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Microbiome in HIV infection

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Abstract

HIV primary infection occurs at mucosa tissues, suggesting an intricate interplay between microbiome and HIV infection. Recent advanced technologies of high-throughput sequencing and bioinformatics allow researchers to explore nonculturable microbes including bacteria, virus and fungi and their association with diseases. HIV/SIV infection is associated with microbiome shifts and immune activation that may affect the outcome of disease progression. Similarly, altered microbiome and inflammation are associated with increased risks of HIV acquisition, suggesting the role of microbiome in HIV transmission. In this review, we will focus on microbiome in HIV infection at various mucosal compartments. Understanding the relationship between microbiome and HIV may offer insights into development of better strategies for HIV prevention and treatment.

Keywords

Microbiome; HIV transmission; HIV pathogenesis; immune activation; microbial translocation

Introduction

Recent studies have demonstrated the important role of microbiota/microbiome in human health and diseases at cellular and molecular levels [1-6]. Interactions among microbes, nutrition, and immune response affect our health. For example, commensal bacteria protect the body from colonizing pathogenic bacteria by competing for space and nutrients [7]. Bacterial metabolites (i.e. indole-3-aldehyde, butyric acid, hydrogen peroxide) could indirectly shape the host immune repertoire [8, 9]. The advancement of techniques in sequencing and bioinformatics has made possible the characterization of microbial

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communities in health and diseased states. With this came an explosion of information shedding light on the important role microbiota in the human body, from nutrition and autoimmunity to its role in brain diseases [10].

An estimated 35.3 million people are living with human immunodeficiency virus (HIV) worldwide in addition to more than 2 million new cases since 2012 (UNAIDS 2013). Increasing evidence indicates microbiome plays a crucial role in HIV transmission and pathogenesis [11-13]. Alteration of vaginal and rectal microbiome may influence HIV acquisition [11, 14-16] and mother-to-child transmission (MTCT) [17]. Microbiome and immune response co-evolve in response to HIV infection during HIV pathogenesis that may determine the disease progression. Understanding the interplay between microbiome and HIV is vital for developing effective strategies for HIV prevention and treatment. This review will summarize the recent progress on microbiome in HIV transmission and pathogenesis. Although microbes are composed of bacteria, fungi, protozoa and virus, we primarily focus on bacteria due to the availability of published data.

Chronic immune activation in HIV pathogenesis

Persistent immune activation is a key feature of HIV and markers of inflammation are a better predictor of clinical outcome than viral load [18, 19]. Heightened immune activation and inflammation in HIV patients are associated with increased age-related diseases such as cardiovascular, kidney, diabetes mellitus and bone fracture in HIV patients [20, 21]. Immune activation and inflammatory markers decline with anti-retroviral therapy (ART), but always remain high compared to healthy controls [22, 23]. Natural hosts of simian immunodeficiency virus (SIV), despite high viral loads, are able to avoid chronic infection through rapid controlled immune response hence do not develop acquired immune deficiency syndrome (AIDS) [24-26].

Depletion of CD4+ T cells occurs within weeks after HIV infection, notably in the gut compartment [27-30]. Gut-associated interleukin-17 (IL-17) secreting CD4+ cells (Th17), important for mucosal defense against invading pathogens, are preferentially depleted [31-33]. Microbial translocation, translocation of microbes or microbial products without overt bacteremia, occurs after disruption of gut mucosal membrane integrity and mucosal immune homeostasis which then could cause systemic immune activation [18]. Plasma lipopolysaccharide (LPS) was elevated in HIV-infected patients and associated with an increase in plasma IFNα and frequency of activated CD8+ T cells (CD38+HLA-DR+) [18]. Despite their activation status, only small portions of these CD8+ T cells are specific against HIV [30]. Additionally, expression of program death-1 (PD-1) on HIV-specific CD8+ T cells (marker also elevated in Cytomegalovirus (CMV) and Epstein-Barr (EBV) infections) increases cell apoptosis and decreases their proliferative capacity [34]. Thus, in response to HIV infection, microbial translocation may cause chronic activation, leading to inflammatory associated pathology and immune exhaustion. Note that the cause-and-effect relationship between microbial translocation and immune activation during chronic infection remains debatable despite several studies using animal models supporting the contribution of microbial translocation to immune activation (review in [21]). While a recent study demonstrates early blockade of microbial translocation reduces inflammation and viral

