

述评·写作要求

- 1 题名：**简明确切地反映论文的特定内容，鲜明而有特色，阿拉伯数字不宜开头，不用副题名，一般 20 个字。避免用“的研究”或“的观察”等非特定词。
- 2 作者：**作者署名的次序按贡献大小排列，多作者时姓名间用逗号。英文摘要中，先名后姓，首字母大写，如：Ying-Qiu Huang, Ming Li. 需增加第一作者简介。
- 3 单位：**作者后写单位的全称空 1 格后再写省市及邮政编码，不同作者单位分别写出。
- 4 基金资助项目：**可以增加省市级以上基金资助项目，并加基金号。英文摘要中翻译为准确的英文。
- 5 通讯作者：**本刊只设一位通讯作者，不设共同通讯作者，需增加职称。
- 6 摘要：**应包括中英文摘要，一段式非结构摘要，字数应该在 250 字内为宜。
- 7 正文：**首段为“0 引言”，末段为“结论”，中间部分根据文章划分。
- 8 图表：**图表的数量要精选。表应有表序和表题，并有足够具有自明性的信息，使读者不查阅正文即可理解表的内容。表内每一栏均应有表头，表内非公知通用缩写应在表注中说明，表格一律使用三线表(不用竖线)，在正文中该出现的地方应注出。图应有图序、图题和图注，以使其容易被读者理解，所有的图应在正文中该出现的地方注出。同一个主题内容的彩色图、黑白图、线条图，统一用一个注解分别叙述。如：图 1 萎缩性胃炎治疗前后病理变化。A: …; B: …; C: …; D: …; E: …; F: …; G: …。曲线图可按●、○、■、□、▲、△顺序使用标准的符号。统计学显著性用：^a $P < 0.05$, ^b $P < 0.01$ ($P > 0.05$ 不注)。如同一表中另有一套 P 值，则^c $P < 0.05$, ^d $P < 0.01$; 第 3 套为^e $P < 0.05$, ^f $P < 0.01$ 。

9 参考文献: 本刊采用“顺序编码制”的著录方法,即以文中出现顺序用阿拉伯数字编号排序。提倡对国内同行近年已发表的相关研究论文给予充分的反映,并在文内引用处右上角加方括号注明角码。文中如列作者姓名,则需在“Pang 等”的右上角注角码号;若正文中仅引用某文献中的论述,则在该论述的句末右上角注码号。如马连生^[1]报告……,研究^[2-5]认为……;PCR 方法敏感性高^[6-7]。文献序号作正文叙述时,用与正文同号的数字并排,如本实验方法见文献[8]。文献量达 50 条,可以参考本刊相关文献。

10 名词术语: 应标准化,前后统一,如原词过长且多次出现者,可于首次出现时需要包含中英文全称,以后直接用简称。

写作格式实例

述评

肠道与艾滋病

杨贵波

杨贵波,中国疾病预防控制中心性病艾滋病预防控制中心 北京市 102206

杨贵波,研究员,主要从事黏膜免疫、神经内分泌免疫和艾滋病的研究。

国家传染病防治重大专项基金资助项目, No. 2012ZX10001006-002-006

作者贡献分布: 本文由杨贵波完成。

通讯作者: 杨贵波,研究员,102206,北京市昌平区昌百路 155 号,中国疾病预防控制中心性病艾滋病预防控制中心. guiboyang@chinaaids.cn

电话: 010-58900976

收稿日期: 2015-04-25

修回日期:

接受日期:

在线出版日期:

Intestinal tract and acquired immunodeficiency syndrome

Gui-Bo Yang

Gui-Bo Yang, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and

Prevention, Beijing 102206

Supported by: National Major Project for Infectious Diseases Prevention and Treatment, No.

2012ZX10001006-002-006

Correspondence to: Gui-Bo Yang, Researcher, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, 155 Changbai Road, Changping District, Beijing 102206, China.

guiboyang@chinaaids.cn

Received: 2015-04-25

Revised:

Accepted:

Published online:

Abstract

The intestinal tract is closely associated with the transmission, disease progression and the prevention and control of acquired immune deficiency syndrome (AIDS). It has been noticed early in AIDS research that a large percent of AIDS patients presented abnormalities in their intestinal tract, such as diarrhea. Now it is known that the intestinal tract has close and complex relationships with AIDS: (1) the intestinal tract is directly involved in the transmission of human immunodeficiency virus-1 (HIV-1); (2) the damage of the intestinal barrier of HIV/AIDS patients directly promotes AIDS disease progression; (3) and most importantly, the intestinal tract is an important target for the treatment and prevention of HIV/AIDS. The author has previously reviewed the progress in understanding the roles of the intestinal tract in HIV-1 infection and the changes of the intestinal tract after HIV-1 infection. In the current review, I discuss the progress in understanding the roles of the damage of the intestinal mucosal immune system in AIDS disease progression, and the potential application value of the restoration of intestinal mucosal immunity in the treatment of AIDS.

Key Words: Intestinal tract; Mucosal barrier damage; Microbial translocation; Systemic immune activation; AIDS disease progression

摘要

肠道与艾滋病(acquired immune deficiency syndrome, AIDS)的传播、疾病进展和预防控制密切相关。在 AIDS

研究早期人们就注意到相当大一部分 AIDS 患者肠道功能异常, 出现诸如腹泻等症状. 现在已知肠道与 AIDS 有着更深层次的联系: (1)肠道直接参与了人类免疫缺陷病毒(human immunodeficiency virus, HIV)-1 的传播; (2)肠道屏障损伤直接推动了 AIDS 疾病进展; (3)也是更重要的, 肠道是 HIV/AIDS 治疗和预防的重要靶器官. 10年前作者曾经对肠道免疫系统在 HIV-1 感染中的作用和感染后的变化进行了综述. 本文将就近十年来人们对肠道黏膜免疫系统损伤在 AIDS 疾病进展中的作用的研究进展和修复黏膜免疫损伤在 AIDS 治疗中的潜在应用价值进行简要综述.

关键词: 肠道; 黏膜屏障损伤; 微生物移位; 全身免疫活化; 艾滋病疾病进展

核心提示: 人类免疫缺陷病毒(human immunodeficiency virus)-1 感染导致肠道黏膜屏障损伤、微生物菌群异常和微生物移位、促进系统免疫活化、推动艾滋病疾病进展. 人为干预这些病理过程有可能促进艾滋病及其相关疾病的治疗.

0 引言

艾滋病(acquired immune deficiency syndrome, AIDS)是人类免疫缺陷病毒(human immunodeficiency virus, HIV)感染引起的当今最为严重地威胁着人类健康的重大疾病之一, 已经夺走了约 4000 万人的生命. 现在约有三千多万人携带 HIV 病毒, 而且新发感染还在不断发生. 截至 2013 年底, 我国报告现存活 HIV/AIDS 患者 43.68 万人, 死亡 13.63 万人. 虽然对 AIDS 的研究已经进行了三十多年, 但是到目前为止几乎没有有效的预防疫苗和治愈方法. 虽然 HIV/AIDS 涉及宿主免疫系统、神经系统等多个器官系统的各种组织, 但是黏膜组织在 HIV/AIDS 的自然发生过程中起着十分关键的作用.

肠道黏膜是覆盖面积最大的黏膜组织, 含有体内大部分的免疫细胞, 是包括 HIV-1 在内的绝大多数病原体因子入侵机体的门户^[1,2], 也是 HIV-1 感染的主要靶组织. 不仅如此, HIV-1 感染可以导致肠道黏膜免疫屏障功能减弱或丧失, 引起微生物移位(microbial translocation), 并通过活化免疫系统推动疾病进展. 在 HIV/AIDS 治疗方面, 肠道黏膜是宿主体内最大的潜伏病毒储存库, 是实现 AIDS 功能性治愈的主要障碍之一. 在 AIDS 预防方面, 肠黏膜是接触病毒后最容易被感染的黏膜部位, 是预防疫苗或局部杀微生物剂阻止或预防 HIV 感染的主要靶组织. 迄今为止, 已有研究表明除了肠黏膜之外, 尚无任何免疫器官系统既参与 HIV-1 的传播, 又参与推动 AIDS 的疾病进展, 同时还是诱导黏膜免疫保护和阻止 HIV-1 感染的关键部位. 因此, 有关 HIV-1 与宿主肠道黏膜的相互作用的知识, 不仅能够加深对 HIV-1 致病机制的认识, 还能促进 AIDS 的预防和控制.

在十年前作者曾经对肠道免疫系统在 HIV-1 感染中的作用和感染后的变化进行了综述^[3]. 近十年来, 人

们对肠道黏膜免疫系统在 HIV-1 感染后的损伤及机制、肠道免疫系统损伤在 AIDS 疾病进展中的作用、和修复肠道黏膜免疫损伤在 AIDS 治疗中的应用等方面进行了大量的研究. 本文就相关领域所取得的主要研究进展进行简要综述, 旨在引起读者对该领域的研究兴趣.

