先天性寨卡综合征及其致病机制研究进展

贺梦娇, 秦成峰, 李晓峰*

军事科学院军事医学研究院微生物流行病学研究所, 病原微生物生物安全国家重点实验室, 北京 100071

* 联系人, E-mail: xiaofeng_li_bj@163.com

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摘要 寨卡病毒起初一直被看作传统的虫媒病毒, 在其发现后的60年时间里仅导致零星散发病例而一直未受重视。但在2015年南美洲暴发的寨卡疫情中发现, 该病毒也能经性传播。更令人震惊的是, 其感染孕妇后可导致大量的以新生儿小头畸形、脑膜炎和视力障碍为特征的先天性寨卡综合征病例, 引发全球高度关注。世界卫生组织也因此宣布此次寨卡疫情为国际关注的突发公共卫生事件。疫情暴发以来, 全球科学家通力合作, 对先天性寨卡综合征的临床表型、动物模型和致病机制等开展了系统研究, 不仅极大加深了我们对该疾病的认识, 同时为研发有效的抗病毒手段提供了科学依据和研究工具。本文主要对先天性寨卡综合征及其致病机制领域的重要进展作了综述, 并对未来的研究重点作了展望。

关键词 寨卡病毒, 先天性寨卡综合征, 小头畸形, 致病机制

寨卡病毒(Zika virus, ZIKV)于1947年在乌干达境内寨卡森林中的一只恒河猴体内分离获得。之后的60年里在全球仅零星散发, 故而一直未受到关注。2007~2014年间, 太平洋雅浦岛和法属波利尼西亚等地接连暴发寨卡疫情, 导致近4万人感染^[1]。2015年, ZIKV再次在巴西蔓延, 之后迅速传至南美洲和中北美洲多个国家。2016年2月, 世界卫生组织宣布此次寨卡疫情为全球关注的突发公共卫生事件。截至2017年2月, 全球超过80个国家和地区报告了寨卡病例, 仅美洲在流行期间报告的疑似和确诊病例就超过80万例^[2]。

早期的寨卡病例症状多为自限性疾病, 主要表现为发热、关节痛和肌痛、结膜炎或皮疹等。但自2014年起, 包括吉兰-巴雷综合征和小头畸形等ZIKV感染相关的神经系统疾病病例突增, 引发全球关注。孕妇感染ZIKV可能导致胎盘功能不全、胎儿宫内发育迟缓、胎死宫内和新生儿先天性寨卡综合征(congenital Zika

syndrome, CZS)。全球科学家协同攻关, 在CZS方面取得了许多重要突破。

1 寨卡病毒概述

寨卡病毒与登革病毒(dengue virus, DENV)、西尼罗病毒(West Nile virus, WNV)、黄热病毒(yellow fever virus, YFV)、日本脑炎病毒(Japanese encephalitis virus, JEV)和蜱传脑炎病毒(tick-borne encephalitis virus, TBEV)等同为黄病毒科黄病毒属成员, 是严重威胁人类健康的病原体。寨卡病毒主要通过蚊虫叮咬传播, 同时具有性传播和垂直传播等多种传播途径。ZIKV是一种有包膜的单股正链RNA病毒, 基因组全长约为11 kb, 包含两个非编码区(untranslated region, UTR)和一个开放阅读框(open reading frame, ORF)。ORF翻译产生超过3000个氨基酸残基的多聚蛋白体, 之后被宿主和病毒蛋白酶裂解为3个结构蛋白(衣壳蛋白C、前膜蛋白prM

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和包膜蛋白E)和7个非结构蛋白(NS1、NS2A、NS2B、NS3、NS4A、NS4B和NS5)。结构蛋白主要参与病毒颗粒的装配、病毒与细胞的吸附和侵入,含有病毒的主要抗原表位。非结构蛋白及非编码区主要负责病毒基因组复制、翻译,同时参与调节宿主的免疫反应和代谢(图1)。