replication in SIV models[35], the reciprocal interaction between microbial translocation and immune activation may contribute to SIV/HIV pathogenesis.

Microbiome shapes immune response

Microbiota has major effects on immune cells and epithelial cells at the mucosa[36]. Mice raised in a clean facility, a condition which prevents natural colonized by microbiota, have an increased mortality, bacteria burden upon challenge, and susceptibility to infection compared to counterparts raised in conventional environment[7, 37], indicating the beneficial effects of early bacterial exposure on shaping host immunity. For instance, *Lactobacillus casei* induces IgA and IL-6 producing cells in mouse gut lamina propia [38], whereas segmented filamentous bacterium (SBF) promotes the differentiation of Th17 cells in the gut [39]. In addition to the direct impact on immune response, microbes facilitate the processing and absorption of nutrients essential for immune functions such as short fatty acids (butyrate and acetate) and amino acids (tryptophan) [40]. Since different bacterial species induce different immune responses, the type of bacterial composition in the compartment could influence the balance between inflammation and homeostasis [7].

Bacterial communities are diverse and their compositions fluctuate with hormones, diet, and immune responses. They can be classified into 3 classes: 1) symbionts, bacteria known to promote health, 2) commensals, permanent residents with no known beneficial or detrimental effect to the host, and 3) pathobionts, permanent residents with possibility to become pathogenic [7]. Patients with HIV infection or other diseases have alterations of microbial compositions [41]. Opportunistic pathogens such as *Pseudomonas aeruginosa* and *Candida albicans* are frequently found in HIV-infected patients who often have low to barely detectable levels of *Bifidobacteria* and *Lactobacilli* species in the gut [42]. *Bifidobacteria* and *Lactobacilli* are known to help improve gut health and immune function [43, 44]. Prebiotics/probiotics supplements in HIV patients on ART enhanced reconstitution of CD4+ T cells in the gastrointestinal (GI) tract, improved Th17 functionality, increased functionality and frequency of antigen presenting cells (APC), and decreased markers of immune activation. Likewise, an increase in *Prevotella* with decreased *Bacteroides* was associated with increased immune activation and microbial translocation [12]. Colonization of commensal *Lactobacillus crispatus, L. jensenii*, and *L. rhamnosus* on vaginal epithelial cell *in vitro* dampened inflammatory cytokine induction via toll-like receptor (TLR) activation [36, 45]. Taken together, symbiotic/commensal bacteria modulate mucosal immune cells and maintain immune homeostasis. When symbiotic/ commensal bacteria are compromised by overgrowth of indigenous pathobionts, leading to dysbiosis, immune cells will be activated to control pathogens. Immune activation and inflammation will result in collateral damage to surrounding tissues [7, 37].

Bacterial metabolic products can modulate immune responses. For instance the lack of butyric acid, a fermentation product from butyrate producing bacteria in the gut, may lead to a decrease in regulatory T cells (Tregs) in inflammatory bowel disease [46]. In HIV patients, enrichment of gut bacteria that catabolizes tryptophan, such as *Pseudomonas fluorescens*, inhibits Th17 cell differentiation and correlates with mucosal disruption [47]. Likewise, intestinal *Lactobacilli* such as *L. reuteri* metabolize tryptophan to produce indole-3-

aldehyde, which promotes IL-22 transcription [8]. Attachment of commensal *L. crispatus* and *L. jensinii* to the vaginal epithelium down-regulates inflammatory cytokines such as IL-6, tumor necrosis factor-α (TNF-α), and IL-8 upon TLR-3 agonist polyinosinic:polycytidylic acid (polyIC) exposure, suggesting the immune-modulatory effect of colonization of commensal bacteria on epithelial cells [36]. This indicates the presence of commensal bacteria regulates immune response of epithelial cells.

