep (Dunphy et al., 2000; Gray et al., 2004).

Most galectins are both intracellularly and extracellularly distributed throughout the body of an organism. Extracellular galectins interact with glycans on the cell surface and induce various cellular responses (Elola et al., 2007). Galectins are expressed in many types of immune cells, including monocytes, macrophages (Mφ), dendritic cells (DCs), mast cells, B cells, and T cells (Dhirapong et al., 2009). The ubiquitous expression of galectins in a large number of cell types and tissues dictates their diverse functions in the developmental processes and defense pathways against invading pathogens. Here we briefly summarize the known properties and major functions of galectins and discuss some examples of host and parasite galectins in regulating host-parasite interactions, including host responses to infections of various parasites.

Gal-1, encoded by lectin galactoside binding soluble (LGALS) 1 gene, is a homodimer of 14 kD subunits that belongs to a family of soluble galactoside-binding proteins (Astorgues-Xerri et al., 2014). It binds β-galactosides and is a potent anti-inflammatory and immunoregulatory molecule that plays a role in pathogenesis of various immune/inflammatory diseases (Yang et al., 2008; Zúñiga et al., 2001a). Gal-3 is an important modulator of biological processes and an emerging player in the pathogenesis of various immune/inflammatory diseases (Dumic et al., 2006). Gal-2 and -4 are mainly expressed in the gastrointestinal tract (Sturm et al., 2004; Kim et al., 2013) and are

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Toxoplasma Chinese 1 Strain of WH3Δ*rop16*$_{I/III}$/*gra15*$_{II}$ Genetic Background Contributes to Abnormal Pregnant Outcomes in Murine Model

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Toxoplasma gondii infection evokes a strong Th1-type response with interleukin (IL)-12 and interferon (IFN)-γ secretion. Recent studies suggest that the infection of pregnant mice with *T. gondii* may lead to adverse pregnancy results caused by subversion of physiological immune tolerance at maternofetal interface rather than direct invasion of the parasite. Genotype-associated dense granule protein GRA15$_{II}$ tends to induce classically activated macrophage (M1) differentiation and subsequently activating NK, Th1, and Th17 cells whereas rhoptry protein ROP16$_{I/III}$ drives macrophages to alternatively activated macrophage (M2) polarization and elicits Th2 immune response. Unlike the archetypal strains of types I, II, and III, type Chinese 1 strains possess both GRA15$_{II}$ and ROP16$_{I/III}$, suggesting a distinct pathogenesis of *Toxoplasma*-involved adverse pregnancies. We constructed *T. gondii* type Chinese 1 strain of WH3Δ*rop16* based on CRISPR/Cas9 technology to explore the ROP16$_{I/III}$-deficient/GRA15$_{II}$-dominant parasites in induction of trophoblast apoptosis *in vitro* and abnormal pregnant outcomes of mice *in vivo*. Our study showed that *Toxoplasma* WH3Δ*rop16* remarkably induced apoptosis of trophoblasts. C57BL/6 pregnant mice injected with the tachyzoites of WH3Δ*rop16* presented increased absorptivity of fetuses in comparison with the mice infected with WH3 wild type (WH3 WT) parasites although no remarkable difference of virulence to mice was seen between the two strains. Additionally, the mice inoculated with WH3Δ*rop16* tachyzoites exhibited a notable expression of both IL-17A and IFN-γ, while the percentage of $CD4^+CD25^+FoxP3$ [T regulatory cells (Tregs)] were diminished in splenocytes and placenta tissues compared to those infected with WH3 WT parasites. Accordingly, expressions of IL-4, IL-10, and transforming growth factor beta 1, the pivotal cytokines of Th2 and Tregs response, were significantly dampened whereas IFN-γ and IL-12 expressions were upregulated in WH3Δ*rop16*-infected mice, which gave rise to more prominent outcomes of abnormal pregnancies. Our results indicated that the WH3Δ*rop16* parasites with *gra15*$_{II}$ background of *T. gondii* type Chinese 1 strains may cause miscarriage and stillbirth due to subversion of the maternal immune tolerance and system immunity of the animals and the GRA15$_{II}$ effector contributes to the process of adverse pregnant consequences.

