热带病学术热点追踪报告

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目　录

一、国际热带病热点研究

1. 疟疾相关

（1）*Testosterone persistently dysregulates hepatic expression of Tlr6 and Tlr8 induced by Plasmodium chabaudi malaria.*

We investigate effects of T and P. chabaudi on mRNA expression and promoter DNA methylation of Tlr1-9 genes in the liver of female C57BL/6 mice. These are treated with T or vehicle for 3 weeks, and then treatment is discontinued for 12 weeks, before challenging with P. chabaudi for 8 days. Our data reveal that T induces a 9.1-fold downregulation of Tlr6 mRNA and 6.3-fold upregulation of Tlr8 mRNA. Blood-stage infections induce significant increases in mRNA expression of Tlr1, 2, 4, 6, 7, and 8 varying between 2.5-fold and 21-fold in control mice. Our data support the view that hepatic expression of Tlr6, but not that of Tlr8 is epigenetically controlled, and that the dysregulations of Tlr6 and Tlr8 critically contribute to T-induced persistent susceptibility to P. chabaudi malaria, possibly by dys-balancing responses of TLR6-mediated pathogen recognition and TLR8-mediated generation of anti-malaria "protective" autoimmunity. [1]

（2）*Strategic use of antimalarial drugs that block falciparum malaria parasite transmission to mosquitoes to achieve local malaria elimination.*

The ultimate aim of malaria chemotherapy is not only to treat symptomatic infection but also to reduce transmission potential. With the absence of clinically proven vaccines, drug-mediated blocking of malaria transmission gains growing interest in the research agenda for malaria control and elimination. In addition to the limited arsenal of antimalarials available, the situation is further complicated by the fact that most commonly used antimalarials are being extensively resisted by the parasite and do not assist in blocking its transmission to vectors. Artemisinin derivatives and 8-aminoquinolines are useful transmission-blocking antimalarials whose optimal actions are on different stages of gametocytes. Strategic use of potent gametocytocides at appropriate timing with artemisinin-based combination therapies should be given attention, at least, in the short run. This review highlights the role that antimalarials could play in blocking gametocyte transmission and infectivity to mosquitoes and,

hence, in reducing the potential of falciparum malaria transmissibility and drug resistance spread. [2]

（3）*Insecticide resistance and role in malaria transmission of Anopheles funestus populations from Zambia and Zimbabwe.*

Mosquitoes were collected inside houses from Nchelenge District, Zambia and Honde Valley, Zimbabwe in 2013 and 2014. WHO susceptibility tests, synergist assays and resistance intensity tests were conducted on wild females and progeny of wild females. ELISA was used to detect Plasmodium falciparum circumsporozoite protein. Specimens were identified to species and mtDNA clades using standard molecular methods. Conclusions: This is the first record of An. funestus mtDNA clade II occurring in Zambia. No evidence was found to suggest that the clades are markers of biologically separate populations. The ability of An. funestus to withstand prolonged exposure to pyrethroids has serious implications for the use of these insecticides, either through LLINs or IRS, in southern Africa in general and resistance management strategies should be urgently implemented. [3]

（4）*Prevalence and intensity of soil-transmitted helminthiasis, prevalence of malaria and nutritional status of school going children in Honduras.*

A cross-sectional study was conducted following PAHO/WHO guidelines to select a sample of school going children of 3rd to 5th grades, representative of ecological regions in the country. A survey questionnaire was filled; anthropometric measurements, stool sample for STH and blood sample for malaria were taken. Kato-Katz method was used for STH prevalence and intensity and rapid diagnostic tests, microscopy, and PCR were used for malaria parasite detection. Conclusions: Biannual deworming campaigns would be necessary in ecological regions II and VI, where STH prevalence is >50%. High prevalence of obesity in school going children is a worrying trend and portends of future increase in obesity related diseases. Malaria prevalence, both symptomatic and asymptomatic, was low and provides evidence for Honduras to embark on elimination of the disease. [4]