1 HIV-1 感染导致肠道黏膜免疫系统损伤

自 AIDS 流行伊始, 人们就注意到 HIV/AIDS 患者的肠道功能异常^[4,5]. 虽然最初关注的主要是肠道消化、吸收和分泌功能异常; 但也已注意到肠道屏障功能的异常改变, 如许多 AIDS 患者出现腹泻. 随后的研究^[6]证明 HIV-1 感染对肠道结构和免疫系统的损伤在 AIDS 疾病进展中具有不可忽视的作用.

肠道免疫系统的主要功能是为肠道黏膜提供固有和获得性免疫保护. HIV-1 感染对肠道黏膜获得性免疫成分的影响的显著标志是肠黏膜 CD4⁺T 淋巴细胞在感染 2-3 wk 内大量耗损^[7,8], 与猿猴免疫缺陷病毒(simian immunodeficiency virus, SIV)感染恒河猴中观察到的结果一致^[9]. 在 SIV 实验感染的恒河猴中胃肠相关淋巴组织(gut-associated lymphoid tissues, GALT)中的 CD4⁺T 淋巴细胞在病毒感染后 2 wk 内可降低 90%^[10]; 在感染 1 wk 内产毒性感染的 CD4⁺T 淋巴细胞可大量出现于 GALT 和脾脏的淋巴滤泡中^[11]. 在 HIV/AIDS 患者中, 肠黏膜 CD4⁺T 淋巴细胞水平的显著降低在抗逆转录病毒治疗(antiretroviral therapy, ART)后仅能部分地恢复^[7,12,13]. 进一步对 HIV 感染者黏膜 CD4⁺T 淋巴细胞亚群的分析发现 Th17 细胞被选择性地耗损, 导致 Th17/Tregs 比例失调^[14,15]. 因此, HIV 感染不仅影响肠道 CD4⁺T 细胞的水平, 而且影响 CD4⁺T 细胞的组成.

HIV-1 感染也对肠道固有免疫成分造成损伤. 肠道黏膜中含有丰富的天然免疫系统的细胞, 如巨噬细胞和树突状细胞, 是病原微生物突破肠道上皮屏障后首先遇到的天然免疫细胞. 已知在 HIV-1 感染者和 SIV 感染的恒河猴中肠道巨噬细胞可以被 HIV-1 或 SIV 感染^[16,17]. 而且 HIV 和 SIV 感染都可以影响肠黏膜中的树突状细胞的功能和丰度^[18-20]. 另外, 肠道黏膜中还具有丰富的固有淋巴样细胞(innate lymphoid cells, ILC). 在 HIV-1 或 SIV 感染后, ILC 的数量和功能也出现异常. 肠道黏膜中的自然杀伤细胞(natural killer, NK)在 HIV-1 感染慢性期显著减少, 在 ART 治疗后部分地恢复. 但在 CD4⁺T 细胞数对 ART 治疗无反应的个体中, NK 细胞数大量增加, 高于正常个体中的水平^[21]. 这些结果表明 HIV-1 感染可以对肠道黏膜内多种固有免疫细胞造成损伤.

不仅如此, HIV 感染也会对肠道黏膜物理屏障造成严重损伤. HIV/AIDS 患者出现腹泻表明肠黏膜通透性出现异常. 肠道对有害大分子的屏障功能发生改变的重要证据是 HIV/AIDS 中的微生物移位. 由于最早对肠道物理屏障损伤的发现是在感染慢性期和 AIDS 患者中, 感染者体内出现持续免疫活化; 因此曾经认为免疫活化产生的细胞因子如肿瘤坏死因子(tumor necrosis factor, TNF)- α 等可能是紧密连接损伤的原因. 但后来研究发现 HIV 病毒本身能够改变紧密连接相关基因的表达和相关分子的分布, 表明紧密连接的损伤可能在感染早期就已发生. Epple 等^[22](2010)发现感染早期上皮细胞凋亡, 可能导致屏障功能损伤. 作者也发现

SHIV/SIV 感染早期紧密连接相关基因的表达也发生了显著变化, 并与白介素(interleukin, IL)-17A 的表达相关联^[23]. 最近 Hirao 等^[24](2014)发现感染早期 SIV 可能通过 Paneth 细胞分泌的 IL-1 β 改变紧密连接的完整性. 因此, 肠道黏膜屏障完整性的改变可能是始于 HIV-1 感染的早期.

2 肠道黏膜上皮紧密连接损伤

紧密连接(tight junction)是位于相邻上皮细胞之间、靠近上皮游离面的胞间连接结构, 又称闭锁小带; 主要封闭上皮细胞之间的间隙, 并防止细胞膜中的分子在上皮细胞游离面与基侧面之间自由扩散. 紧密连接缺陷小鼠在出生后 10 h(*claudin-5*^{-/-})或 24 h(*claudin-1*^{-/-})之内死亡, 表明紧密连接是动物生存所必需的结构^[25,26]. 紧密连接是由多种分子形成的结构和功能复合体^[27,28]. 紧密连接相关蛋白包括跨膜蛋白、胞内附着板蛋白、信号蛋白、和与细胞骨架相连的接头蛋白. 跨膜蛋白具有膜内区和膜外区, 与紧密连接的功能密切相关. 跨膜蛋白分子包括单跨膜区蛋白(JAM、Crb3、和 CAR), 三跨膜区蛋白(Bves)以及含有 claudin 和 TAMP 家族的四跨膜区蛋白(claudins, occludin, tricellulin 和 MarvelD3). 胞质内蛋白包括闭锁小带蛋白(zona occludens, ZO)-1、ZO-2 和 ZO-3, 介导跨膜蛋白与细胞内的肌动球蛋白环(actomyosin ring)之间的相互作用. 另外, 还存在 zonulin 等紧密连接调节蛋白^[29].

HIV 感染可以影响紧密连接的结构和功能. 体外研究^[30]发现多种 HIV-1 蛋白, 包括 HIV-1 gp120、Tat 和 Nef 可以影响脑血管内皮细胞(HBMECs)紧密连接相关基因的表达和分布. HIV-1 gp120 可以通过 HBMECs 表达的趋化因子受体 CCR5(CC-chemokine receptor 5)或 CXCR4(CXC-chemokine receptor 4)调节蛋白激酶 C(protein kinase C, PKC)活性影响紧密连接, 改变血脑屏障(blood brain barrier, BBB)通透性^[31]. 用 HIV-1 gp120 处理 HBMECs 细胞 24 h 可以影响这些细胞中 ZO-1、ZO-2 和 occludin 的表达, 但不影响 claudin-1 和 claudin-5 的表达^[32]. HIV-1 Tat 可以降低细胞内 ZO-1 的总体水平, 但同时上调细胞核中 ZO-1 的水平^[33]. 在 SIV 感染后发生脑炎的恒河猴个体中, 脑血管内皮细胞中紧密连接蛋白 occludin 和 ZO-1 的表达水平下降且分布不连续^[34]. HIV-1 感染致内皮细胞间紧密连接相关蛋白表达变化也见于肺等其他器官系统的血管. 例如, Kanmogne 研究组发现 HIV-1 感染者肺组织中 claudin-5、ZO-1 和 ZO-2 的表达水平下降, 过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor, PPAR)- γ 拮抗剂可使这种改变发生逆转^[35]. Sufiawati 等^[36](2014)观察到 HIV-1 引起口腔上皮细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)1/2 磷酸化导致紧密连接缺损, 促进单纯疱疹病毒(herpes simplex virus, HSV)-1 感染和扩散; 丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)抑制剂(U0126)能部分地抑制 HIV-1 引起的磷酸化.

肠道上皮紧密连接在 HIV-1 感染后也发生显著变化^[37]. 体外研究发现 HIV-1 蛋白如 HIV-1 gp120 可以改变肠道上皮细胞紧密连接蛋白的表达和分布. HIV-1 的 X4 嗜性和 R5 嗜性的实验室适应株和临床分离毒株均可以使体外培养的肠道上皮细胞, 如 T84 细胞单层的跨上皮电阻(trans epithelial electrical resistance, TER)降

低;且 TER 降低与紧密连接蛋白(claudin-1、2、4、occludin 和 ZO-1)的表达和分布异常相关^[38]。但 HIV 蛋白对肠道上皮细胞紧密连接蛋白表达的影响机制尚待深入研究。

3 肠黏膜损伤是导致微生物移位的主要原因

现已知肠道上皮物理屏障损伤和紧密连接异常是 HIV/AIDS 患者中的常见现象^[39-41]。早在 AIDS 发现后不久人们就观察到肠道黏膜的通透性发生了变化^[42-44]。HIV/AIDS 患者中有高达 40%左右的腹泻患者,无可鉴定的致腹泻病原,可能与肠道上皮屏障缺陷相关^[45,46]。然而,早期对肠道黏膜屏障损伤与 HIV/AIDS 疾病进展的关系缺乏更深入的认识。后来人们在 HIV-1 感染者和 AIDS 患者血液中检测到高水平的微生物产物,如脂多糖(lipopolysaccharide, LPS)和细菌的 16S RNA;这些细菌成分在 HIV/AIDS 患者血浆中的含量显著高于正常人^[47-49]。表明 HIV/AIDS 患者肠黏膜屏障异常可能导致微生物移位。