Keywords: ***Toxoplasma gondii*, dense granule protein GRA15, rhoptry protein ROP16, CRISPR/Cas9, adverse pregnant outcome**

nature medicine

Transitory presence of myeloid-derived suppressor cells in neonates is critical for control of inflammation

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Myeloid-derived suppressor cells (MDSCs) are pathologically activated and relatively immature myeloid cells that have been implicated in the immunological regulation of many pathologic conditions[1,2]. Phenotypically and morphologically, MDSCs are similar to neutrophils (PMN-MDSCs) and monocytes (M-MDSCs). However, they have potent suppressive activity and distinct gene expression profiles and biochemical characteristics[3]. No or very few MDSCs are observed in steady-state physiological conditions. Therefore, until recently, accumulation of MDSCs was considered a consequence of pathological processes or pregnancy. Here, we report that MDSCs with a potent ability to suppress T cells are present during the first weeks of life in mice and humans. MDSC suppressive activity was triggered by lactoferrin and mediated by nitric oxide, PGE2, and S100A9 and S100A8 proteins. MDSCs from newborns had a transcriptome similar to that of tumor MDSCs, but with strong upregulation of an antimicrobial gene network, and had potent antibacterial activity. MDSCs played a critical role in control of experimental necrotizing enterocolitis (NEC) in newborn mice. MDSCs in infants with very low weight, who are prone to NEC, had lower MDSC levels and suppressive activity than did infants with normal weight. Thus, the transitory presence of MDSCs may be critical for regulation of inflammation in newborns.

Although MDSCs are largely absent in healthy adults, recent evidence has indicated that MDSCs may play a role in the maintenance of maternal–fetal tolerance[4]. The roles of MDSCs in pregnancy appear to be consistent with a myeloid-cell response to partial genetic incomparability between mother and child. In this study, we tested the possible roles of MDSCs in steady-state conditions during the first weeks of life.

Populations of myeloid cells were evaluated in the spleens and bone marrow (BM) of adult mice (AM; 6–8 weeks of age), newborn mice (NBM), and adult mice within 7 d after giving birth (postpartum mice, PM). In comparison to AM and PM, 7- to 10-d-old NBM had substantially more splenic $CD11b^+Ly6C^{hi}Ly6G^-$ monocytes and $CD11b^+Ly6C^{lo}Ly6G^+$ neutrophils (**Supplementary Fig. 1a**). Cells from NBM and AM had similar morphology (**Supplementary Fig. 1b**). The proportion of these populations was highest on day 1 after birth and gradually decreased to levels comparable to those in AM by the end of week 2 (**Fig. 1a**). The population of spleen macrophages was not different, whereas dendritic cells were lower in NBM than AM (**Supplementary Fig. 1c**). In contrast to those in AM, monocytes from 7- to 10-d-old NBM potently inhibited proliferation of $CD4^+$ and $CD8^+$T cells (**Fig. 1b**), and neutrophils demonstrated potent suppression of antigen-specific proliferation of $CD8^+$ T cells (**Fig. 1c**). Thus, these cells fit the criteria of M-MDSCs and PMN-MDSCs, respectively[3]. In NBM, MDSC suppressive activity was not observed during the first 3 d and disappeared after day 14 (**Fig. 1d**,**e**). Spleen macrophages did not have suppressive activity (**Supplementary Fig. 1d**). In lactating PM, the number of monocytes and neutrophils did not differ from that in AM, and no suppressive activity was detected (**Supplementary Fig. 1e–h**). Thus, MDSCs were found exclusively in NBM.

To assess the ability of NBM MDSCs to control autoimmune inflammation, AM were sensitized and challenged with intranasal administration of ovalbumin (OVA) (**Supplementary Fig. 2a**). Administration of NBM MDSCs, but not AM neutrophils, decreased lung inflammation (**Supplementary Fig. 2b**,**c**), the presence of leukocytes, and the amounts of IL-13 and IL-4 in bronchoalveolar lavage (**Supplementary Fig. 2d–g**), and IgE in sera (**Supplementary Fig. 2h**).

$CD11b^+Ly6C^{lo}Ly6G^+$ and $CD11b^+Ly6C^{hi}Ly6G^-$ cells from the spleens of AM and 7-d-old NBM were sorted, and whole transcriptome analysis was performed through RNA-seq (**Supplementary Fig. 3a**). Ingenuity Pathway Analysis (IPA) revealed upregulation of 55 key transcriptional regulators in NBM including lactoferrin (*Ltf*), *S100a8*, and *S100a9*. Prostaglandin E synthase (*Ptges*) was upregulated in PMN-MDSCs. Ptges controls synthesis of the prostaglandin PGE2,

