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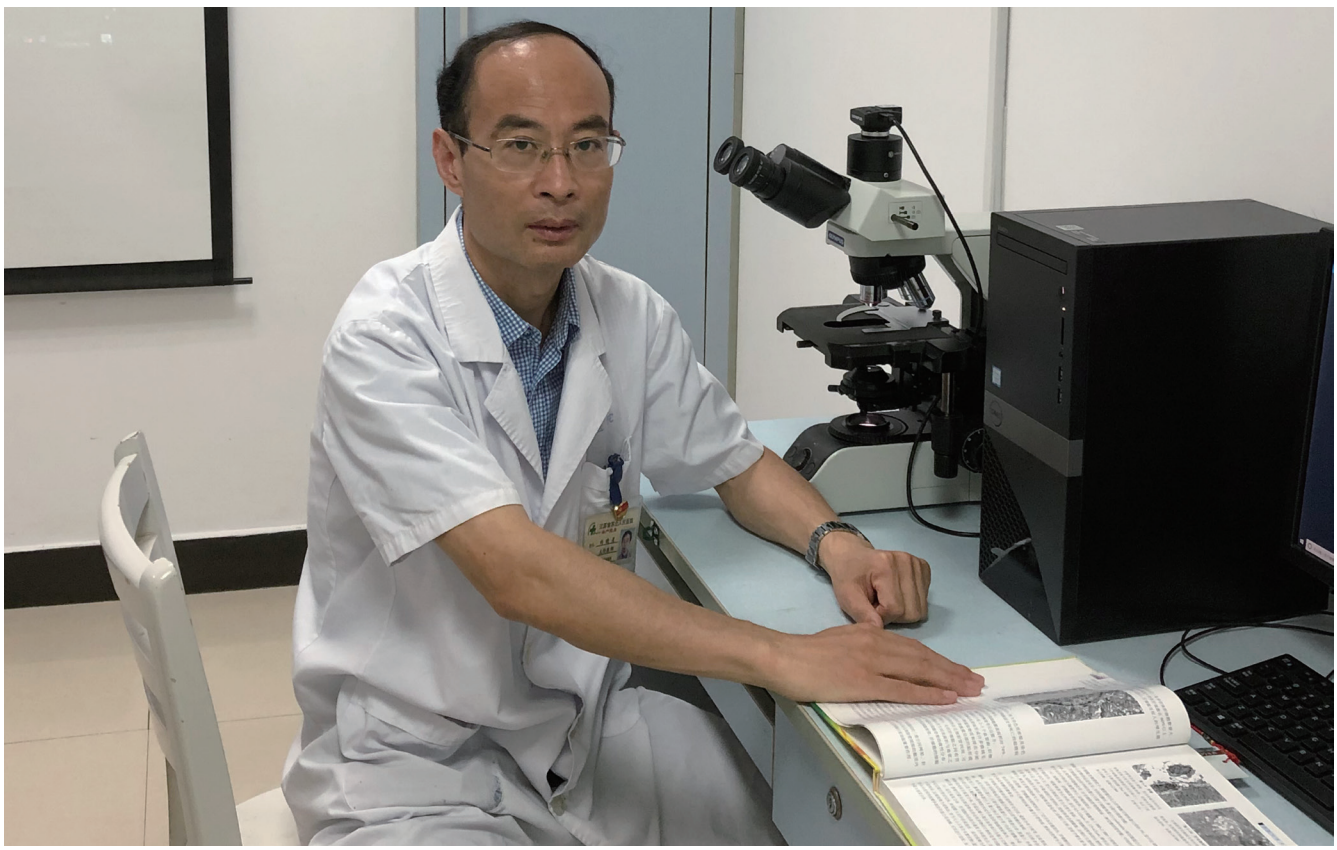

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述评 EDITORIAL

人类免疫缺陷病毒的传播途径及影响因素

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Transmission routes of human immunodeficiency virus and affecting factors