微生物移位是 HIV/AIDS 患者中的普遍现象;在病毒抑制和抑制失败的 ART 治疗儿童体内肠道微生物移位持续存在^[50]。HIV-1 病毒粒子、HIV Tat 和 HIV-1 gp120 均能够引起紧密连接异常,并可以促进人乳头瘤病毒、单纯疱疹病毒 HSV-1 和 HSV-2 从上皮细胞间侵入口腔黏膜^[36,51]。在 SIV 感染恒河猴中,伴随着肠黏膜中 CD4⁺T 淋巴细胞的减少,黏膜上皮细胞间的紧密连接结构和功能完整性逐步丧失,结果导致大量沙门氏菌(*Salmonella*)侵入肠黏膜,感染动物疾病进展加快^[52]。Estes 等^[53](2010)也利用 SIV 感染恒河猴这一动物模型证明 SIV 感染致微生物移位与肠上皮完整性损伤有关。在 SIV 感染豚尾猴(*Pigtailed Macaques*)中人们也观察到 AIDS 进展速度与胃肠道上皮功能完整性相关^[54]。另外,在无 SIV 感染的豚尾猴中也发现胃肠道屏障完整性与微生物移位和免疫活化相关^[55]。这些结果表明黏膜屏障功能完整性损伤导致 HIV/AIDS 中的微生物移位。

HIV/AIDS 患者中慢性全身性/系统免疫活化与肠道上皮屏障损伤密切相关。虽然早期对 HIV-1 感染者的肠黏膜上皮屏障损伤的观察主要在 HIV-1 感染慢性期和 AIDS 患者中进行,但是体外研究和最近的动物模型研究表明紧密连接异常可能出现在感染早期^[22,56]。我们在 SHIV/SIV 感染早期恒河猴中观察到紧密连接相关基因(*CLAUDIN-1*、*OCCLUDIN* 和 *ZO-1*)转录水平显著下调^[23];随后的研究^[24]也表明 SIV 可在感染的 3 d 内引起紧密连接的变化。因此,在 HIV-1 感染早期紧密连接很可能就已经出现损伤,导致微生物或其产物进入机体。黏膜(包括肠道)上皮完整性损伤导致微生物移位、引起全身/系统性免疫活化是 HIV/AIDS 的重要致病机制。肠道黏膜屏障损伤引起的微生物移位可能是推动 HIV/AIDS 疾病进展的主要因素^[57-63]。

4 微生物移位导致系统免疫活化

正常情况下肠腔内微生物及其产物被黏膜屏障阻止在体外。HIV-1 感染后肠道物理屏障,如紧密连接在感染早期即发生显著变化。进入黏膜的微生物产物可能被黏膜中的吞噬细胞摄取清除。然而在黏膜吞噬细胞受

到损伤或侵入微生物产物量超过吞噬细胞清除能力后, 微生物产物将进入黏膜血管系统, 通过肝门静脉进入肝脏. 肝脏吞噬细胞, Kupffer 细胞是清除入侵微生物产物和阻止微生物产物进入全身血液循环的主要细胞. 由于在 HIV-1 感染后肠道免疫系统及肝脏都受到损伤, 因此微生物及其产物得以进入全身血液循环^[64]. 微生物产物通过携带的病原相关分子模式(pathogen-associated molecular pattern, PAMP)分子与宿主细胞的病原分子识别受体(pattern recognition receptor, PRR)相互作用, 活化宿主天然和获得性免疫系统.

如上所述, 微生物移位是 HIV-1/AIDS 中的普遍现象. 与此相一致, 持续的系统免疫活化是 HIV 感染和 AIDS 的另一个显著病理特点^[65]. 在 HIV/AIDS 患者中, 全身性免疫活化的一个显著标志是血浆炎症细胞因子水平显著上升, 如干扰素(interferon, INF)- α 、IFN- γ 、IL-6、IL-8、 γ -干扰素诱导蛋白(interferon- γ -inducible protein, IP)-10 和 TNF- α 等^[47,66-68]; 另一个标志是具活化表型的免疫细胞增多, 如 HIV/AIDS 患者中出现大量多克隆活化的 B 淋巴细胞, 活化的 T 淋巴细胞, 如 CD38⁺HLA-DR⁺CD8⁺T 细胞、Ki67⁺CD4⁺和 CD8⁺T 细胞所占比例显著增加^[69]. 另外, 还出现持续的单核细胞/巨噬细胞活化, 反映单核细胞和巨噬细胞活化水平的 sCD14 水平显著上升^[47,70].

HIV/AIDS 中的系统免疫活化的主要原因是微生物移位^[71]. 已知给未感染自愿者注射 14 pg/mL 微生物产物 LPS 便可以导致系统免疫活化^[72]. 在慢性 HIV-1 感染者和 SIV 感染的恒河猴中均出现高水平的血液 LPS, 可高达 75 μ g/mL; 且 LPS 水平与感染个体中的系统免疫活化程度成正相关关系^[71]. 近十年来多个研究团队的临床研究都表明 HIV/AIDS 患者中血浆微生物产物水平与免疫系统活化程度密切相关. 移位微生物水平与免疫活化水平的正相关关系不局限于未治疗个体中^[73]. 在接受了治疗的个体中, 虽然 ART 可以使血浆微生物产物水平降低, 同时伴有免疫活化水平随降低, 但移位微生物水平仍然与系统免疫活化水平成正相关关系^[74,75]. 在 ART 治疗后 CD4⁺T 淋巴细胞数没有恢复的患者中存在与微生物移位相关的高水平的免疫活化^[76]. 新近研究发现在感染急性期阻止微生物移位可以显著降低免疫活化和炎症水平、并且还能轻微降低病毒复制水平, 直接证明微生物移位促进系统免疫活化^[77].

在 HIV-1 感染中持续系统免疫活化与 AIDS 疾病进展密切相关^[57,78]. 免疫活化可导致淋巴结纤维化、效应 T 淋巴细胞滞留在淋巴结内、胸腺功能失调、克隆耗竭、记忆细胞库枯竭以及提供大量靶细胞供 HIV-1 复制. HIV-1 感染者中能反映宿主系统免疫活化的高水平血清 sCD14 与疾病进展和临床事件相关, 是可以独立预测死亡的指标^[79-81]. 微生物移位可能导致宿主 CD4⁺T 细胞损失、病毒载量上升、以及对免疫刺激的反应性出现缺陷^[82]. 在 ART 治疗的 HIV 感染人群中, 肠道屏障损伤、免疫活化和炎症可以独立地预测死亡^[83]. 在 SIV 感染恒河猴中, 肠道上皮屏障破损与微生物移位相关, 而在 SIV 感染的非洲绿猴中未发现上皮屏障损伤、无上升的微生物移位、无病理性免疫活化^[84]. 这些研究表明肠道免疫系统的损伤, 包括肠道黏膜屏障的损伤与 AIDS 疾病进展密切相关.

5 肠道微生物菌群失调

早在十年之前就有关于 HIV 对黏膜表面微生物菌群(microbiota)的影响的报道。目前已确知 HIV 感染可导致肠道微生物菌群失调^[85]。正常情况下肠道存在种类繁多的共生微生物，它们与免疫系统之间存在着复杂的相互作用；一方面宿主免疫压力和摄取的食物能够影响肠道相关微生物群落的性质；另一方面某些共生微生物也影响局部和全身免疫系统的发育和功能^[86-90]。微生物的生长和抑制之间的微妙平衡由免疫系统进行调控。然而，这种平衡在 HIV-1 感染后被打破，可能在肠道免疫病理变化中起作用。

HIV-1 感染可以显著地改变包括肠道黏膜免疫系统在内的整个免疫系统和肠道微环境，引起肠道黏膜屏障和肠道共生微生物区系发生显著改变^[91-96]。近年研究表明，虽然总的微生物水平和多样性在 HIV 感染组与未感染组之间没有显著差异，但感染组的微生物组成出现了明显的变化。变形菌(Proteobacteria)，尤其是肠杆菌科(Enterobacteriaceae)细菌，包括诸如沙门氏菌(*Salmonella*)，埃希氏菌(*Escherichia*)和志贺氏菌(*Shigella*)等在 HIV 感染组肠道中更为丰富；而拟杆菌(*Bacteroides*)和另枝菌(*Alistipes*)则变少^[85]。在 HIV-1 感染后增多的多种细菌具有吲哚胺 2,3 双加氧酶(indoleamine-2,3-dioxygenase, IDO)类似酶活性物质，能够通过产生 Kyn 促进它们的生长。已知在 HIV 感染者中 IDO-1 与疾病进展相关^[14]。

在 ART 治疗个体中，总的来说微生物菌群与未治疗的 HIV-1 感染者更相似，而与未感染的 HIV-1 阴性个体不同。在 ART 治疗后，HIV-1 感染导致的共生微生物的相对丰度的改变会出现不同程度的恢复，不同菌群的恢复速度和恢复程度各不相同。在 ART 治疗者中，不仅微生物的相对丰度出现了变化，而且微生物的组成也发生了改变。未治疗 HIV-1 感染者的共生微生物多样性通常保持不变，甚至有所增加；而 ART 治疗后多样性变小，虽然原因尚不清楚，但可能与药物的使用有关。已知有些抗逆转录病毒药物具有诱导非感染性腹泻的不良反应，高达 40% 的接受 ART 治疗的 HIV 阳性个体出现中度到重度腹泻^[97,98]，而腹泻可以改变肠道共生微生物的多样性^[99]。