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Triggering Receptors Expressed on Myeloid Cells 2 Promotes Corneal Resistance Against *Pseudomonas aeruginosa* by Inhibiting Caspase-1-Dependent Pyroptosis

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Triggering receptors expressed on myeloid cells 2 (TREM2) is a novel cell surface receptor and functions as an immunomodulatory receptor in infectious diseases. In this study, we investigated the function and regulatory mechanism of TREM2 in *Pseudomonas aeruginosa* (*P. aeruginosa*) keratitis. We found that *P. aeruginosa* keratitis was more severe in *Trem2*$^{-/-}$ versus wild type C57BL/6 mice as indicated by the increased clinical scores, bacterial load, and cornea pathology. The exacerbated disease progression caused by TREM2 deficiency was associated with boosted activation of caspase-1 and subsequent pyroptosis as well as increased expression of IL-1β. In addition, blockage of pyroptosis by caspase-1 inhibitor not only recovered the severe cornea pathology developed in *Trem2*$^{-/-}$ mice but also restored the *P. aeruginosa* clearance suppressed by TREM2 deficiency. Our study demonstrated that TREM2 promotes host resistance against *P. aeruginosa* keratitis by inhibiting caspase-1-dependent pyroptosis, which provides new insights of TREM2-mediated anti-bacterial immunity.

Keywords: *Pseudomonas aeruginosa*, triggering receptors expressed on myeloid cells 2, corneal infection, pyroptosis, inflammation, bacterial killing

INTRODUCTION

Pseudomonas aeruginosa (*P. aeruginosa*) is one of the most common Gram-negative bacteria that cause diverse opportunistic infectious diseases, including keratitis in extended wear contact lens users (1). Clinically, *P. aeruginosa* keratitis progresses rapidly and results in severe corneal damage, including perforation and vision loss (1, 2). Both bacteria virulence factors and host inflammatory mediators contribute to the destruction of the cornea after infection (3).

Upon *P. aeruginosa* infection, diverse pathogen-associated molecular patterns were specifically recognized by corresponding pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) (4, 5) and Nod-like receptors (NLRs) (6). In *P. aeruginosa*-induced keratitis (corneal infection), the TLR-induced inflammatory response promotes bacteria clearance and repairs injured tissues. However, if out of control, the excessive inflammation also leads to tissue damage and corneal ulceration. Except for TLRs, *P. aeruginosa* infection was able to activate certain numbers of the NLR family, such as the NLRC4 (7) and NLRP3 (8), which function as core receptor molecules

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Wolbachia spread dynamics in multi-regimes of environmental conditions

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ABSTRACT

Mosquito-borne diseases such as dengue fever and Zika kill more than 700,000 people each year in the world. A novel strategy to control these diseases employs the bacterium *Wolbachia* whose infection in mosquitoes blocks virus replication. The prerequisite for this measure is to release *Wolbachia* - infected mosquitoes to replace wild population. Due to the fluctuation of environmental conditions for mosquito growth, we develop and analyze a model of differential equations with parameters randomly changing over multiple environmental regimes. By comparing the dynamics between the stochastic system and constructed auxiliary systems, combined with other techniques, we provide sharp estimates on the threshold releasing level for *Wolbachia* fixation. We define the alarm period of disease transmission to measure the risk of mosquito-borne diseases. Our numerical simulations suggest that more frequent inter-regime transitions help reduce the alarm period, and the disease transmission is more sensitive to the average climatic conditions than the number of sub-regimes over a given time period. Further numerical examples also indicate that the reduction in the waiting time to suppress 95% of wild population is more evident when the releasing amount is increased up to a double of the wild population.

1. Introduction

Mosquito-borne diseases, such as Zika and dengue fever, cause a serious threat to the health of human beings (Calisher, 2005; Kyle and Harris, 2008; Rasmussen et al., 2016; Troncoso, 2016). The most effectual prevention and control measure for such diseases is to control *Aedes* mosquito vectors. A novel strategy uses maternally inherited bacteria *Wolbachia*, whose infection in *Aedes* mosquitoes may greatly block the replication of the viruses (Bian et al., 2010; Dutra et al., 2016; Iturbe-Ormaetxe et al., 2011). The invasion of *Wolbachia* in wild mosquito populations is facilitated by a mechanism called cytoplasmic incompatibility (CI), which causes embryonic death when infected males mate with uninfected females (Fine, 1978; Laven, 1956). However, most *Wolbachia* infection brings fitness cost to their host such as reduced fecundity or longevity (McMeniman et al., 2009; Walker et al., 2011; Weeks et al., 2002). It remains a challenging question on how the disadvantage to the growth of infected females and the advantage to their reproduction, in conjunction with the variation in environmental conditions, regulate the spread dynamics of *Wolbachia* in mosquito populations.