2 先天性寨卡综合征

2.1 先天性寨卡综合征的定义

ZIKV感染妊娠期间胎儿后导致的各种先天性异常表现统称为CZS。CZS包括三类神经病变,即破坏、发育不全和迁移障碍以及钙化。第一种类型表现为较重的脑积水,主要是由中脑损伤和导水管阻塞所致;第

二种类型主要表现为大脑变小,脑室出现轻、中度肿大;第三种脑发育良好,但伴有轻度钙化。前两者多发生在妊娠早期感染,第三种多由妊娠晚期感染所致。Fonteles等人^[3]开展的研究描述了CZS中畸形病例的面部特征:患儿脸宽且短、齿间距离缩短、鼻根突出、鼻翅宽、耳高而长,并建议将下巴高度指数作为最准确的诊断指标。

2.2 主要临床表现

CZS在妊娠期感染ZIKV的妇女中的发生率为5%~14%^[4],其特有的临床症状包括:(1)严重小头畸形,部分颅骨塌陷;(2)大脑皮质变薄并发生皮层下钙化;(3)黄斑瘢痕和局灶性色素性视网膜色斑;(4)先天性挛缩;(5)明显的早期高张力和锥体外系受累的症状^[5]。癫痫

图1 (网络版彩色)寨卡病毒颗粒结构与基因组组成

Figure 1 (Color online) The particle structure and genome of ZIKV

是CZS的主要神经学特征,在患有CZS且临床表现为小头畸形的儿童中,48%~96%被检测出患有癫痫^[6]。

(i) 小头畸形. 2015年起巴西暴发寨卡疫情,其东北部地区1个月内报道的小头畸形患儿数量比往年的平均值显著增加^[7]。对2013年法属波利尼西亚暴发的寨卡疫情的回顾性分析也发现,妊娠期间寨卡病毒感染与胎儿小头畸形病例高度关联^[8]。通过逆转录-聚合酶链式反应(reverse transcription-polymerase chain reaction, RT-PCR)、原位杂交和电子显微镜观察等手段进一步发现,感染ZIKV孕妇的流产胎儿的大脑和胎盘中含有ZIKV的核酸和感染性病毒颗粒,这为ZIKV感染与小头畸形症的关联提供了直接证据^[9]。神经影像的结果显示,ZIKV感染所致的小头畸形胎儿的大脑皮层出现钙化、皮层下白质减少、皮质畸形、小脑和脑干发育不全^[10]。此外,与ZIKV相关的小头畸形患儿更容易出现窒息和呼吸暂停^[11],进而导致更高的死亡率。

(ii) 脑膜脑炎. ZIKV感染可导致以弥漫性神经元死亡和弥漫性血管损伤为特征的脑膜脑炎^[12],还能引起严重的脑萎缩。Beaufrière等人^[13]对妊娠22~25周终止妊娠后的3个胎儿进行了胎盘检查与神经病理学和神经生物学研究发现,3例感染均发生在妊娠早期,胎盘中出现霍夫鲍尔细胞增生,有炎症迹象,并出现脑膜脑炎和脑积水等神经病理学表现。此外,ZIKV引起的脑炎症状比其他原因引起的脑炎消退得更快,推测ZIKV感染导致脑脊液中的淋巴细胞增多,并引起大脑表达大量的细胞因子^[14],进而有助于脑炎的快速消退。

(iii) 视力障碍. ZIKV可以穿过血眼屏障,在眼睛的前、后腔细胞内持续复制,导致中、重度眼部后遗症,包括结膜炎、黄斑病变和葡萄膜炎,甚至失明。最常见的病理改变是视网膜局限性色素黄斑和脉络膜视网膜萎缩。CZS的眼部异常患病率约为25%^[15]。产前超声或核磁共振成像发现,ZIKV感染的孕妇的胎儿出现单侧小眼球或无眼^[16]。van den Pol等人^[17]发现,ZIKV感染可引起早期发育期间失明。出生后发现的光学异常情况更普遍,包括视交叉发育不全、视网膜缺损和白内障。