HIV-1 感染导致肠道微生物菌群改变的原因可能与 HIV-1 感染导致宿主肠道黏膜免疫损伤有关。已知一些在 HIV-1 感染后显著减少的细菌，如脆弱拟杆菌(*Bacteroides fragilis*)，依赖其产物 PSA(polysaccharide A)与肠道免疫细胞相互作用，通过诱导调节性 T 细胞以建立其在肠道中的生态位^[100]。由于 HIV-1 感染导致肠道 CD4⁺T 细胞大量减少，HIV 感染可能通过耗损 CD4⁺T 细胞打破肠道共生微生物与肠道免疫系统之间的动态平衡，导致肠道微生物菌群失调。因此，肠道免疫损伤可能是肠道菌群失调的重要原因^[101]，而肠道共生微生物失调又会加重肠道黏膜屏障的损伤。

6 肠道与 AIDS 治愈的机遇与挑战

黏膜既参与 HIV-1 传播又与疾病进展密切相关，自然是 HIV-1/AIDS 疾病治疗和预防的关键部位。由于 HIV-1 具有高度变异的特性，因此免疫逃逸毒株很快可以出现；又由于 HIV-1 可形成稳定的潜伏病毒库，免

疫系统很难清除和控制体内的病毒. 因此, 在黏膜表面成功阻止病毒感染应是最理想的预防疫苗思路. 事实上 AIDS 黏膜疫苗的研究已受到了广泛关注, 并是 AIDS 疫苗研究的重要方向^[102,103].

就 AIDS 治疗而言, 肠黏膜是体内最大的 HIV-1 病毒储存库, 而免疫活化是该病毒储存库能够长期持续存在的主要原因. 由于即使在高效抗病毒药物治疗下免疫活化仍然不能被有效抑制^[104,105], 因此免疫活化成为了抗病毒药物治疗失败的主要原因之一. 另外, 系统性免疫活化还与 AIDS 并发症, 如肝纤维化的发生密切相关^[106]. 因此, 修复黏膜损伤、抑制系统免疫活化是 HIV/AIDS 治疗的新思路^[107-110].

目前, 修复黏膜屏障、抑制微生物移位、抑制系统免疫活化已开始应用于 HIV/AIDS 治疗的尝试^[111,112]; 临床前动物实验^[61]和临床实验^[113,114]均有报道. 已有多个研究组报道了利用益生菌来改善 HIV-1 感染者的肠道功能的研究结果^[61,108,115,116]. 最近一个双盲随机安慰剂对照临床试验研究^[114]表明用食用酵母菌 (*Saccharomyces boulardii*) 处理 12 wk 可以显著减少 HIV-1 感染者体内微生物移位, 并降低炎症水平, 其效果在停止处理后 3 mo 仍然明显. 然而目前对黏膜屏障损伤的机理认识不清是更为精准和理性治愈方案的主要障碍, 加深对 HIV/AIDS 患者黏膜屏障, 包括紧密连接这一黏膜屏障关键结构病理变化机制的认识, 必将为新的干预措施的提出提供重要的基础.

7 结论

近年来关于 HIV-1 感染致宿主肠道黏膜免疫屏障损伤、微生物移位、系统免疫活化和肠道共生微生物种类和组成变化等的知识不断增加. HIV-1 通过肠道黏膜传播、快速在肠道黏膜中建立潜伏病毒库、并通过损伤黏膜屏障推动疾病进展, 为 AIDS 防治提出了严峻的挑战; 而深入认识病毒与肠道黏膜免疫系统(包括共生微生物)之间的相互作用和机制则可为 AIDS 的防治提供新的机遇.

8 参考文献

1 Royce RA, Seña A, Cates W, Cohen MS. Sexual transmission of HIV. *N Engl J Med* 1997; **336**: 1072-1078

[PMID: 9091805 DOI: 10.1056/NEJM199704103361507]

2 Tugizov SM, Herrera R, Veluppillai P, Greenspan D, Soros V, Greene WC, Levy JA, Palefsky JM. Differential transmission of HIV traversing fetal oral/intestinal epithelia and adult oral epithelia. *J Virol* 2012; **86**: 2556-2570

[PMID: 22205732 DOI: 10.1128/JVI.06578-11]

3 杨贵波, 邵一鸣. 人类免疫缺陷病毒与黏膜免疫. *世界华人消化杂志* 2005; **13**: 1750-1759

4 Kotler DP, Gaetz HP, Lange M, Klein EB, Holt PR. Enteropathy associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **101**: 421-428 [PMID: 6476631 DOI: 10.7326/0003-4819-101-4-421]

5 Rodgers VD, Fassett R, Kagnoff MF. Abnormalities in intestinal mucosal T cells in homosexual populations

including those with the lymphadenopathy syndrome and acquired immunodeficiency syndrome. *Gastroenterology* 1986; **90**: 552-558 [PMID: 2935443 DOI: 10.1016/0016-5085(86)91108-X]

6 **Douek D**. HIV disease progression: immune activation, microbes, and a leaky gut. *Top HIV Med* 2007; **15**: 114-117 [PMID: 17720995]

7 **Brenchley JM**, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, Nguyen PL, Khoruts A, Larson M, Haase AT, Douek DC. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004; **200**: 749-759 [PMID: 15365096 DOI: 10.1084/jem.20040874]

8 **Mehandru S**, Poles MA, Tenner-Racz K, Horowitz A, Hurley A, Hogan C, Boden D, Racz P, Markowitz M. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* 2004; **200**: 761-770 [PMID: 15365095 DOI: 10.1084/jem.20041196]

9 **Veazey RS**, DeMaria M, Chalifoux LV, Shvetz DE, Pauley DR, Knight HL, Rosenzweig M, Johnson RP, Desrosiers RC, Lackner AA. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. *Science* 1998; **280**: 427-431 [PMID: 9545219 DOI: 10.1126/science.280.5362.427]

10 **Mattapallil JJ**, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. *Nature* 2005; **434**: 1093-1097 [PMID: 15793563 DOI: 10.1038/nature03501]

11 **Yang GB**, Alexander L, Aye P, Alvarez X, Desrosiers RC, Lackner AA. Localization of productively infected cells in the spleen and Peyer's patches of rhesus macaques during acute infection with SIVmac239 Δ nef-enhanced green fluorescent protein. *AIDS Res Hum Retroviruses* 2014; **30**: 738-739 [PMID: 25026557 DOI: 10.1089/AID.2014.0160]

12 **Schneider T**, Jahn HU, Schmidt W, Riecken EO, Zeitz M, Ullrich R. Loss of CD4 T lymphocytes in patients infected with human immunodeficiency virus type 1 is more pronounced in the duodenal mucosa than in the peripheral blood. Berlin Diarrhea/Wasting Syndrome Study Group. *Gut* 1995; **37**: 524-529 [PMID: 7489940 DOI: 10.1136/gut.37.4.524]

13 **Guadalupe M**, Reay E, Sankaran S, Prindiville T, Flamm J, McNeil A, Dandekar S. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol* 2003; **77**: 11708-11717 [PMID: 14557656 DOI: 10.1128/JVI.77.21.11708-11717.2003]

14 **Favre D**, Mold J, Hunt PW, Kanwar B, Loke P, Seu L, Barbour JD, Lowe MM, Jayawardene A, Aweeka F, Huang Y, Douek DC, Brenchley JM, Martin JN, Hecht FM, Deeks SG, McCune JM. Tryptophan catabolism by

indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. *Sci Transl Med* 2010; **2**: 32ra36 [PMID: 20484731 DOI: 10.1126/scitranslmed.3000632]

15 **Chege D**, Sheth PM, Kain T, Kim CJ, Kovacs C, Loutfy M, Halpenny R, Kandel G, Chun TW, Ostrowski M, Kaul R. Sigmoid Th17 populations, the HIV latent reservoir, and microbial translocation in men on long-term antiretroviral therapy. *AIDS* 2011; **25**: 741-749 [PMID: 21378536 DOI: 10.1097/QAD.0b013e328344cefb]

16 **Smith PD**, Meng G, Shaw GM, Li L. Infection of gastrointestinal tract macrophages by HIV-1. *J Leukoc Biol* 1997; **62**: 72-77 [PMID: 9225996]

17 **Moore AC**, Bixler SL, Lewis MG, Verthelyi D, Mattapallil JJ. Mucosal and peripheral Lin- HLA-DR+ CD11c/123- CD13+ CD14- mononuclear cells are preferentially infected during acute simian immunodeficiency virus infection. *J Virol* 2012; **86**: 1069-1078 [PMID: 22090100 DOI: 10.1128/JVI.06372-11]