Several mathematical models of differential equations have been developed to discuss the invasion of *Wolbachia* in mosquito populations; see, for example (Farkas and Hinow, 2010; Hancock et al., 2011; Huang et al., 2015; Keeling et al., 2003; Zhang et al., 2015b; Zheng et al., 2014; Zheng and Yu, 2018). Let $x_F(t)$ and $x_M(t)$ denote the numbers of infected females and males, and $y_F(t)$ and $y_M(t)$ denote the numbers of uninfected females and males at time t, respectively. Let a_0 and b_0 be the constant birth rates of infected and uninfected mosquitoes, respectively, and c and d be the density-dependent decay rates of infected adults and uninfected adults. Under the basic assumptions of perfect maternal transmission, equal sex determination and complete CI observed experimentally in McMeniman et al. (2009), Walker et al. (2011) and

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Zika virus elicits inflammation to evade antiviral response by cleaving cGAS via NS1-caspase-1 axis

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Abstract

Viral infection triggers host innate immune responses, which primarily include the activation of type I interferon (IFN) signaling and inflammasomes. Here, we report that Zika virus (ZIKV) infection triggers NLRP3 inflammasome activation, which is further enhanced by viral non-structural protein NS1 to benefit its replication. NS1 recruits the host deubiquitinase USP8 to cleave K11-linked polyubiquitin chains from caspase-1 at Lys134, thus inhibiting the proteasomal degradation of caspase-1. The enhanced stabilization of caspase-1 by NS1 promotes the cleavage of cGAS, which recognizes mitochondrial DNA release and initiates type I IFN signaling during ZIKV infection. NLRP3 deficiency increases type I IFN production and strengthens host resistance to ZIKV *in vitro* and *in vivo*. Taken together, our work unravels a novel antagonistic mechanism employed by ZIKV to suppress host immune response by manipulating the interplay between inflammasome and type I IFN signaling, which might guide the rational design of therapeutics in the future.

Keywords antiviral immunity; inflammasome; type I interferon signaling; Zika virus

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Introduction

Zika virus (ZIKV) is an arthropod-borne flavivirus in the *Flaviviridae* family, which was initially discovered from Rhesus macaque in Uganda in 1947 (Dick *et al*, 1952). ZIKV contains a positive-sense single-stranded RNA genome and is closely related to several other important viruses that cause disease globally, including Dengue (DENV), hepatitis C, yellow fever, West Nile, and Japanese encephalitis viruses (Pierson & Diamond, 2013). ZIKV genome encodes a single polyprotein which can be processed to produce three structural (C, prM, and E) and seven non-structural (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) proteins (Pierson & Diamond, 2013). ZIKV infection was originally thought as a mild and self-limiting viral illness and caught little attention (Rossi *et al*, 2016; Miner & Diamond, 2017). However, it became a global health emergency since accumulating evidence has suggested that ZIKV infection is associated with the increasing incidence of microcephaly in newborns and Guillain–Barré syndrome during the outbreak of ZIKV in Brazil from 2015 (Ioos *et al*, 2014; Petersen *et al*, 2016; Rubin *et al*, 2016).

Type I interferon (IFN) response serves as the first line of defense to combat viral infection (Schneider *et al*, 2014). Recently, we and other groups have demonstrated that ZIKV evolved several strategies to counter human IFN antiviral response (Fernandez-Garcia *et al*, 2009; Grant *et al*, 2016; Kumar *et al*, 2016; Wu *et al*, 2017; Xia *et al*, 2018). The IFN-antagonistic strategies can be mainly divided into two types (Fernandez-Garcia *et al*, 2009): The first strategy employed by ZIKV is to reduce and delay the activation of IFN production. For example, we recently reported that NS1 and NS4B of ZIKV blocked virus-mediated IFN signaling by targeting TBK1 (Wu *et al*, 2017). Xia *et al* showed the similar result of NS1 and found that residue 188 is critical for the inhibition of IFN (Xia *et al*, 2018). ZIKV could also utilize the other strategy to evade innate immunity by antagonizing IFN-mediated downstream signaling transduction. It has been reported that NS5 of ZIKV promoted the degradation of STAT2 (Grant *et al*, 2016; Kumar *et al*, 2016), while our study also revealed that NS2B3 can degrade JAK1 (Wu *et al*, 2017), thus inhibiting JAK-STAT signaling and coincidentally impairing downstream ISG expressions. Taken together, different non-structural proteins of ZIKV attenuate innate antiviral response at different levels of IFN signaling pathway and cooperatively assist ZIKV to evade host immune response (Bowen *et al*, 2018).