（5）*Poverty and malaria in the Yunnan province, China.*

Poverty and malaria appear to have an intertwined link. This paper aims to define the relationship between poverty and malaria in Yunnan, China, and to make recommendations for future research in this important area. Data on malaria prevalence and the population's income in each county between 2005 and 2010 were obtained from the Yunnan Center for Disease Control and Prevention and the Yunnan Bureau of Statistics, respectively. Geographic mapping shows an apparent spatial convergence of poverty and the incidence of malaria at a county level, and suggests that poverty may be one of the drivers of malaria transmission in Yunnan. Future research should focus on: 1. measuring and quantifying the relationship between poverty and the malaria burden at the individual, community, county and regional level in Yunnan; and 2. developing the GIS-based spatial decision support system (SDSS) framework in malaria endemic areas, particularly along the border areas in Yunnan. [5]

2. 血吸虫相关

（1）*No apparent reduction in schistosome burden or genetic diversity following four years of school-based mass drug administration in Mwea, Central Kenya, a heavy transmission area*

We followed 67 children enrolled in a MDA program in Kenya. Infection status and egg counts were measured each year prior to treatment. For 15 of these children, we collected microsatellite genotype data from schistosomes passed in fecal samples as a representation of the force of transmission between drug treatments. We compared prevalence, egg counts, and genetic measures including allelic richness, gene diversity (expected heterozygosity), adult worm burdens and effective number of breeders among time points to search for evidence for a change in transmission or schistosome populations during the MDA program. Our data show that in an endemic area, such a program has had no obvious effect on reducing transmission or of significantly impacting the schistosome population as sampled by the children we studied in depth. Results like these, in combination with other sources of information, suggest more integrated approaches for interrupting transmission and significantly diminishing schistosome populations will be required to achieve sustainable control. [6]

（2）*Evaluation of real-time PCR assay to detect Schistosoma mansoni infections in a low endemic setting.*

The objective of this study was to evaluate the performance of a TaqMan quantitative polymerase chain reaction (qPCR) technique in serum and feces DNA samples using the techniques of Kato-Katz (KK), Hoffman, Pons and Janer (HH) as references, during an epidemiological survey using fecal samples and sera from randomized residents from an ALE. A cross-sectional study conducted from April to December 2011 using a probabilistic sampling that collected 572 fecal and serum samples. This study presents a control perspective, pointing to the possibility of using combined laboratory tools in the diagnosis of schistosomiasis in ALE. [7]

（3）*Impact of Schistosoma mansoni on Malaria Transmission in Sub-Saharan Africa.*

We developed a co-epidemic model of malaria and S. mansoni transmission dynamics which takes into account key epidemiological interaction between the two diseases in terms of elevated malaria incidence among individuals with S. mansoni high egg output. The model was parameterized for S. mansoni high-risk endemic communities, using epidemiological and clinical data of the interaction between S. mansoni and malaria among children in sub-Saharan Africa. We evaluated the potential impact of the S. mansoni-malaria interaction and mass treatment of schistosomiasis on malaria prevalence in co-endemic communities. Conclusions: Schistosomiasis treatment and control programmes in regions where S. mansoni and malaria are highly prevalent may have indirect benefits on reducing malaria transmission as a result of disease interactions. In particular, mass praziquantel administration may not only have the direct benefit of reducing schistosomiasis infection, it may also reduce malaria transmission and disease burden. [8]

（4）*Worm Proteins of Schistosoma mansoni Reduce the Severity of Experimental Chronic Colitis in Mice by Suppressing Colonic Proinflammatory Immune Responses.*