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Abstract

Acquired immunodeficiency syndrome (AIDS) was first reported more than 30 years ago among homosexuals in the United States. The epidemiology of this disease indicates that there are three modes of transmission: Blood, mother-to-child, and sexual contact transmission. The pathogen of AIDS is human immunodeficiency virus (HIV), primarily HIV-1. HIV-1 could not break through the structurally and functionally integral skin, and primarily invades the human body through the mucosa irrespective of their integrity. Therefore, the mucosae are the natural transmission routes for HIV-1. The mucosae involved in HIV-1 transmission include the mucosae of the gastrointestinal tract and the urogenital tract. The risks of HIV-1 transmission vary significantly between mucosal sites and individuals, and are associated with mucosal integrity, abundance of target cells, immune status of the host, commensal microbes, and host genetic background. Many factors are closely related to the barrier function of the mucosa, and studies on their roles in HIV-1 invasion could promote the prevention and control of mucosal transmission of HIV-1.

Key Words: Human immunodeficiency virus; Acquired immunodeficiency syndrome; Route of transmission; Affecting factors

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摘要

在30多年前美国首次报道了同性恋人群中发现的获得性免疫缺陷综合症(acquired immunodeficiency syndromes, AIDS), 其流行特征表明AIDS通过性接

触、母婴和血液三种方式传播. AIDS的病原体为人免疫缺陷病毒(human immunodeficiency virus, HIV), 主要为HIV-1. HIV-1几乎不能突破结构和功能完整的皮肤, 主要由黏膜(包括结构和功能完整的黏膜)侵入人体. 因此, 黏膜是HIV-1的自然传播途径. 与HIV-1传播有关的黏膜包括消化道黏膜和泌尿生殖道黏膜. 黏膜传播风险存在显著的部位和个体差异, 黏膜结构和功能的完整性、黏膜中靶细胞的丰度、机体免疫状态、黏膜表面共生微生物及宿主遗传背景等都与黏膜传播有关. 许多因素与黏膜屏障功能密切相关, 关于它们在HIV-1入侵中的作用的研究将促进HIV-1黏膜传播的预防和控制.

关键词: 人免疫缺陷病毒; 艾滋病; 传播途径; 影响因素

核心提要: 黏膜是人免疫缺陷病毒入侵人体的主要途径. 不同个体及不同黏膜部位的病毒传播风险差异极大. 多种黏膜屏障结构和功能的影响因素可能与人免疫缺陷病毒黏膜传播风险有关, 相关研究将为艾滋病的防控提供新思路.

文献来源: 杨贵波. 人类免疫缺陷病毒的传播途径及影响因素. 世界华人消化杂志 2020; 28(18): 873-883
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0 引言

艾滋病是人类免疫缺陷病毒(human immunodeficiency virus, HIV), 主要是HIV-1, 感染引发的免疫缺陷综合症(acquired immunodeficiency syndromes, AIDS). 据UNAIDS官方网站(2020-03-18), 2018年新发生的HIV-1感染人数170万, 存活的HIV-1感染者3700万, 死于艾滋病相关疾病者77万. 艾滋病自被发现以来, 一直在全球流行, 是全球公共卫生和人类健康的重大挑战. 虽然对艾滋病的研究已开展了三十多年, 各相关领域也取得了长足的进展, 但仍然缺乏安全、有效、经济适用的艾滋病治愈方法、疫苗或局部杀微生物剂. 虽然近年有零星的治愈报道, 但治愈病例数少, 不仅费用高, 风险极大, 且需要特殊设施和资源, 难以大规模开展[1-3]. 事实上, 已有报道观察到CXCR4嗜性HIV-1在CCR5Delta32干细胞治疗后出现反弹[4]. 由于HIV/AIDS主要的自然传播方式是性接触传播, 流行病学干预方法的效果已经很难有大幅提升的空间. 显然, 要从根本上遏制艾滋病必需依靠新的生物学干预措施, 包括能够有效阻止HIV-1传播的方法(保护未感染者)或能够全面清除感染者体内病毒(治愈感染者)的方法[3,5]. 而前者(预防)既可免去罹患疾病的困扰, 又不大量耗费个人财富和国家医疗资源, 应是最为经济有效的方法.