18 **Choi YK**, Whelton KM, Mlechick B, Murphey-Corb MA, Reinhart TA. Productive infection of dendritic cells by simian immunodeficiency virus in macaque intestinal tissues. *J Pathol* 2003; **201**: 616-628 [PMID: 14648666 DOI: 10.1002/path.1482]

19 **Reeves RK**, Evans TI, Gillis J, Wong FE, Kang G, Li Q, Johnson RP. SIV infection induces accumulation of plasmacytoid dendritic cells in the gut mucosa. *J Infect Dis* 2012; **206**: 1462-1468 [PMID: 22711907 DOI: 10.1093/infdis/jis408]

20 **Lehmann C**, Jung N, Förster K, Koch N, Leifeld L, Fischer J, Mauss S, Drebber U, Steffen HM, Romerio F, Fäkenheuer G, Hartmann P. Longitudinal analysis of distribution and function of plasmacytoid dendritic cells in peripheral blood and gut mucosa of HIV infected patients. *J Infect Dis* 2014; **209**: 940-949 [PMID: 24259523 DOI: 10.1093/infdis/jit612]

21 **Sips M**, Sciaranghella G, Diefenbach T, Dugast AS, Berger CT, Liu Q, Kwon D, Ghebremichael M, Estes JD, Carrington M, Martin JN, Deeks SG, Hunt PW, Alter G. Altered distribution of mucosal NK cells during HIV infection. *Mucosal Immunol* 2012; **5**: 30-40 [PMID: 21993602 DOI: 10.1038/mi.2011.40]

22 **Epple HJ**, Allers K, Tröger H, Köhl A, Erben U, Fromm M, Zeitz M, Loddenkemper C, Schulzke JD, Schneider T. Acute HIV infection induces mucosal infiltration with CD4+ and CD8+ T cells, epithelial apoptosis, and a mucosal barrier defect. *Gastroenterology* 2010; **139**: 1289-1300 [PMID: 20600014 DOI: 10.1053/j.gastro.2010.06.065]

23 **Zhang WJ**, Wang Y, Yu K, Duan JZ, Yao WR, Wang Y, Yang RG, Yang GB. Associated changes in the transcription levels of IL-17A and tight junction-associated genes in the duodenal mucosa of rhesus macaques repeatedly exposed to simian/human immunodeficiency virus. *Exp Mol Pathol* 2014; **97**: 225-233 [PMID:

25034324 DOI: 10.1016/j.yexmp.2014.07.007]

24 **Hirao LA**, Grishina I, Bourry O, Hu WK, Somrit M, Sankaran-Walters S, Gaulke CA, Fenton AN, Li JA, Crawford RW, Chuang F, Tarara R, Marco ML, Bäumler AJ, Cheng H, Dandekar S. Early mucosal sensing of SIV infection by paneth cells induces IL-1 β production and initiates gut epithelial disruption. *PLoS Pathog* 2014; **10**: e1004311 [PMID: 25166758 DOI: 10.1371/journal.ppat.1004311]

25 **Furuse M**, Hata M, Furuse K, Yoshida Y, Haratake A, Sugitani Y, Noda T, Kubo A, Tsukita S. Claudin-based tight junctions are crucial for the mammalian epidermal barrier: a lesson from claudin-1-deficient mice. *J Cell Biol* 2002; **156**: 1099-1111 [PMID: 11889141 DOI: 10.1083/jcb.200110122]

26 **Nitta T**, Hata M, Gotoh S, Seo Y, Sasaki H, Hashimoto N, Furuse M, Tsukita S. Size-selective loosening of the blood-brain barrier in claudin-5-deficient mice. *J Cell Biol* 2003; **161**: 653-660 [PMID: 12743111 DOI: 10.1083/jcb.200302070]

27 **Runkle EA**, Mu D. Tight junction proteins: from barrier to tumorigenesis. *Cancer Lett* 2013; **337**: 41-48 [PMID: 23743355 DOI: 10.1016/j.canlet.2013.05.038]

28 **Günzel D**, Yu AS. Claudins and the modulation of tight junction permeability. *Physiol Rev* 2013; **93**: 525-569 [PMID: 23589827 DOI: 10.1152/physrev.00019.2012]

29 **Fasano A**. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. *Physiol Rev* 2011; **91**: 151-175 [PMID: 21248165 DOI: 10.1152/physrev.00003.2008]

30 **Annunziata P**. Blood-brain barrier changes during invasion of the central nervous system by HIV-1. Old and new insights into the mechanism. *J Neurol* 2003; **250**: 901-906 [PMID: 12928906 DOI: 10.1007/s00415-003-1159-0]

31 **Kanmogne GD**, Schall K, Leibhart J, Knipe B, Gendelman HE, Persidsky Y. HIV-1 gp120 compromises blood-brain barrier integrity and enhances monocyte migration across blood-brain barrier: implication for viral neuropathogenesis. *J Cereb Blood Flow Metab* 2007; **27**: 123-134 [PMID: 16685256 DOI: 10.1038/sj.jcbfm.9600330]

32 **Kanmogne GD**, Primeaux C, Grammas P. HIV-1 gp120 proteins alter tight junction protein expression and brain endothelial cell permeability: implications for the pathogenesis of HIV-associated dementia. *J Neuropathol Exp Neurol* 2005; **64**: 498-505 [PMID: 15977641]

33 **Zhong Y**, Zhang B, Eum SY, Toborek M. HIV-1 Tat triggers nuclear localization of ZO-1 via Rho signaling and cAMP response element-binding protein activation. *J Neurosci* 2012; **32**: 143-150 [PMID: 22219277 DOI: 10.1523/JNEUROSCI.4266-11.2012]

- 34 **Luabeya MK**, Dallasta LM, Achim CL, Pauza CD, Hamilton RL. Blood-brain barrier disruption in simian immunodeficiency virus encephalitis. *Neuropathol Appl Neurobiol* 2000; **26**: 454-462 [PMID: 11054186 DOI: 10.1046/j.1365-2990.2000.00275.x]
- 35 **Li H**, Singh S, Potula R, Persidsky Y, Kanmogne GD. Dysregulation of claudin-5 in HIV-induced interstitial pneumonitis and lung vascular injury. Protective role of peroxisome proliferator-activated receptor- γ . *Am J Respir Crit Care Med* 2014; **190**: 85-97 [PMID: 22345580 DOI: 10.1164/rccm.201106-1151OC]
- 36 **Sufiawati I**, Tugizov SM. HIV-associated disruption of tight and adherens junctions of oral epithelial cells facilitates HSV-1 infection and spread. *PLoS One* 2014; **9**: e88803 [PMID: 24586397 DOI: 10.1371/journal.pone.0088803]
- 37 **Chung CY**, Alden SL, Funderburg NT, Fu P, Levine AD. Progressive proximal-to-distal reduction in expression of the tight junction complex in colonic epithelium of virally-suppressed HIV+ individuals. *PLoS Pathog* 2014; **10**: e1004198 [PMID: 24968145 DOI: 10.1371/journal.ppat.1004198]
- 38 **Nazli A**, Chan O, Dobson-Belaire WN, Ouellet M, Tremblay MJ, Gray-Owen SD, Arsenault AL, Kaushic C. Exposure to HIV-1 directly impairs mucosal epithelial barrier integrity allowing microbial translocation. *PLoS Pathog* 2010; **6**: e1000852 [PMID: 20386714 DOI: 10.1371/journal.ppat.1000852]
- 39 **Keating J**, Bjarnason I, Somasundaram S, Macpherson A, Francis N, Price AB, Sharpstone D, Smithson J, Menzies IS, Gazzard BG. Intestinal absorptive capacity, intestinal permeability and jejunal histology in HIV and their relation to diarrhoea. *Gut* 1995; **37**: 623-629 [PMID: 8549936 DOI: 10.1136/gut.37.5.623]
- 40 **Obinna FC**, Cook G, Beale T, Dave S, Cunningham D, Fleming SC, Claydon E, Harris JW, Kapembwa MS. Comparative assessment of small intestinal and colonic permeability in HIV-infected homosexual men. *AIDS* 1995; **9**: 1009-1016 [PMID: 8527072 DOI: 10.1097/00002030-199509000-00005]
- 41 **Epple HJ**, Schneider T, Troeger H, Kunkel D, Allers K, Moos V, Amasheh M, Loddenkemper C, Fromm M, Zeitz M, Schulzke JD. Impairment of the intestinal barrier is evident in untreated but absent in suppressively treated HIV-infected patients. *Gut* 2009; **58**: 220-227 [PMID: 18936106 DOI: 10.1136/gut.2008.150425]
- 42 **Smith PD**, Lane HC, Gill VJ, Manischewitz JF, Quinnan GV, Fauci AS, Masur H. Intestinal infections in patients with the acquired immunodeficiency syndrome (AIDS). Etiology and response to therapy. *Ann Intern Med* 1988; **108**: 328-333 [PMID: 2829677 DOI: 10.7326/0003-4819-108-3-328]
- 43 **Colebunders R**, Lusakumuni K, Nelson AM, Gigase P, Lebughe I, van Marck E, Kapita B, Francis H, Salaun JJ, Quinn TC. Persistent diarrhoea in Zairian AIDS patients: an endoscopic and histological study. *Gut* 1988; **29**: 1687-1691 [PMID: 3220308 DOI: 10.1136/gut.29.12.1687]