Changes in microbial communities in response HIV/SIV infection and their association with immune activation have been recently documented [14, 18, 26, 42, 47, 48]. HIV-infected patients given prebiotic/probiotic supplements exhibited reduced inflammation, enhanced CD4 reconstitution and a subsequent improvement of prognosis, all highlighting the role of microbiota in HIV pathogenesis [5]. In the following sections, we summarize microbiome in various compartments in context of HIV infection.

Oral and periodontal microbiome

Oral lesions, frequently observed in HIV-positive patients without ART, are considered as indicators of disease progression [49]. Oral lesions are often the first manifestation of HIV in places where the access to regular health care or ART is limited. Periodontal pathogens are more prevalent in HIV-infected individuals [50]. Oral microbial diversity with increased levels of total *Lactobacillus* species and *Candida* species was found to be greater in HIV-infected patients than uninfected controls [41]. Conversely, HIV seropositive children have lower saliva bacterial species than uninfected children [51]. Macaques with infection by SIVmac251 intravenously had fewer oral bacterial species than uninfected animals followed by an outgrowth of *Gemella morbillorum* [52]. Certain microbial species are frequently found in HIV-infected patients but not in healthy individuals [53]. Preferential overgrowth of bacterial taxa such *Candida spp*. *Gemella*, *Streptococcus*, *Veillonella*, and *Porphyromonas gingivalis* in HIV-infected patients has been described [28, 48, 49]. Bacterial culture supernatant of *P. gingivalis* reactivates HIV infection in cells lines with latent HIV proviruses through butyric acid-mediated histone acetylation and chromatin remodeling [54]. Elevated inflammatory cytokines such as IL-6, IL-8, and granulocyte macrophage colony stimulating factor (GM-CSF) in periodontal pockets is observed in HIV-infected patients which could be immune response to opportunistic bacteria [49].

ART decreases oral lesions such as candidiasis in HIV-infected patients [49, 55], although the mechanism is not well defined. Reduction in viral load may have a direct impact on microbiota composition and oral epithelial cells. In monkeys, SIV down-regulates genes involved in oral epithelial regeneration, leading to slow healing of lesions [56]. A positive correlation between viral copies and bacterial growth has also been described [48]. In healthy rhesus macaques, *Streptococcus*, *Gemella*, and *Granulicatella* are three major genera in the lingual epithelium of the tongue dorsum, whereas *Streptococcus* and *Lachnospiraceae* are the core bacterial taxa in the dental plaque [52]. In response to intravenous SIV infection, there is a reduction of bacterial community diversity. Additionally, *Gemella* species became predominant and *Streptococcus* species were significantly reduced in the tongue dorsum. This dysbiosis is accompanied by induction of IFNγ signaling pathways in tongue tissues. In vitro stimulation of oral epithelial cells with IFNγ results in the reduction of antimicrobial

peptides, suggesting that SIV infection changes the microbial community through IFNγ-mediated down-regulation of antimicrobial peptides [52]. The findings in SIV-infected macaques are similar to those in humans. *Streptococcus* is one of the predominant commensal genera in the human lingual epithelium [57]. The outgrown of *Gemella* species is also found in HIV-infected patients [48]. Specifically, *Gemella morbillorum* is a common opportunistic pathogen in HIV-infected patients with periodontitis [28].