阻止人免疫缺陷病毒感染预防艾滋病传播的潜在措施包括使用疫苗和局部杀微生物剂[6-12]. 虽然疫苗是在感染性疾病预防中被证明最为经济有效的方法, 但由于HIV-1具有复杂的免疫逃逸机制(如潜伏和突变)使得疫苗研究仍然任重而道远[13]. 由于HIV-1主要经性途径传播, 黏膜疫苗、局部杀微生物剂及抗病毒药物局部应用等都有大量研究, 但绝大多数在临床试验显示无效, 有的甚至有促进感染的效果[14]. 暴露前用药的“预防”效果不仅有限, 且受多种因素影响, 并存在耐药和毒副作用等问题[11]. 因此, 迄今仍然缺乏能够完全阻断HIV-1性接触传播的安全、有效和经济适用的方法. 抗病毒药物阻止HIV-1母婴传播(mother-to-child transmission, MTCT)似乎较为成功, 能将围产期MTCT风险从大约25%-30%降低到2%-5%[15,16]; 但近年研究发现, 尽管抗病毒药物可以使许多婴孩不被HIV-1感染, 但那些接触过HIV-1和抗病毒药物的HIV-1未感染的儿童比未接触HIV-1和药物的未感染儿童具有显著增高(70%)的死亡风险[17,18].

尽管人们至今尚未找到预防HIV/AIDS的方法, 但反复接触病毒而未被感染的HIV-1接触未感染者(HIV-1 exposed seronegative, HESN)个体的存在说明人类的免疫系统中存在完全阻止HIV-1黏膜入侵的机制[19-21]. 意味着有可能发现并利用HESN保护机制使更多的人具有HIV-1免疫力. 由于获得与HESN中同样有效的HIV-1感染阻止方法的唯一途径是深入了解HIV-1的传播过程及相关的关键生物学因素. 因此几十年来人们对HIV-1传播早期的病毒宿主相互作用、病毒入侵事件、病毒特征及游离与细胞携带病毒传播效率、各种免疫和天然限制因子等进行了大量研究[22]. 绝大部分对HESN(以及进展速度不同的HIV-1/AIDS患者)的HIV-1相关免疫保护因素的研究仅为相关性研究, 缺乏实验验证. 如对HESN抵抗HIV-1感染的生物学因素的研究中, 发现许多因素与保护相关, 但由于不可能在人体上进行实验验证, 这些保护性因素的实际作用并未得以实验验证. 另一方面, 由于黏膜保护因素复杂, 而大部分研究只是聚焦单一因子, 与体内的实际情况相差甚远. 如一些研究发现CCR5配体水平与HESN有关, 但并非所有HESN中CCR5配体水平都高[23,24]; 又如抗体和细胞毒性T淋巴细胞(cytotoxic T lymphocyte, CTL), 虽然它们各自都具有保护作用, 但无论是诱导抗体的疫苗还是诱导CTL的疫苗在临床试验中都未能显示很好的保护作用[9,25,26]. 另外已有的研究几乎都是聚焦HIV-1与其靶细胞, 很少聚焦

黏膜上皮细胞屏障. 本文将对黏膜传播相关生物学因素研究的主要结果进行综述.

1 黏膜是HIV-1入侵人体的主要途径, 具有阻止HIV-1感染的能力

关于HIV-1入侵人体的途径及相关影响因素的知识是理性设计阻断HIV-1感染预防艾滋病传播的干预措施的科学基础. 要有效阻断HIV-1传播, 必须要针对性地干预HIV-1传播主要途径上的关键节点. 流行病学调查表明艾滋病有三种不同的传播方式(血液途径、性接触途径和MTCT), 而性接触传播是艾滋病的自然传播方式, 也是最主要的传播方式[27]. 尽管我国曾经是以血液途径传播为主, 但世界范围内性接触传播一直是主要的传播方式[28-30]. 而近年我国艾滋病传播的主要方式也已经与世界上的主要传播方式一致, 即以性接触传播为主.