- 44 **Ullrich R**, Zeitz M, Heise W, L'age M, Höffken G, Riecken EO. Small intestinal structure and function in patients infected with human immunodeficiency virus (HIV): evidence for HIV-induced enteropathy. *Ann Intern Med* 1989; **111**: 15-21 [PMID: 2500046 DOI: 10.7326/0003-4819-111-11-954_1]
- 45 **Kapembwa MS**, Fleming SC, Sewankambo N, Serwadda D, Lucas S, Moody A, Griffin GE. Altered small-intestinal permeability associated with diarrhoea in human-immunodeficiency-virus-infected Caucasian and African subjects. *Clin Sci (Lond)* 1991; **81**: 327-334 [PMID: 1655333]
- 46 **Stockmann M**, Fromm M, Schmitz H, Schmidt W, Riecken EO, Schulzke JD. Duodenal biopsies of HIV-infected patients with diarrhoea exhibit epithelial barrier defects but no active secretion. *AIDS* 1998; **12**: 43-51 [PMID: 9456254 DOI: 10.1097/00002030-199801000-00006]
- 47 **Nockher WA**, Bergmann L, Scherberich JE. Increased soluble CD14 serum levels and altered CD14 expression of peripheral blood monocytes in HIV-infected patients. *Clin Exp Immunol* 1994; **98**: 369-374 [PMID: 7527738 DOI: 10.1111/j.1365-2249.1994.tb05499.x]
- 48 **Jiang W**, Lederman MM, Hunt P, Sieg SF, Haley K, Rodriguez B, Landay A, Martin J, Sinclair E, Asher AI, Deeks SG, Douek DC, Brechley JM. Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. *J Infect Dis* 2009; **199**: 1177-1185 [PMID: 19265479 DOI: 10.1086/597476]
- 49 **Brechley JM**, Douek DC. Microbial translocation across the GI tract. *Annu Rev Immunol* 2012; **30**: 149-173 [PMID: 22224779 DOI: 10.1146/annurev-immunol-020711-075001]
- 50 **Pilakka-Kanthikeel S**, Huang S, Fenton T, Borkowsky W, Cunningham CK, Pahwa S. Increased gut microbial translocation in HIV-infected children persists in virologic responders and virologic failures after antiretroviral therapy. *Pediatr Infect Dis J* 2012; **31**: 583-591 [PMID: 22333700 DOI: 10.1097/INF.0b013e31824da0f5]
- 51 **Tugizov SM**, Herrera R, Chin-Hong P, Veluppillai P, Greenspan D, Michael Berry J, Pilcher CD, Shiboski CH, Jay N, Rubin M, Chein A, Palefsky JM. HIV-associated disruption of mucosal epithelium facilitates paracellular penetration by human papillomavirus. *Virology* 2013; **446**: 378-388 [PMID: 24074602 DOI: 10.1016/j.virol.2013.08.018]
- 52 **Raffatellu M**, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, Godinez I, Sankaran S, Paixao TA, Gordon MA, Kolls JK, Dandekar S, Bämler AJ. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. *Nat Med* 2008; **14**: 421-428 [PMID: 18376406 DOI: 10.1038/nm1743]
- 53 **Estes JD**, Harris LD, Klatt NR, Tabb B, Pittaluga S, Paiardini M, Barclay GR, Smedley J, Pung R, Oliveira KM,

Hirsch VM, Silvestri G, Douek DC, Miller CJ, Haase AT, Lifson J, Brenchley JM. Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog* 2010; **6**: e1001052 [PMID: 20808901 DOI: 10.1371/journal.ppat.1001052]

54 **Canary LA**, Vinton CL, Morcock DR, Pierce JB, Estes JD, Brenchley JM, Klatt NR. Rate of AIDS progression is associated with gastrointestinal dysfunction in simian immunodeficiency virus-infected pigtail macaques. *J Immunol* 2013; **190**: 2959-2965 [PMID: 23401593 DOI: 10.4049/jimmunol.1202319]

55 **Klatt NR**, Harris LD, Vinton CL, Sung H, Briant JA, Tabb B, Morcock D, McGinty JW, Lifson JD, Lafont BA, Martin MA, Levine AD, Estes JD, Brenchley JM. Compromised gastrointestinal integrity in pigtail macaques is associated with increased microbial translocation, immune activation, and IL-17 production in the absence of SIV infection. *Mucosal Immunol* 2010; **3**: 387-398 [PMID: 20357762 DOI: 10.1038/mi.2010.14]

56 **Sankaran S**, George MD, Reay E, Guadalupe M, Flamm J, Prindiville T, Dandekar S. Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. *J Virol* 2008; **82**: 538-545 [PMID: 17959677 DOI: 10.1128/JVI.01449-07]

57 **Hazenber MD**, Otto SA, van Benthem BH, Roos MT, Coutinho RA, Lange JM, Hamann D, Prins M, Miedema F. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. *AIDS* 2003; **17**: 1881-1888 [PMID: 12960820 DOI: 10.1097/01.aids.0000076311.76477.6e]

58 **Kuller LH**, Tracy R, Bellosso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Neuhaus J, Nixon D, Paton NI, Neaton JD. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008; **5**: e203 [PMID: 18942885 DOI: 10.1371/journal.pmed.0050203]

59 **Redd AD**, Dabaito D, Bream JH, Charvat B, Laeyendecker O, Kiwanuka N, Lutalo T, Kigozi G, Tobian AA, Gamiel J, Neal JD, Oliver AE, Margolick JB, Sewankambo N, Reynolds SJ, Wawer MJ, Serwadda D, Gray RH, Quinn TC. Microbial translocation, the innate cytokine response, and HIV-1 disease progression in Africa. *Proc Natl Acad Sci U S A* 2009; **106**: 6718-6723 [PMID: 19357303 DOI: 10.1073/pnas.0901983106]

60 **Romero-Sánchez M**, González-Serna A, Pacheco YM, Ferrando-Martínez S, Machmach K, García-García M, Álvarez-Ríos AI, Vidal F, Leal M, Ruiz-Mateos E. Different biological significance of sCD14 and LPS in HIV-infection: importance of the immunovirology stage and association with HIV-disease progression markers. *J Infect* 2012; **65**: 431-438 [PMID: 22728172 DOI: 10.1016/j.jinf.2012.06.008]

61 **Klatt NR**, Canary LA, Sun X, Vinton CL, Funderburg NT, Morcock DR, Quiñones M, Deming CB, Perkins M, Hazuda DJ, Miller MD, Lederman MM, Segre JA, Lifson JD, Haddad EK, Estes JD, Brenchley JM.

Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques. *J Clin Invest* 2013; **123**: 903-907 [PMID: 23321668 DOI: 10.1172/JCI66227]

62 **Santos-Oliveira JR**, Regis EG, Giacoia-Gripp CB, Valverde JG, Alexandrino-de-Oliveira P, Lindoso JÂ, Goto H, Oliveira-Neto MP, Guerra JO, Grinsztejn B, Jerônimo SB, Morgado MG, Da-Cruz AM. Microbial translocation induces an intense proinflammatory response in patients with visceral leishmaniasis and HIV type 1 coinfection. *J Infect Dis* 2013; **208**: 57-66 [PMID: 23539743 DOI: 10.1093/infdis/jit135]

63 **Brickman C**, Palefsky JM. Human papillomavirus in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era. *Curr HIV/AIDS Rep* 2015; **12**: 6-15 [PMID: 25644977 DOI: 10.1007/s11904-014-0254-4]

64 **Balagopal A**, Philp FH, Astemborski J, Block TM, Mehta A, Long R, Kirk GD, Mehta SH, Cox AL, Thomas DL, Ray SC. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. *Gastroenterology* 2008; **135**: 226-233 [PMID: 18457674 DOI: 10.1053/j.gastro.2008.03.022]

65 **Papasavvas E**, Azzoni L, Foulkes A, Violari A, Cotton MF, Pistilli M, Reynolds G, Yin X, Glencross DK, Stevens WS, McIntyre JA, Montaner LJ. Increased microbial translocation in ≤ 180 days old perinatally human immunodeficiency virus-positive infants as compared with human immunodeficiency virus-exposed uninfected infants of similar age. *Pediatr Infect Dis J* 2011; **30**: 877-882 [PMID: 21552185 DOI: 10.1097/INF.0b013e31821d141e]

66 **Fan J**, Bass HZ, Fahey JL. Elevated IFN-gamma and decreased IL-2 gene expression are associated with HIV infection. *J Immunol* 1993; **151**: 5031-5040 [PMID: 8409454]

67 **Breen EC**, Rezai AR, Nakajima K, Beall GN, Mitsuyasu RT, Hirano T, Kishimoto T, Martinez-Maza O. Infection with HIV is associated with elevated IL-6 levels and production. *J Immunol* 1990; **144**: 480-484 [PMID: 2295799]