(iv) 其他症状. ZIKV感染会对内耳造成广泛损害^[18],CZS患儿可能存在听力丧失、吞咽困难、舌系带改变、神经精神运动和语言发育迟缓等语言和听力障碍^[19]。此外,严重运动障碍轴张力减退和阑尾张力增高在CZS患儿中也普遍存在^[20]。

3 先天性寨卡综合征的研究模型

开发和建立能够真实模拟CZS的研究模型是深入认识其致病机制、研发有效的治疗和预防手段的基础。实验小鼠因其操作简便、遗传背景一致、数量多等优势仍是建立CZS模型的首选。同时,新生儿小头畸形是最严重的CZS临床表现,因此建立ZIKV小头畸形的小鼠模型是疫情暴发后全球科学家的主攻方向。研究人员通过直接注射胎鼠大脑、腹腔或皮下途径感染孕鼠等方式,成功建立了ICR的胎鼠小头畸形模型^[21],以及BALB/c、C57BL/6等的小鼠垂直传播模型^[22],为ZIKV感染导致小头畸形提供了直接的实验证据。

非人灵长类动物是ZIKV的敏感动物,其胎盘和大脑发育与人类最为接近,因此也是研究CZS最为理想的动物模型。研究人员通过皮下接种途径,建立了恒河猴、食蟹猴、猪尾猕猴的ZIKV垂直传播模型。孕期猕猴感染ZIKV后,胎儿显示出与患有CZS的人类胎儿相似的损伤,包括流产、小头畸形、视力障碍和大脑损伤^[23]。上述模型为研究CZS的致病机制提供了可靠的研究工具。

大脑类器官具有与大脑类似的形态和功能特征,有助于更好地理解大脑的组织生理学和大脑形成过程,可为研究ZIKV的神经致病机制提供更真实的科学数据。研究人员通过使用脑类器官研究表明,ZIKV感染可导致Toll样受体3(Toll-like receptors-3, TLR3)表达水平上调,进而诱导神经祖细胞凋亡,最终导致小头畸形^[24]。

4 先天性寨卡综合征的致病机制

病毒感染性疾病的临床表现是病毒与宿主对抗并相互适应的结果。在建立了不同类型CZS相关的类器官和动物模型的基础上,全球科学家对CZS的致病机制开展了系列研究。他们发现了ZIKV在大脑中感染的主要靶细胞及其效应,并从病毒自身毒力进化、拮抗宿主免疫和宿主应答等方面为CZS的致病机制提出了多种科学阐释,极大丰富了对CZS的认识。

4.1 小头畸形的致病机制

研究发现,ZIKV侵入大脑后,关键的靶细胞可为小头畸形的发生提供根本的解释。神经前体细胞经过对称性细胞分裂可产生足够多的神经元,形成了神经发生的细胞池^[25],这是大脑皮层发育过程中非常重要的早期发育事件。放射状胶质细胞是负责大脑皮层发

育的主要神经前体细胞,也是ZIKV感染的主要靶细胞^[22]. ZIKV侵入大脑后,通过干扰细胞对称性分裂使神经前体细胞的增殖速率降低,产生的神经元也随之减少,最终导致小头畸形^[26].

ZIKV的基因突变可能是南美洲ZIKV疫情中小头畸形发病率升高的重要原因之一. 通过系统进化分析发现, ZIKV在2010~2013年先后出现了多个点突变. 利用小鼠的小头症模型进一步发现, 病毒前膜蛋白中的S139N突变显著增加了病毒感染人和小鼠神经前体细胞的能力, 并导致胎鼠大脑发育受限而出现更严重的小头畸形^[27]. 该研究从病毒自身进化角度为ZIKV为何导致小头畸形提供了重要线索.