艾滋病性接触传播包括同性间性接触传播和异性间性接触传播, 是最先确认的艾滋病传播方式[27,29]. 世界范围内大多数HIV-1感染是通过性接触发生的, 约占所有HIV-1感染的80%[27,30]. 性接触传播的病毒(HIV-1)来自于HIV-1阳性个体的黏膜分泌液或精液. 研究表明精液、宫颈和阴道分泌液中均含有游离的病毒和HIV-1感染过的细胞, 游离病毒可以感染未感染的CD4+T淋巴细胞, HIV-1感染细胞可释放病毒或直接通过细胞与细胞之间的直接传播感染新的靶细胞[31]. 另外, 在唾液、乳汁和泪液中也可检出病毒[29,31]. HIV-1感染者与未感染个体在性接触过程中, 携带游离病毒和HIV-1感染细胞的黏膜分泌液或精液与未感染者的黏膜(主要包括直肠黏膜、宫颈和阴道黏膜等)接触, 病毒跨越黏膜侵入未感染者的上皮及上皮下组织, 完成对新个体的感染. 口腔黏膜也可能在性接触传播中发挥作用[29].

MTCT又称垂直传播, 指HIV-1感染母亲将病毒直接传给其孩子的传播方式. MTCT可发生在子宫内、婴儿生产过程中或哺乳过程中[31,32]. 病毒污染的乳汁及其它液体可以接触到婴儿的口腔、咽喉、食道和胃黏膜. 虽然成人的上消化道接触HIV-1后感染风险较低, 但婴儿上消化道发育尚不成熟, 病毒及感染细胞携带的病毒能够通过婴儿的上消化道黏膜侵入体内.

艾滋病血液传播是HIV-1通过携带病毒血液或血液制品的传播. 主要见于静脉吸毒者、血友病患者、接受输血的患者和职业暴露者. 大多数血液传播发生在医疗、静脉吸毒或意外事件中锐器(针具或刀片)刺破皮肤之后, 因此许多文献中称之为经皮肤途径的传播或医源性传播[33]. 我国HIV-1传播一度以血液传播, 包括输血、静脉吸毒等为主要传播方式. 随着血液传播的控制, 近年我国90%以上的新发感染都是经性接触途径传播的, 血液传播已不再是主要的传播方式.

由于艾滋病的主要传播方式为性接触传播[30], 且性接触传播和MTCT中HIV-1都通过黏膜入侵宿主, 而血液传播所占比例越来越小, 因此黏膜是HIV-1入侵人体的主要途径, 是HIV-1入侵的门户.

有证据表明, 黏膜具有阻止HIV-1入侵的能力, 但个体差异较大, 部分个体的黏膜具有完全阻止HIV-1入侵的能力. 首先, 一些个体经黏膜反复接触HIV-1而能长期保持血清学检测和病毒核酸检测阴性, 称HESN. 据Jennes等[34](2004)报道, 40位HESN中仅8位(20%)具有低水平的HIV-1特异的T淋巴细胞, 而100%的HIV-1阳性个体具有HIV-1特异的T淋巴细胞, 表明生殖道黏膜具有天然抗HIV-1感染的抵抗力, 尽管并不是所有个体都具备. 其次, 流行病学研究发现HIV-1经血液传播的风险可高达100%[35], 而黏膜传播风险则相对较低, 直肠接触传播风险为1:20到1:300, 阴道接触传播风险为1:1000到1:10000[36-38], 表明虽然大部分个体的黏膜未能完全阻止HIV-1感染, 但黏膜屏障显著降低了HIV-1感染风险, 而病毒进入机体之后几乎未遇到任何抵抗. 第三, 在灵长类动物攻毒实验中, 黏膜攻毒导致动物感染所需的病毒剂量或攻毒次数都显著大于血液途径. 第四, 体外组织细胞培养实验证明黏膜上皮具有HIV-1屏障作用, HIV-1不能自由跨越肠道上皮[39]. 这些数据不仅证明黏膜具有天然抵抗HIV-1感染的能力, 更重要的是它表明在黏膜部位可以有效(HESN中100%)阻止HIV-1感染, 预防HIV/AIDS传播.