68 **Noel N**, Boufassa F, Lécuroux C, Saez-Cirion A, Bourgeois C, Dunyach-Remy C, Goujard C, Rouzioux C, Meyer L, Pancino G, Venet A, Lambotte O. Elevated IP10 levels are associated with immune activation and low CD4⁺ T-cell counts in HIV controller patients. *AIDS* 2014; **28**: 467-476 [PMID: 24378753 DOI: 10.1097/QAD.000000000000174]

69 **Ciccone EJ**, Read SW, Mannon PJ, Yao MD, Hodge JN, Dewar R, Chairez CL, Proschan MA, Kovacs JA, Sereti I. Cycling of gut mucosal CD4⁺ T cells decreases after prolonged anti-retroviral therapy and is associated with plasma LPS levels. *Mucosal Immunol* 2010; **3**: 172-181 [PMID: 19956090 DOI: 10.1038/mi.2009.129]

70 **Wallet MA**, Rodriguez CA, Yin L, Saporta S, Chinratanapisit S, Hou W, Sleasman JW, Goodenow MM. Microbial translocation induces persistent macrophage activation unrelated to HIV-1 levels or T-cell activation

following therapy. *AIDS* 2010; **24**: 1281-1290 [PMID: 20559035 DOI: 10.1097/QAD.0b013e328339e228]

71 **Brenchley JM**, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006; **12**: 1365-1371 [PMID: 17115046 DOI: 10.1038/nm1511]

72 **Suffredini AF**, Hochstein HD, McMahon FG. Dose-related inflammatory effects of intravenous endotoxin in humans: evaluation of a new clinical lot of Escherichia coli O: 113 endotoxin. *J Infect Dis* 1999; **179**: 1278-1282 [PMID: 10191237 DOI: 10.1086/314717]

73 **Pilakka-Kanthikeel S**, Kris A, Selvaraj A, Swaminathan S, Pahwa S. Immune activation is associated with increased gut microbial translocation in treatment-naive, HIV-infected children in a resource-limited setting. *J Acquir Immune Defic Syndr* 2014; **66**: 16-24 [PMID: 24378729 DOI: 10.1097/QAI.0000000000000096]

74 **d'Ettorre G**, Paiardini M, Zaffiri L, Andreotti M, Ceccarelli G, Rizza C, Indinnimeo M, Vella S, Mastroianni CM, Silvestri G, Vullo V. HIV persistence in the gut mucosa of HIV-infected subjects undergoing antiretroviral therapy correlates with immune activation and increased levels of LPS. *Curr HIV Res* 2011; **9**: 148-153 [PMID: 21457131]

75 **Cassol E**, Malfeld S, Mahasha P, van der Merwe S, Cassol S, Seebregts C, Alfano M, Poli G, Rossouw T. Persistent microbial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. *J Infect Dis* 2010; **202**: 723-733 [PMID: 20629534 DOI: 10.1086/655229]

76 **Marchetti G**, Bellistrì GM, Borghi E, Tincati C, Ferramosca S, La Francesca M, Morace G, Gori A, Monforte AD. Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. *AIDS* 2008; **22**: 2035-2038 [PMID: 18784466 DOI: 10.1097/QAD.0b013e3283112d29]

77 **Kristoff J**, Haret-Richter G, Ma D, Ribeiro RM, Xu C, Cornell E, Stock JL, He T, Mobley AD, Ross S, Trichel A, Wilson C, Tracy R, Landay A, Apetrei C, Pandrea I. Early microbial translocation blockade reduces SIV-mediated inflammation and viral replication. *J Clin Invest* 2014; **124**: 2802-2806 [PMID: 24837437 DOI: 10.1172/JCI75090]

78 **Marchetti G**, Tincati C, Silvestri G. Microbial translocation in the pathogenesis of HIV infection and AIDS. *Clin Microbiol Rev* 2013; **26**: 2-18 [PMID: 23297256 DOI: 10.1128/CMR.00050-12]

79 **Lien E**, Aukrust P, Sundan A, Müller F, Frøland SS, Espevik T. Elevated levels of serum-soluble CD14 in human immunodeficiency virus type 1 (HIV-1) infection: correlation to disease progression and clinical events.

Blood 1998; **92**: 2084-2092 [PMID: 9731066]

80 **Sandler NG**, Wand H, Roque A, Law M, Nason MC, Nixon DE, Pedersen C, Ruxrungtham K, Lewin SR, Emery S, Neaton JD, Brechley JM, Deeks SG, Sereti I, Douek DC. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* 2011; **203**: 780-790 [PMID: 21252259 DOI: 10.1093/infdis/jiq118]

81 **Vassallo M**, Mercier P, Cottalorda J, Ticchioni M, Dellamonica P. The role of lipopolysaccharide as a marker of immune activation in HIV-1 infected patients: a systematic literature review. *Virol J* 2012; **9**: 174 [PMID: 22925532 DOI: 10.1186/1743-422X-9-174]

82 **Nowroozalizadeh S**, Månsson F, da Silva Z, Repits J, Dabo B, Pereira C, Biague A, Albert J, Nielsen J, Aaby P, Fenyö EM, Norrgren H, Holmgren B, Jansson M. Microbial translocation correlates with the severity of both HIV-1 and HIV-2 infections. *J Infect Dis* 2010; **201**: 1150-1154 [PMID: 20199244 DOI: 10.1086/651430]

83 **Hunt PW**, Sinclair E, Rodriguez B, Shive C, Clagett B, Funderburg N, Robinson J, Huang Y, Epling L, Martin JN, Deeks SG, Meinert CL, Van Natta ML, Jabs DA, Lederman MM. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. *J Infect Dis* 2014; **210**: 1228-1238 [PMID: 24755434 DOI: 10.1093/infdis/jiu238]

84 **Brechley JM**, Silvestri G, Douek DC. Nonprogressive and progressive primate immunodeficiency lentivirus infections. *Immunity* 2010; **32**: 737-742 [PMID: 20620940 DOI: 10.1016/j.immuni.2010.06.004]

85 **Vujkovic-Cvijin I**, Dunham RM, Iwai S, Maher MC, Albright RG, Broadhurst MJ, Hernandez RD, Lederman MM, Huang Y, Somsouk M, Deeks SG, Hunt PW, Lynch SV, McCune JM. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. *Sci Transl Med* 2013; **5**: 193ra91 [PMID: 23843452 DOI: 10.1126/scitranslmed.3006438]

86 **Sekirov I**, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiol Rev* 2010; **90**: 859-904 [PMID: 20664075 DOI: 10.1152/physrev.00045.2009]

87 **Clemente JC**, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell* 2012; **148**: 1258-1270 [PMID: 22424233 DOI: 10.1016/j.cell.2012.01.035]

88 **Underhill DM**, Iliev ID. The mycobiota: interactions between commensal fungi and the host immune system. *Nat Rev Immunol* 2014; **14**: 405-416 [PMID: 24854590 DOI: 10.1038/nri3684]

89 **Cullen TW**, Schofield WB, Barry NA, Putnam EE, Rundell EA, Trent MS, Degnan PH, Booth CJ, Yu H, Goodman AL. Gut microbiota. Antimicrobial peptide resistance mediates resilience of prominent gut commensals during inflammation. *Science* 2015; **347**: 170-175 [PMID: 25574022 DOI: 10.1126/science.1260580]

90 **Chassaing B**, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact

the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015; **519**: 92-96 [PMID: 25731162 DOI: 10.1038/nature14232]

91 **Ellis CL**, Ma ZM, Mann SK, Li CS, Wu J, Knight TH, Yotter T, Hayes TL, Maniar AH, Troia-Cancio PV, Overman HA, Torok NJ, Albanese A, Rutledge JC, Miller CJ, Pollard RB, Asmuth DM. Molecular characterization of stool microbiota in HIV-infected subjects by panbacterial and order-level 16S ribosomal DNA (rDNA) quantification and correlations with immune activation. *J Acquir Immune Defic Syndr* 2011; **57**: 363-370 [PMID: 21436711 DOI: 10.1097/QAI.0b013e31821a603c]

92 **Lozupone CA**, Li M, Campbell TB, Flores SC, Linderman D, Gebert MJ, Knight R, Fontenot AP, Palmer BE. Alterations in the gut microbiota associated with HIV-1 infection. *Cell Host Microbe* 2013; **14**: 329-339 [PMID: 24034618 DOI: 10.1016/j.chom.2013.08.006]

93 **Yu G**, Fadrosch D, Ma B, Ravel J, Goedert JJ. Anal microbiota profiles in HIV-positive and HIV-negative MSM. *AIDS* 2014; **28**: 753-760 [PMID: 24335481 DOI: 10.1097/QAD.0000000000000154]

94 **McHardy IH**, Li X, Tong M, Ruegger P, Jacobs J, Borneman J, Anton P, Braun J. HIV Infection is associated with compositional and functional shifts in the rectal mucosal microbiota. *Microbiome* 2013; **1**: 26 [PMID: 24451087 DOI: 10.1186/2049-2618-1-26]

95 **Dinh DM**, Volpe GE, Duffalo C, Bhalchandra S, Tai AK, Kane AV, Wanke CA, Ward HD. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. *J Infect Dis* 2015; **211**: 19-27 [PMID: 25057045 DOI: 10.1093/infdis/jiu409]