We investigated the therapeutic potential and the underlying immunological mechanisms of Schistosoma mansoni soluble worm proteins (SmSWP) in an adoptive T cell transfer mouse model of chronic colitis. The curative administration of SmSWP resulted in a significant improvement of the clinical disease score, colonoscopy, macroscopic and microscopic inflammation score, colon length and myeloperoxidase activity. The therapeutic potential of the preventive SmSWP treatment was less pronounced compared with the curative SmSWP treatment but still resulted in an improved clinical disease score, body weight loss, colon length and microscopic inflammation score. In conclusion, SmSWP treatment reduced the severity of colitis in the adoptive transfer mouse model via the suppression of proinflammatory cytokines and the induction of an anti-inflammatory response in the colon. [9]

3. 其他寄生虫相关

（1）*Chromobacterium Csp_P Reduces Malaria and Dengue Infection in Vector Mosquitoes and Has Entomopathogenic and In Vitro Anti-pathogen Activities.*

Here we present a bacterium of the genus Chromobacterium (Csp_P), which was isolated from the midgut of field-caught Aedes aegypti. Csp_P can effectively colonize the mosquito midgut when introduced through an artificial nectar meal, and it also inhibits the growth of other members of the midgut microbiota. Csp_P colonization of the midgut tissue activates mosquito immune responses, and Csp_P exposure dramatically reduces the survival of both the larval and adult stages. Ingestion of Csp_P by the mosquito significantly reduces its susceptibility to Plasmodium falciparum and dengue virus infection, thereby compromising the mosquito's vector competence. This bacterium also exerts in vitro anti-Plasmodium and anti-dengue activities, which appear to be mediated through Csp_P -produced stable bioactive factors with transmission-blocking and therapeutic potential. The anti-pathogen and entomopathogenic properties of Csp_P render it a potential candidate for the development of malaria and dengue control strategies. [10]

（2）*Genetic Characterization of Human-Derived Hydatid Cysts of Echinococcus granulosus Sensu Lato in Heilongjiang Province and the First Report of G7 Genotype of E. canadensis in Humans in China.*

To understand and to speculate on possible transmission patterns of E. granulosus s.l., we molecularly identified and genotyped 10 hydatid cysts from hepatic CE patients in Heilongjiang Province based on mitochondrial cytochrome c oxidase subunit I (cox1), cytochrome b (cytb) and NADH dehydrogenase subunit 1 (nad1) genes. Two genotypes were identified, G1 genotype (n=6) and G7 genotype (n=4). All the six G1 genotype isolates were identical to each other at the cox1 locus; three and two different sequences were obtained at the cytb and nad1 loci, respectively, with two cytb gene sequences not being described previously. G7 genotype isolates were identical to each other at the cox1, cytb and nad1 loci; however, the cytb gene sequence was not described previously. This is the first report of G7 genotype in humans in China. Three new cytb gene sequences from G1 and G7 genotypes might reflect endemic genetic characterizations. Pigs might be the main intermediate hosts of G7 genotype in our investigated area by homology analysis. The results will aid in making more effective control strategies for the prevention of transmission of E. granulosus s.l. [11]

（3）*Loss of Cln3 Function in the Social Amoeba Dictyostelium discoideum Causes Pleiotropic Effects That Are Rescued by Human CLN3.*

Here we establish new overexpression and knockout Dictyostelium cell lines for JNCL research. Dictyostelium Cln3 fused to GFP localized to the contractile vacuole system and to compartments of the endocytic pathway. cln3$^-$ cells displayed increased rates of proliferation and an associated reduction in the extracellular levels and cleavage of the autocrine proliferation repressor, AprA. Mid- and late development of cln3$^-$ cells was precocious and cln3- slugs displayed increased migration. Expression of either Dictyostelium Cln3 or human CLN3 in cln3$^-$ cells suppressed the precocious development and aberrant slug migration, which were also suppressed by calcium chelation. Taken together, our results show that Cln3 is a pleiotropic protein that negatively regulates proliferation and development in Dictyostelium. This new model system, which allows for the study of Cln3 function in both single cells and a

multicellular organism, together with the observation that expression of human CLN3 restores abnormalities in Dictyostelium cln3$^-$ cells, strongly supports the use of this new model for JNCL research. [12]