2 黏膜上皮屏障是黏膜免疫系统的重要成分, 是在HIV-1入侵路径上最重要的分水岭

HIV-1能否跨越黏膜上皮在很大程度上决定着HIV-1感染是否成功. 虽然宿主遗传因素可影响靶细胞抵抗HIV-1感染的能力和宿主针对HIV-1的免疫应答, 少数个体(如携带CCR5Delta32的个体)具有HIV-1抗性; 但研究表明, 虽然体内都具有抑制HIV-1感染靶细胞和复制的各种因素, 但由于HIV-1具有逃逸甚至利用宿主天然和获得性免疫保护机制的能力, 绝大多数宿主都未能阻止侵入体内的HIV-1感染靶细胞和复制[40-45]. 由于黏膜, 尤其是肠道黏膜, 具有十分丰富的HIV-1靶细胞, 包括巨噬细胞、树突状细胞和CD4+T淋巴细胞, 一旦病毒跨越黏膜上皮屏障, 感染几乎是不可避免的[5,46]. 这也可从血液传播风险可高达100%得到印证.

HIV-1黏膜传播的主要过程包括HIV-1污染精液或黏膜分泌液沉淀在黏膜表面, 病毒跨越黏膜上皮, 然后病毒与黏膜中的靶细胞通过受体结合, 进入靶细胞. 由于黏膜中HIV-1的靶细胞, 包括树突状细胞、巨噬细胞

和CD4+T淋巴细胞十分丰富, HIV-1一旦跨越上皮层便有足够的机会与靶细胞相遇[47,48]. 近年有研究发现黏膜中几乎无处不在的成纤维细胞也能促进HIV-1感染CD4+T淋巴细胞[49]. 因此, 虽然对于大多数病原体黏膜上皮屏障是机体的第一道屏障, 但对于HIV-1来说几乎是HIV-1与靶细胞间的最后一道屏障.

经黏膜途径反复接触HIV-1的HESN可能是黏膜上皮屏障成功地阻止HIV-1感染的最好例证. 在这些HESN中, 有感染和复制能力的HIV-1很可能未能跨越黏膜上皮, 因为虽然在部分HESN个体中能够检测到HIV-1特异的T淋巴细胞, 但并无证据表明具有感染能力的HIV-1成功地进入了这些个体. 而HIV-1特异T淋巴细胞的存在可能是HIV-1分解后的抗原通过抗原摄取机制进入黏膜, 活化黏膜B淋巴细胞, 或通过树突状细胞交叉呈递活化T淋巴细胞[34]. 另外, 动物体内实验证明用抗体阻止SIV跨越黏膜就能够阻止SIV感染, 而无论是抗体还是CTL在感染个体中的作用都非常有限[50,51]. 这些结果表明阻止HIV-1跨越上皮屏障就有可能成功地阻止HIV-1和艾滋病传播. 而当病毒跨越黏膜屏障后, 无论是抗体还是CTL都无法完全控制或清除体内的病毒.

与HIV-1入侵有关的黏膜包括泌尿生殖道和消化道黏膜, 上皮层为单层柱状上皮(如直肠黏膜上皮、子宫内膜、和子宫内颈黏膜)或复层扁平上皮(如口腔黏膜、阴道和子宫外颈). 其中单层柱状上皮仅由一层柱状上皮细胞及紧密连接蛋白连接而成, 是物理屏障最薄弱的黏膜上皮[52]. 由于在艾滋病同性、异性和MTCT中都涉及单层上皮细胞屏障, 对单层上皮屏障在阻止HIV-1入侵中的作用和影响因素的认识可促进艾滋病预防研究[19]. 现有的报道包括基于体外培养人肠上皮细胞单层和肠黏膜组织培养模型的研究[53,54]、基于HESN及不同进展人群的相关性研究和基于各种实验动物模型的研究[19,55,56], 所得结果表明HIV-1可能通过上皮细胞之间的缝隙和上皮细胞胞体跨越肠上皮屏障[57]. 上皮细胞之间的细胞间隙具有紧密连接封闭, 是肠黏膜上皮阻止病原体及其产物的重要屏障; 迄今未见关于HIV-1跨越结构和功能完整的紧密连接的报道. 但HIV-1有可能通过破坏紧密连接实现跨黏膜屏障入侵[58,59]. HIV-1经肠上皮细胞内跨越上皮屏障的研究表明HIV-1至少存在两条潜在的路径穿越上皮细胞: 一是HIV-1感染肠道上皮细胞并释放病毒到体内[60,61], 二是肠上皮细胞摄取HIV-1通过穿胞转运跨越上皮屏障[39,53,54].