96 **Lozupone CA**, Rhodes ME, Neff CP, Fontenot AP, Campbell TB, Palmer BE. HIV-induced alteration in gut microbiota: driving factors, consequences, and effects of antiretroviral therapy. *Gut Microbes* 2014; **5**: 562-570 [PMID: 25078714 DOI: 10.4161/gmic.32132]

97 **Max B**, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. *Clin Infect Dis* 2000; **30 Suppl 2**: S96-116 [PMID: 10860894 DOI: 10.1086/313859]

98 **Kartalija M**, Sande MA. Diarrhea and AIDS in the era of highly active antiretroviral therapy. *Clin Infect Dis* 1999; **28**: 701-705; quiz 706-707 [PMID: 10825021 DOI: 10.1086/515191]

99 **Chang JY**, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM, Young VB. Decreased diversity of the fecal Microbiome in recurrent *Clostridium difficile*-associated diarrhea. *J Infect Dis* 2008; **197**: 435-438 [PMID: 18199029 DOI: 10.1086/525047]

100 **Avci FY**, Kasper DL. How bacterial carbohydrates influence the adaptive immune system. *Annu Rev Immunol* 2010; **28**: 107-130 [PMID: 19968562 DOI: 10.1146/annurev-immunol-030409-101159]

- 101 **Voigt RM**, Keshavarzian A, Losurdo J, Swanson G, Siewe B, Forsyth CB, French AL, Demarais P, Engen P, Raeisi S, Mutlu E, Landay AL. HIV-associated mucosal gene expression: region-specific alterations. *AIDS* 2015; **29**: 537-546 [PMID: 25587909 DOI: 10.1097/QAD.0000000000000569]
- 102 **Belyakov IM**, Derby MA, Ahlers JD, Kelsall BL, Earl P, Moss B, Strober W, Berzofsky JA. Mucosal immunization with HIV-1 peptide vaccine induces mucosal and systemic cytotoxic T lymphocytes and protective immunity in mice against intrarectal recombinant HIV-vaccinia challenge. *Proc Natl Acad Sci U S A* 1998; **95**: 1709-1714 [PMID: 9465081 DOI: 10.1073/pnas.95.4.1709]
- 103 **Bomsel M**, Tudor D, Drillet AS, Alfsen A, Ganor Y, Roger MG, Mouz N, Amacker M, Chalifour A, Diomedede L, Devillier G, Cong Z, Wei Q, Gao H, Qin C, Yang GB, Zurbriggen R, Lopalco L, Fleury S. Immunization with HIV-1 gp41 subunit virosomes induces mucosal antibodies protecting nonhuman primates against vaginal SHIV challenges. *Immunity* 2011; **34**: 269-280 [PMID: 21315623 DOI: 10.1016/j.immuni.2011.01.015]
- 104 **Sinha B**, Rubens M. Systemic immune activation in HIV and potential therapeutic options. *Immunopharmacol Immunotoxicol* 2014; **36**: 89-95 [PMID: 24552614 DOI: 10.3109/08923973.2014.890217]
- 105 **Wada NI**, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, Martínez-Maza O, Bream JH. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. *AIDS* 2015; **29**: 463-471 [PMID: 25630041 DOI: 10.1097/QAD.0000000000000545]
- 106 **Sacchi P**, Cima S, Corbella M, Comolli G, Chiesa A, Baldanti F, Klersy C, Novati S, Mulatto P, Mariconti M, Bazzocchi C, Puoti M, Pagani L, Filice G, Bruno R. Liver fibrosis, microbial translocation and immune activation markers in HIV and HCV infections and in HIV/HCV co-infection. *Dig Liver Dis* 2015; **47**: 218-225 [PMID: 25544657 DOI: 10.1016/j.dld.2014.11.012]
- 107 **Hummelen R**, Hemsworth J, Chagalucha J, Butamanya NL, Hekmat S, Habbema JD, Reid G. Effect of micronutrient and probiotic fortified yogurt on immune-function of anti-retroviral therapy naive HIV patients. *Nutrients* 2011; **3**: 897-909 [PMID: 22254084 DOI: 10.3390/nu3100897]
- 108 **Gori A**, Rizzardini G, Van't Land B, Amor KB, van Schaik J, Torti C, Quirino T, Tincati C, Bandera A, Knol J, Benlhassan-Chahour K, Trabattoni D, Bray D, Vriesema A, Welling G, Garssen J, Clerici M. Specific prebiotics modulate gut microbiota and immune activation in HAART-naive HIV-infected adults: results of the "COPA" pilot randomized trial. *Mucosal Immunol* 2011; **4**: 554-563 [PMID: 21525866 DOI: 10.1038/mi.2011.15]
- 109 **Irvine SL**, Hummelen R, Hekmat S. Probiotic yogurt consumption may improve gastrointestinal symptoms, productivity, and nutritional intake of people living with human immunodeficiency virus in Mwanza, Tanzania. *Nutr Res* 2011; **31**: 875-881 [PMID: 22153512 DOI: 10.1016/j.nutres.2011.10.005]

- 110 **Tenorio AR**, Chan ES, Bosch RJ, Macatangay BJ, Read SW, Yesmin S, Taiwo B, Margolis DM, Jacobson JM, Landay AL, Wilson CC. Rifaximin has a marginal impact on microbial translocation, T-cell activation and inflammation in HIV-positive immune non-responders to antiretroviral therapy - ACTG A5286. *J Infect Dis* 2015; **211**: 780-790 [PMID: 25214516 DOI: 10.1093/infdis/jiu515]
- 111 **Routy JP**, Angel JB, Patel M, Kanagaratham C, Radzioch D, Kema I, Gilmore N, Ancuta P, Singer J, Jenabian MA. Assessment of chloroquine as a modulator of immune activation to improve CD4 recovery in immune nonresponding HIV-infected patients receiving antiretroviral therapy. *HIV Med* 2015; **16**: 48-56 [PMID: 24889179 DOI: 10.1111/hiv.12171]
- 112 **Nakanjako D**, Ssinabulya I, Nabatanzi R, Bayigga L, Kiragga A, Joloba M, Kaleebu P, Kambugu AD, Kamya MR, Sekaly R, Elliott A, Mayanja-Kizza H. Atorvastatin reduces T-cell activation and exhaustion among HIV-infected cART-treated suboptimal immune responders in Uganda: a randomised crossover placebo-controlled trial. *Trop Med Int Health* 2015; **20**: 380-390 [PMID: 25441397 DOI: 10.1111/tmi.12442]
- 113 **Trois L**, Cardoso EM, Miura E. Use of probiotics in HIV-infected children: a randomized double-blind controlled study. *J Trop Pediatr* 2008; **54**: 19-24 [PMID: 17878180 DOI: 10.1093/tropej/fmm066]
- 114 **Villar-García J**, Hernández JJ, Guerrero-Fernández R, González A, Lerma E, Guelar A, Saenz D, Sorlí L, Montero M, Horcajada JP, Knobel Freud H. Effect of probiotics (*Saccharomyces boulardii*) on microbial translocation and inflammation in HIV-treated patients: a double-blind, randomized, placebo-controlled trial. *J Acquir Immune Defic Syndr* 2015; **68**: 256-263 [PMID: 25469528 DOI: 10.1097/QAI.0000000000000468]
- 115 **Wilson NL**, Moneyham LD, Alexandrov AW. A systematic review of probiotics as a potential intervention to restore gut health in HIV infection. *J Assoc Nurses AIDS Care* 2013; **24**: 98-111 [PMID: 22853885 DOI: 10.1016/j.jana.2012.04.004]
- 116 **González-Hernández LA**, Jave-Suarez LF, Fafutis-Morris M, Montes-Salcedo KE, Valle-Gutierrez LG, Campos-Loza AE, Enciso-Gómez LF, Andrade-Villanueva JF. Synbiotic therapy decreases microbial translocation and inflammation and improves immunological status in HIV-infected patients: a double-blind randomized controlled pilot trial. *Nutr J* 2012; **11**: 90 [PMID: 23101545 DOI: 10.1186/1475-2891-11-90]

虽然对艾滋病防治的研究已进行了 30 多年，但有效的艾滋病疫苗和治愈方法仍然处在探索阶段。科学防治艾滋病需要我们对艾滋病本身有更深入的了解。近十年来的研究表明，肠道在艾滋病的自然发生过程中起着不可忽视的作用，可能成为艾滋病及其并发症治疗的新靶点。

研究前沿

肠道免疫系统的损伤机制、肠道免疫系统损伤的修复方法、肠道病毒存储库的建立和维持机制、肠道潜伏病毒的清除方法等是该领域亟待研究的问题。

创新盘点

系统阐述了人类免疫缺陷病毒(human immunodeficiency virus, HIV)感染中肠道黏膜屏障损伤、微生物移位、系统慢性免疫活化、以及共生微生物失调等与艾滋病疾病进展的关系。

应用要点

修复黏膜屏障、抑制微生物移位和系统免疫活化对艾滋病及其并发症的治疗具有潜在的应用前景。