（4）*Chemotherapeutic Potential of 17-AAG against Cutaneous Leishmaniasis Caused by Leishmania (Viannia) braziliensis.*

Here we expand the current knowledge on the leishmanicidal activity of 17-AAG against cutaneous leishmaniasis, employing an experimental model of infection with L. (V.) braziliensis. Exposure of axenic L. (V.) braziliensis promastigotes to 17-AAG resulted in direct dose-dependent parasite killing. These results were extended to L. (V.) braziliensis-infected macrophages, an effect that was dissociated from the production of nitric oxide (NO), superoxide (O-2) or inflammatory mediators such as TNF-α, IL-6 and MCP-1. The leishmanicidal effect was then demonstrated in vivo, employing BALB/c mice infected with L. braziliensis. In this model, 17-AAG treatment resulted in smaller skin lesions and parasite counts were also significantly reduced. Lastly, 17-AAG showed a similar effect to amphotericin B regarding the ability to reduce parasite viability. 17-AAG effectively inhibited the growth of L. braziliensis, both in vitro and in vivo. Given the chronicity of L. (V.) braziliensis infection and its association with mucocutaneous leishmaniasis, 17-AAG can be envisaged as a new chemotherapeutic alternative for cutaneous Leishmaniasis. [13]

二、国内热带病热点研究

1. 疟疾相关

（1）疟疾疫苗研制进展

近年来疟疾疫苗的研制取得了很大进展，进展最快的 RTS，S 疫苗已完成Ⅲ期临床试验，相信成功研制临床应用的疟疾疫苗已为期不远，但要成功研制更为高效的疟疾疫苗用于控制乃至消除疟疾将是一项艰巨和富有挑战的工作。该文综述和讨论了疟疾疫苗研制在近几年中的进展。[14]

（2）输入性恶性疟原虫 Pf60.1 基因多态性初步研究

采用 PCR 方法扩增武汉市 2010-2013 年经镜检和巢式 PCR 确诊的 101 份国外输入性恶性疟病例血样的 Pf60.1 基因，研究 Pf60.1 基因多态性。PCR 结果显示，共 92 份血样扩增出 3 类基因片段，其中 52 份扩增出 313 bp 片段，占 56.5%；34 份扩增出 340 bp 片段，占 37.0%；6 份扩增出 313 bp 和 340 bp 混合型片段，占 6.5%。83 份自非洲地区输入病例血样中，46 份扩增出 313 bp 片段，占 55.4%，31 份扩增出 340 bp 片段，占 37.1%，6 份扩增出混合型片段，占 7.2%；9 份自东南亚地区输入病例血样中，6 份扩增出 313 bp 片段，3 份扩增出 340 bp 片段。提示输入性恶性疟 Pf60.1 基因以 313 bp 基因型较多，并且可能存在多克隆感染情况。[15]

（3）脑型疟疾的诊治进展

疟疾是目前全球发病率最高的热带感染性疾病，而脑型疟疾是引起疟疾患者死亡的主要原因之一，其临床表现主要以神经系统病变为主，可见不同程度的嗜睡、昏迷、谵妄、抽搐、烦躁等意识障碍。早期的诊断和及时干预对于患者预后有积极效果。该文就脑型疟疾的病理生理学机制、病理变化、临床表现及国内外报道的诊断和治疗方案与经验进行综述。[16]

（4）四川省疟疾流行态势与消除疟疾进展

分析四川省疟疾流行态势与消除疟疾工作进展情况。方法是对全省疟疾发病与流行态势进行描述性研究。结果为1950－2012 年四川省疟疾发病人数由最高时的58 多万下降到近年的100 余人，下降达99. 98%以上，已连续19 年年发病率控制在1 /万以下；自2011 年及以后全省本地疟疾病例报告均为0，全年均有发病，无明显季节分布；人群感染以男性为主;职业以农民及农民工和工人为多；年龄