3 多种因素参与上皮屏障完整性调节, 是HIV-1跨越上皮屏障的潜在影响因素

在MTCT(尤其是HIV-1阳性母亲哺乳)和性接触(尤其是男男性接触)传播中胃肠道黏膜上皮都是HIV-1入侵的主要屏障. 胃肠道黏膜上皮主要由位于黏膜最外层的柱状上皮细胞构成. 已有研究表明肠上皮细胞不仅是肠上皮物理屏障的主要结构成分, 也是肠上皮屏障的主要调节者[62]. 由于肠黏膜上皮细胞位于黏膜最表浅层, 可以直接与肠腔内的各种物质接触, 通过其表达的各种受体感知肠腔内的共生微生物及其代谢产物和食物及其携带的病原微生物及其它有害物质. 肠上皮细胞可表达能够识别微生物的模式识别受体(pattern recognition receptor, PRR)如Toll样受体(toll-like receptors, TLRs)、NOD样受体和RIG-1样受体等, 微生物表达的微生物相关分子模式(microorganism-associated molecular patterns, MAMPs), 病原微生物表达的常称为病原相关分子模式分子, 如脂多糖、脂磷壁酸、肽聚糖和双链病毒RNA等[63-65]. 肠道微生物可通过MAMPs与PRRs的相互作用调节肠上皮细胞的基因表达, 包括PRRs自身(如两歧双歧杆菌上调TLR3)的表达[64,66], 从而影响肠道屏障结构和免疫功能. 例如通过肠上皮细胞内的TLR2信号通路, 肠道微生物可以影响抗微生物肽的表达和紧密连接的完整性[67,68]. 另外, 一些微生物成分(如phenazines和naphthoquinone phthiocol)可以直接与宿主细胞核转录调控因子AhR相结合诱导固有免疫抗菌反应[69].

肠道微生物除通过MAMP与肠上皮细胞相互作用外, 还可以通过其代谢产物影响那些能够调节上皮屏障功能的免疫细胞[如辅助性T细胞17 (T helper 17, Th17)], 进而影响肠上皮屏障功能[63,70]. 例如, 胆酸是肝脏合成释放到十二指肠的胆固醇衍生物, 其在肠道共生微生物等的作用下可产生次生物如3-OxoLCA. 最新研究发现3-OxoLCA能够与ROR γ t结合从而抑制Th17细胞分化[71]. 由于Th17细胞可以通过表达IL-17A和IL-22等细胞因子参与上皮屏障(如紧密连接)功能的维持. 一些共生微生物的代谢产物, 如短链脂肪酸(short-chain fatty acids, SCFAs), 不仅能够调节黏膜调节性T细胞[72], 还能为结肠的肠细胞提供能量(如丁酸盐), 并且可以直接与肠上皮细胞内的PPAR-γ相互作用调节肠上皮细胞的多种基因的表达[73]. 早有研究表明SCFA可以直接影响肠上皮屏障通透性[74], 丁酸盐(重要SCFA之一)可以通过升高AMPK活性来促进紧密连接组装[75]从而促进肠上皮的屏障功能. 因此, 肠腔内容物(包括共生微生物及其代谢产物)可能是肠道上皮屏障调节的重要因素之一.