To infect the fetus and affect the neural development of fetus, ZIKV should first cross the placental barrier and reach the fetus (Li *et al*, 2016; Miner *et al*, 2016). However, there is no commonly accepted mechanism employed by ZIKV to achieve mother-to-fetus transmission so far. One of the possible mechanisms utilized by ZIKV is to use monocytes as the carrier (Parekh *et al*, 2010; Khaiboullina *et al*, 2017). Monocytes are able to detect several kinds of pathogens and

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Zika Virus Liquid Biopsy: A Dendritic $Ru(bpy)_3^{2+}$-Polymer-Amplified ECL Diagnosis Strategy Using a Drop of Blood

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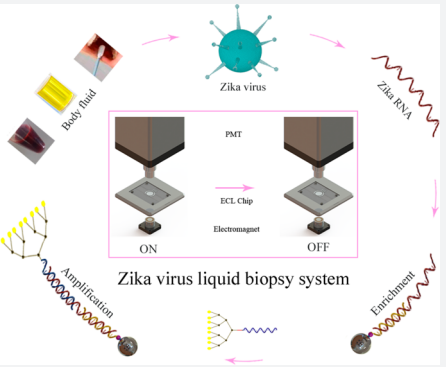
Supporting Information

ABSTRACT: Zika virus (ZIKV) is a mosquito-borne flavivirus that leads to devastating consequences for fetal development. However, accurate diagnosis of ZIKV is made difficult by the fact that most infected patients are asymptomatic or present with symptoms similar to those of other febrile illnesses. Thus, the development of a simple, accurate, highly sensitive, and reliable method for the biomedical analysis and diagnosis of ZIKV is needed. Herein, a novel ZIKV liquid biopsy system was constructed via a dendritic $Ru(bpy)_3^{2+}$-polymer-amplified electro-chemiluminescence (ECL) strategy. This system accomplished amplification-free analysis of ZIKV using a drop of blood, and simultaneously achieved a high sensitivity of 500 copies and superior specificity. This strategy adopted the humoral biomarker as the diagnostic index, which greatly simplified the analysis process, and established a nondestructive detection mode. Furthermore, the performance index for biomedical analysis of clinical ZIKV samples was investigated, and the results indicated that the dendritic $Ru(bpy)_3^{2+}$-polymer-amplified ECL strategy reliably responded to ZIKV from the body fluid (blood, saliva, and urine). Hence, this system suitably met the strict clinical requirements for ZIKV detection and thus has the potential to serve as a new paradigm for the biomedical analysis and diagnosis of ZIKV.



INTRODUCTION

The Zika virus (ZIKV) is an *Aedes* mosquito-borne flavivirus that could produce devastating consequences for the process of fetal development.[1−3] Furthermore, ZIKV has been declared a public health emergency of international concern by the World Health Organization (WHO) because of the large-scale outbreak of the virus in the Americas.[4,5] ZIKV mainly spreads via infected mosquito bite, but can also be transmitted by mother-to-fetus transmission, sexual contact, or blood transfusion.[6−10] Additionally, it has been indicated that the infection of ZIKV was the main cause of Guillain-Barré syndrome,[11,12] congenital microcephaly,[13,14] and neurological defects in newborns.[15,16] Thus, the development of a simple, accurate, highly sensitive, and reliable method for the biomedical analysis and diagnosis of ZIKV would be of great significance for the prevention and control of ZIKV. However, biomedical analysis and accurate diagnosis of ZIKV are made difficult by the fact that most infected patients are asymptomatic or present symptoms similar to those of other febrile illnesses.[17]

The existing immunoassays for ZIKV detection, such as the enzyme-linked immunosorbent assay (ELISA),[18,19] provide an inexpensive and instrumentless approach, but their poor sensitivity and specificity limited the application of these immunoassays applied to the clinical detection and diagnosis of ZIKV.[20,21] In particular, the antibody used in the immunoassay for ZIKV detection would also respond to homologous flaviviruses, such as Dengue virus.[22,23] Thus, the specificity of immunoassays cannot meet the requirements for the accurate detection and early diagnosis of ZIKV.[24] Conversely, the enzymatic amplification-based detection

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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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