集中在青壮年占95.15%；输入病例中，恶性疟占输入总病例的57.42%，主要输入地为非洲和东南亚。结论：四川省疟疾发病大幅度下降，疟防进程已由控制阶段走向消除阶段。在此基础上，应进一步加强疟疾监测和流动人员管理，加快消除疟疾工作。[17]

2. 血吸虫相关

（1）日本血吸虫重组 SjTsp2 /Sj29 ku 蛋白疫苗对小鼠免疫效果的研究

探讨日本血吸虫重组 Tsp2 /Sj29 ku 表膜蛋白疫苗对小鼠的抗病免疫效果。方法为 pet32a /SjTsp2 /Sj29 ku 重组菌经异丙基硫代-β-D-半乳糖苷(IPTG) 诱导表达，制备纯化的重组蛋白。结论为日本血吸虫 Tsp2 /Sj29 ku 重组表膜蛋白疫苗对小鼠抗感染有一定的保护性;该重组蛋白免疫引起的是 Th1 /Th2 混合型免疫反应。[18]

（2）血吸虫蛋白激酶研究进展

蛋白激酶在血吸虫生长发育、生殖发育及与宿主的相互作用等方面起着重要作用。蛋白激酶 C(SmPKCl)、p38 促分裂原激活蛋白激酶(p38 MAPK)分别抑制和促进血吸虫从毛蚴到母胞蚴的发育；Polo 样激酶(SmPlks)、Ste 样激酶(SmSLK)、细胞酪氨酸激酶(SmTK3，SmTK4，SmTK5 和 SmTK6)、金星激酶受体(SmVKRl 和 SmVKR2)、TGF-β受体(SmTGFβ-R Ⅰ和 SmTGFβ-R Ⅱ)和 cGMP 依赖性蛋白激酶(SmcGKl)等分子可能与血吸虫的生殖发育有重要关系；而表面蛋白激酶(ecto-PK)、分泌蛋白激酶(exo-PK)、cAMP 依赖蛋白激酶(PKA)和 SmcGKl 蛋白不仅与血吸虫的生长发育有关，还可能与血吸虫一宿主的相互作用有关。因此，血吸虫激酶可以作为阻断其生长与生殖发育的一个潜在的药物靶标。[19]

（3）大麻素受体 1 与 FAK 在血吸虫肝纤维化小鼠肝组织中的表达

探讨大麻素受体 1(CB1)与黏着斑激酶(FAK)在血吸虫肝纤维化小鼠肝组织中的表达。方法是将 32 只昆明小鼠分为正常组(n=10)和模型组(n=22)，两组动物均普通喂养，8 周后处死取肝组织。模型组小鼠采用腹壁贴附法建立血吸虫肝纤维化小鼠模型。根据纤维化程度将模型组分为Ⅰ级肝纤维化组(n=4)、Ⅱ级肝纤维化组(n=8)和Ⅲ级肝纤维化组(n=10)。HE 染色观察病理变化，Masson 染色观察肝纤维化程度，免疫组织化学法检测不同纤维化组 CB1 的表达，RT-PCR 法检测各组 CB1 mRNA 及 FAK mRNA 的表达。结论为 CB1 和 FAK 参与了血吸虫肝纤维化的发生与发展。[20]

（4）富硒螺旋藻对日本血吸虫肝硬化小鼠肝组织端粒酶活性的影响

探讨富硒螺旋藻抑制血吸虫肝硬化组织恶性变的作用及其机制。方法是 80 只小鼠感染日本血吸虫尾蚴后，随机均分为 A、B、C、D 4 组，每组 20 只。A 组（模型组）小鼠不作任何治疗。B 组小鼠（吡喹酮组）在感染尾蚴 6 周时予吡喹酮 500 mg/(kg·d)灌胃 2 d，C 组小鼠在感染尾蚴 6 周时予富硒螺旋藻 100 mg/（kg·d）（富硒螺旋藻组）灌胃 8 周，D 组小鼠在感染尾蚴 6 周时予吡喹酮 500 mg/（kg·d）治疗 2 d 后再以富硒螺旋藻 100 mg/（kg·d）（富硒螺旋藻+吡喹酮组）灌胃 8 周。另取 10 只小鼠作为正常组（E 组）。第 14 周末分别留取各组小鼠肝组织，观察肝组织病理改变，测定其肝脏 MDA 含量、SOD 活性以及端粒酶活性与端粒酶逆转录酶（TERT）表达变化。结论为晚期血吸虫肝硬化组织因端粒酶活性增高具有恶变可能，富硒螺旋藻可通过降低肝组织氧化应激水平、抑制肝组织 TERT 表达及端粒酶活性而发挥抑制恶性变的作用。[21]