神经内分泌物质对黏膜免疫系统的影响已经研究了很多年, 虽然生殖系统激素与HIV-1性接触传播的关系已基本确立[48,76,77], 但肠道神经内分泌物质与艾滋病相关肠道免疫功能关系的研究几乎是空白. 越来越多的研究表明神经和内分泌系统对黏膜免疫系统的影响是

不容忽视的. 尤其是近年越来越多的关于脑-肠轴、肠道菌群与肠道免疫及大脑关系的研究表明黏膜免疫系统并非独立的, 与肠道菌群(如上述)、神经和内分泌系统密切关联[78,79]. 如研究显示VIP(血管活性肠肽: 肠道内分泌细胞和神经元都可分泌)可以通过固有淋巴细胞(innate lymphoid cells, ILC) 3表达的VIP受体促进肠黏膜中ILC3表达IL-22. 而IL-22不仅参与肠黏膜抗感染免疫, 而且参与维持肠上皮屏障的完整性[79,80]. 虽然神经内分泌因素参与肠道黏膜屏障功能的调节, 但在抗HIV-1入侵的免疫屏障中的作用尚待研究.

精液不仅是艾滋病性接触传播中HIV-1的载体, 也是HIV-1传播效率的重要影响因素[81,82]. 精液中含有游离的HIV-1病毒粒子、HIV-1感染的白细胞和附着在精子上的HIV-1病毒, 游离病毒和感染过的白细胞在病毒传播中发挥主要作用. 精液一方面可以促进HIV-1感染: 如精子可以促进HIV-1传给树突状细胞(dendritic cells, DC)、精液可以改变阴道内的pH值而促进HIV-1感染、精液可以诱导女性生殖道炎症反应促进HIV-1感染、精液中的淀粉样原纤维可促进HIV-1感染、精液中含有高浓度免疫调节因子可通过抑制对HIV-1的免疫应答促进HIV-1感染[81,83-85]. 另一方面精液也可能抑制HIV-1感染: 如精液可以抑制HIV-1与DC-SIGN的结合及HIV-1从DC向CD4+T细胞的传播[86]. 精液中也含有多种能够影响黏膜屏障的激素和细胞因子等成分[48], 是否和如何参与HIV-1跨上皮入侵缺乏系统深入的研究.

4 结论

近四十年来人们就HIV-1感染相关生物学因素进行了海量的研究[87-92]. 不仅研究了HESN, 还研究了长期不进展者、高级控制者和进展快慢不同的各种人群[93]. 研究涉及(1)获得性免疫应答各环节, 如抗原呈递(ERAP2)、免疫调节及体液和细胞免疫保护; (2)固有免疫应答各环节, 如模式识别受体(TLR3)、调节和效应分子(如抗菌肽); (3)各种宿主限制因子(APBEC3G、TRIM5和Mx2等); (4)病毒生物学特性及感染过程各个环节, 如病毒定向转运到靶细胞、病毒进入(CCR5)和复制等. 接触未感染者在反复接触HIV-1后并不被感染[94-96], 可能的保护机制包括: (1)病毒辅助受体CCR5的表达缺乏或低表达[97]; (2)趋化因子MIP-α/β、RANTES或SDF-1表达水平高[98]; (3)靶细胞凋亡[99]; (4)SLPI、Defensins、Cathelicidin、TRIM5α、APOBEC-3G、SAMHD1、Serpina1和Elafin等宿主抗病毒因子或限制因子[100]; (5)IRF-1表达水平低[101]; (6)自然杀伤细胞和DC细胞活性高[102,103]; (7)存在具中和活性的IgA[104]; (8)存在有效的多功能性CD4+T和CD8+T细胞应答[105-107]. 虽然大部分结果来自相关性研究, 但一些保护性机制, 特别是中和抗体、CTL和CCR5突变的保护作用可以说是进行了机制性研究和概念验证[11]. 然而随着基于抗体和CTL的各种疫苗的相继失败和CCR5突变细胞移植治愈病例数量十分有限的客观现实[1,108-111]摆在人们面前, 我们应该清楚地认识到, 虽然研究了近40年, 也取得了长足的进展[1-3], 但目前对许多关键的保护因素及其相互作用的认识仍然不足, 成为研发HIV-1感染预防措施的主要科学障碍[21].