ZIKV穿过胎盘屏障和血脑屏障是致畸的前提^[28]. 研究发现, ZIKV可感染胎盘巨噬细胞和滋养层细胞, 在滋养层细胞内质网采用胎盘外泌体途径通过胎盘滋养层^[29]. 单核细胞是ZIKV进入大脑的载体^[30], 大脑中的多种脑细胞在发育过程中表达高水平的受体TAM家族(Tyro3/Axl/Merceptortyrosinekinase)的酪氨酸蛋白激酶受体(AXL). ZIKV可能与AXL具有高亲和力而能高效感染大脑中的神经前体细胞、星形胶质细胞、少突胶质前体细胞和小胶质细胞^[31], 导致细胞周期停滞、凋亡和分化异常, 出现皮质变薄和小头畸形^[21].

宿主的免疫应答在小头畸形发病过程中也发挥重要作用. ZIKV感染后促使含半胱氨酸的天冬氨酸蛋白水解酶-1(cysteiny aspartate specific proteinase-1, caspase-1)精确完成自剪接活化, 进而特异性识别、切割并激活膜穿孔蛋白(Gasdermin D, GSDMD)后引发细胞凋亡, 最终影响神经祖细胞发育而导致小头畸形^[32]. 但也有研究表明, ZIKV存在可以直接将GSDMD切割成GSDMD-NT片段的蛋白酶, 导致细胞出现非caspase诱导的细胞焦亡. 该研究在亚细胞水平上为ZIKV感染的发病机制提供了新认识^[33]. 此外, ZIKV可通过阻断干扰素信号通路、自然杀伤细胞、补体系统、B细胞和T细胞反应来逃避宿主免疫识别^[34]. NS4A以核膜重组调节因子ANKLE2依赖性方式抑制大脑发育, NS5通过抑制聚合酶相关因子1复合物C(the RNA polymerase II associated factor 1 complex, Paf1C)的募集来抑制干扰素刺激基因^[35]. CXCL10是一种与先天性畸形相关的细胞因子. 感染ZIKV的孕妇会出现以高水平CXCL10为特征的抗炎反应, 推测其可能是导致小头畸形的原因之一^[14].

4.2 脑膜脑炎的致病机制

通过免疫组化分析发现, 感染ZIKV的胎儿表现出T淋巴细胞性脑膜炎和弥漫性脑蛛网膜炎症状. 通过原位杂交进一步发现, 脑实质中的室下区和皮层板内存在大量的ZIKV颗粒, 同时出现大量死亡的神经祖细胞, 部分神经祖细胞的内质网结构也发生破坏, 推测其是导致弥漫性脑膜脑炎的重要原因之一. ZIKV感染的孕妇通常出现较强的M1巨噬细胞介导的促炎反应, 同时M2巨噬细胞介导的抗炎反应较弱, 提示妊娠诱导的免疫失调在新生儿病理, 尤其是脑膜炎发生发展过程中也具有潜在的促进作用^[36].

4.3 视力障碍的致病机制

ATP结合盒转运蛋白F1(ATP-binding cassette sub-family F member 1, ABCF1)是一种参与视网膜视觉光传导的重要蛋白. ABCF1可与光感受器外节(photoreceptor outer segments, POSs)结合, 促进POSs被视网膜色素上皮细胞(retinal pigment epithelial, RPE)吞噬, 完成光信号到电信号的转化, 同时参与视网膜的再生^[37]. Nguyen等人^[38]通过靶向蛋白质组学研究发现, ZIKV感染可能会触发宿主细胞中的ABCF1失调, 进而在发育的关键时刻扰乱视网膜稳态, 导致长期视网膜异常^[39]. Beaver等人^[40]通过小鼠模型发现, 减少抗神经节苷类抗体可以改善ZIKV引起的眼部病变.