3. 其他寄生虫相关

（1）猪带绦虫 TSO45W-4B-TSOL18 融合基因在长双歧杆菌中的表达

在成功构建猪带绦虫大肠杆菌－双歧杆菌穿梭表达质粒 pGEX-TSO45W-4B-TSOL18 的基础上，研究猪带绦虫 TSO45W-4B-TSOL18 融合

基因在长双歧杆菌中的表达情况。方法是将猪带绦虫大肠杆菌-双歧杆菌穿梭表达质粒 pGEX-TSO45W-4B-TSOL18 电转化入长双歧杆菌，IPTG 诱导表达，SDS－PAGE 和 Western Plot 分析表达情况。结论是猪带绦虫 TSO45W-4B-TSOL18 融合基因能够在长双歧杆菌中获得表达，表达的重组蛋白具有特异的抗原性。[22]

（2）黑热病对儿童造血系统的影响

探讨黑热病对儿童造血系统功能的影响。方法是选择 34 例黑热病患儿作为研究的观察组，同时选择此期间进行健康体验的 30 例健康儿童作为对照组，通过对两组血常规及生化检查结果进行对比，分析黑热病对儿童造血系统的影响。结论为黑热病会严重影响患儿的造血系统功能，减少患儿血液中的白细胞、红细胞及血小板等重要成分的数量，因此在黑热病的临床诊断中要结合骨髓检查及免疫血清检测以提高诊断的准确性。[23]

（3）酶联免疫法与间接血凝法检测实验动物家兔弓形虫抗体的结果比较

分析比较酶联免疫法（ELISA）和间接血凝法（IHA）在本实验室检测实验用家兔弓形虫特异性抗体的可行性。方法是应用 ELISA 和 IHA 两种方法平行检测实验感染弓形虫的 12 只家兔阳性血清和未感染过弓形虫的 30 只正常家兔阴性血清中的弓形虫特异性抗体。比较两种方法敏感性、特异性、检测效率及 Youden 指数并运用 kappa 值进行一致性的评价。结论为 ELISA 法与 IHA 法在本次平行检测中的一致性较差。ELISA 方法敏感性、特异性明显优于 IHA 方法，更适用于实验动物家兔的弓形虫特异性抗体的检测。[24]

（4）旋毛虫肌幼虫排泄分泌物激活的巨噬细胞和成肌细胞共培养对成肌细胞分化的影响

体外研究与旋毛虫肌幼虫排泄分泌物（ML ES）作用后的巨噬细胞共培养对成肌细胞分化的影响，为深入了解旋毛虫包囊形成机理提供新的思路。方法是通

过共培养技术对旋毛虫 ML ES 激活的巨噬细胞与成肌细胞进行共培养，建立 J774A.1-C2C12 细胞共培养模型。细胞免疫荧光法以及 Western Plot 分析与旋毛虫 ML ES 处理的巨噬细胞共培养对成肌细胞分化以及成肌调节因子表达的影响。结论为旋毛虫 ML ES 可以直接通过调节巨噬细胞活性来影响成肌细胞的分化，为研究旋毛虫与宿主细胞及旋毛虫感染后，宿主细胞间相互作用复杂机制提供了新的思路。[25]

【参考文献】

（如需参考文献中论文全文，请发送论文标题至 yaoyaoyu1987@163.com）

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