由于黏膜是HIV-1入侵人体的主要门户, 关闭HIV-1入侵的大门[112]使病毒无门可入, 是预防HIV-1感染和艾滋病的理想方法. 疫苗是阻止和预防病原体黏膜传播的重要手段. 对HIV-1疫苗的研究自HIV-1发现以来从来没有间断过. 几乎是人们能够想到的可以作为疫苗靶点的HIV-1组分和宿主分子都进行过研究, 包括那些在HIV-1感染过程中与HIV-1相互作用的宿主分子或病毒携带宿主分子, 如CCR5和MHC分子等[113,114]. 疫苗形式包括蛋白疫苗、核酸疫苗、载体疫苗等, 疫苗效应机制包括抗体和CTL等. 但无一例外地, 所有疫苗要么没能进入临床试验, 要么在临床试验中未显示出足够的临床保护效果, 有的甚至具有促进感染的作用[25,26,109,115]. 被动免疫的方法也有不少尝试. 分泌型IgA和IgM是黏膜保护的主要免疫效应分子, 在临床观察和体外研究中都证明其与黏膜保护有关. 但能够诱导黏膜HIV-1特异分泌型抗体的疫苗并未能100%地阻止病毒经黏膜途径感染受试动物, 中和抗体(包括广谱中和抗体)也未能100%阻止病毒经黏膜途径感染受试动物[116]. 事实上, 临床研究中也发现一些接触未感染者黏膜分泌液中检测不到HIV-1特异的IgA或IgM[21]. 体外上皮细胞模型研究证明HIV-1 Env特异的dIgA和IgM可以阻止HIV-1跨越上皮屏障, 但其抑制作用分别为60%和80%, 不能100%阻止HIV-1跨越完整的上皮屏障, 且在上皮顶端加入抗体几乎无阻断作用[53]. 即使是广谱中和抗体(2F5、2G12和IgG1b12)也不一定能有效阻止病毒的穿胞转运[117,118]. 至于CTL是否及如何阻止HIV-1跨上皮入侵尚不清楚[119,120].

局部杀微生物剂也是人类阻断黏膜传播的重要方法. 对HIV-1局部杀微生物剂的研究也从来没有停止过. 按效应机制抗HIV-1的微生物杀菌剂包括: 直接灭活HIV-1病毒(如N-9和BufferGel), 抑制病毒复制(如UC-781和TMC120), 阻止病毒进入(如PRO2000、CV-N和BMS378806), 阻止宿主分子与病毒相互作用(如APO-RANTES和TNX355)等[121], 但绝大多数未能通过临床试验. 虽然抗病毒药物[如替诺福韦(tenofovir, TFV)和达匹维林(dapivirine, DPV)等]在局部杀微生物剂中的应用虽然显示出一定的效果, 但临床实验显示其效果(TFV: 39%-54%; DPV: 27%-37%)也大有提升空间[122,123].

值得特别注意的是, 由于TFV和DPV等抗病毒药物也是HIV-1治疗用药, 存在加快耐药株产生和对耐药株黏膜传播无阻止作用的风险[124]. 因此, 虽然许多候选局部杀微生物剂进入了临床试验, 但人们依然缺乏安全、完全有效和适合临床应用的局部杀微生物剂[47]. 另外, 虽然口服抗病毒药物也用于“预防”性传播, 但效果尚不如安全套[125,126], 不仅需要较高的药物依从性, 而且还存在毒副作用、促进耐药株流行、甚至感染上耐药株的风险[124,127].

虽然HESN的存在告诉我们存在阻止HIV-1传播的方法, 但人们通过近40年的探索并未找到. 充分说明人们关于HIV-1传播、感染和复制等生物学过程的知识存在明显缺口. 虽然黏膜上皮屏障在HIV-1传播路径上占据着十分独特的位置, 可能是HIV-1性接触(尤其是经直肠黏膜)传播和MTCT中病毒入侵的关键部位[128]; 成功阻止HIV-1跨越这些部位的黏膜上皮, 将有望显著降低HIV-1的感染率[112,129]. 但人们对影响HIV-1跨越这些薄弱部位的影响因素研究薄弱, 缺乏人为干预的靶点, 因此亟待研究.

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