5 展望

2015年暴发于南美洲的寨卡疫情让世界重新认识了寨卡病毒. 一方面, 寨卡病毒能通过蚊虫叮咬、性行为和垂直传播等多种方式传播, 彻底颠覆了人们对虫媒病毒的经典认识; 另一方面, 寨卡病毒感染孕妇后能导致先天性寨卡综合征, 被列入新的潜在的TORCH病原体. 目前已经建立了包括人脑类器官、小鼠、猴体和孕猴的感染、致病和传播模型, 借助这些研究工具初步明确了寨卡病毒感染导致小头症的关键环节, 确证了寨卡病毒的性传播和垂直传播途径. 但是对寨卡病毒呈现出的全新传播和致病特征的潜在机制仍不了解, 特别是先天性寨卡综合征的致病机制仍存在多个空白. 如, 不同发育阶段的胎盘对寨卡病毒的敏感性如何、寨卡病毒如何突破母胎屏障靶向感染胎儿、寨卡病毒在孕期感染胎儿的长期致病效应是什么、预存的黄病毒免疫记忆是否影响寨卡病毒的致畸效应、如何

研发适于孕妇的阻断寨卡病毒垂直传播的手段等。上述科学问题也将是未来寨卡病毒相关领域的研究热点和重点, 回答这些问题将加深我们对这个老病毒新特征的科学认识。

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Summary for “先天性寨卡综合征及其致病机制研究进展”

Advances in congenital Zika syndrome and its pathogenesis

Mengjiao He, Chengfeng Qin & Xiaofeng Li*

State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences, Beijing 100071, China

* Corresponding author, E-mail: xiaofeng_li_bj@163.com

Zika virus (ZIKV), originally discovered in a sentinel rhesus monkey in Zika valley in Uganda in 1947, has long been viewed as a classical mosquito-borne flavivirus. Due to its association with only a mild and self-limiting illness, ZIKV was a neglected pathogen following 60 years since its identification. However, this virus became a serious public health concern in 2015–2016 outbreak in the Americas because of its association with congenital Zika syndrome (CZS). World Health Organization (WHO) declared the ZIKV outbreak a public health emergency of international concern in 2016.

CZS is a pattern of birth defects found among fetuses and babies infected with ZIKV during pregnancy. The main clinical features of CZS are variable including severe microcephaly, decreased brain tissue, meningitis, damage to the back of the eye, hearing defects, arthrogryposis as well as hypertonia restricting body movement soon after birth. Benefiting from close collaboration of the international scientific community, intensive studies have been performed in development of experimental models to gain insights into the molecular basis of CZS in humans. These models include cultured neuroprogenitor stem cells, cortical organoids, especially mouse and nonhuman primate animal models which recapitulate many features of CZS in humans. Thanks to these models, questions related to how ZIKV infection causes congenital disease have been largely answered. For example, ZIKV was found to directly infects human neural progenitor cells (hNPCs) of the cerebral cortex, resulting in reduced hNPC proliferation; ZIKV also exhibits tropism for microglia in the brain, leading to production of inflammatory cytokines that inhibit neuronal precursor cell proliferation and differentiation. Additionally, studies have suggested that ZIKV can infect and trigger inflammasome pathways and innate antiviral immune responses of glial cells.

While remarkable progress has been made to explain the associated underlying mechanisms, many unanswered key questions remain as follows: (1) How is the placenta in different developmental stage susceptible to ZIKV infection? (2) How is ZIKV transmitted across the placenta to infect the fetus? (3) What is the neurodevelopmental sequelae of congenital infection? (4) How does pre-existing maternal flavivirus immunity impact pregnancy-associated disease? Overall, due to collaborative and multidisciplinary efforts, a large body of knowledge of ZIKV biology has been obtained that has deepened our understanding of the CZS and informed the development of candidate vaccines and therapies. The lessons we have learned from ZIKV could enable effective preparation for the ultimate control of emergence of new congenital viral diseases in the future.

Zika virus, congenital Zika syndrome, microcephaly, pathogenesis

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