Gut microbiome

Enteropathy is a common disorder in HIV-infected patients with AIDS [58]. Increasing evidence strongly indicates that HIV/SIV infection alters gut microbiome. Microbial analysis of colon biopsies reveals HIV-infected patients have more *Proteobacteria* and less *Firmicutes* than uninfected individuals [12]. Further analysis at a genus level showed an increase in *Prevotella* and a decrease in *Bacteroides* in HIV-infected patients. Alteration of the microbial community is accompanied by an increase in activation of colonic T cells and myeloid dendritic cells [12]. In chimpanzees, SIV infection alters gut microbial communities which become more diverse overtime [59]. The abundances of *Staphylococcus*, *Sarcina*, and *Selenomonas* were increased in response to infection [59]. Similarly, HIV-infected patients on ART with low viral loads have reduced populations of commensal bacteria that are replaced by bacterial communities including Brachyspira, Campylobacter, Catenibacterium, Escherichia, Enterobacteriaceae, Fusobacteriaceae, Mogibacterium, Prevotella and *Ralstonia*, [60]. Total bacterial loads are similar among HIV-positive patients, HIV-positive patients on ART, and uninfected individuals. However there is a difference in microbial compositions between HIV-positive patients and uninfected group [47]. HIV-positive group exhibited a profile of enriched pathobionts (i.e. *Prevotella*, *Salmonella*, *Escherichia*, *Staphylococcus*, and *Campylobacter species*) accompanied reduced symbionts (i.e. *Clostridia* and *Bacteroides*), a microbial profile referred as disease-associated microbial communities (DMC) [47, 60]. HIV-positive patients on ART have intermediate DMC profile between untreated HIV-positive patients and uninfected individuals. ART results in a shift in the DMC that resembles microbial communities in uninfected individuals. Studies of HIV-infected patients on ART, comparing partial immunological responders (>200/ l CD4 count) and immunological non-responders (<200/ l), indicate that immunological nonresponders have increased microbial translocation with elevated circulating 16S rDNA levels of more pathogenic *Enterobacteriaceae* and less of immunomodulatory *Lactobacillus* species [61]. Enrichment of genus *Prevotella* in HIV-positive patients was associated with increased immune activation and microbial translocation [12]. *Prevotella malaninogenica* enhanced HIV-1 expression in THP-1/NL4-3luc cells by induction TLR-2 in vitro [62]. Gut mucosal dysbiosis characterized by pathobionts, a common feature in HIV infected individuals, is strongly associated with microbial translocation, immune activation, and viral persistence. The role of microbiome on the immune response inHIV-infected patients was demonstrated by administration of probiotics/prebiotics in conjunction with ART leading to improved reconstitution of CD4 T cells, enhanced IL-23 secretion and number of APC, and increased the percentage of multifunctional Th17 cells in the gut [5, 44, 63].

Altered microbiome in HIV-positive patients is also associated with high T cell activation, plasma inflammation markers (IL-6, TNF), diminished mucosal IL-17 and IL-22 secreting

cells, and increased tryptophan catabolism [47, 60]. Diminished gut Th17 CD4+ T cells in HIV are believed to be the catalyst in the disruption of mucosal barrier [42]. Indeed, Th17 cells are essential to mucosal homeostasis by orchestrating immune responses against invading pathogens and promoting mucosal barrier integrity through supporting the production of tight junction proteins and claudins [64]. Th17 cells are preferentially infected by the HIV leading to diminished numbers [31-33]. Recent evidence suggests gut microbiota may determine the fate of Th17 cells [7, 31]. *Firmicutes*, a segmented filamentous bacterium, is essential for the development of Th17 cells [39]. By contrast, the gut bacteria *Pseudomonas fluorescens* is enriched in HIV-infected patients and has the capacity to catabolize tryptophan, generating catabolites that inhibit Th17 differentiation [47]. Indolamine-2,3-dioxygenase (IDO1) generated by myeloid dendritic cells catabolizes tryptophan to skew the differentiation of Tregs over Th17 cells [9].

Gut microbiota provides the host the necessary nutrients and is critical in the development of a proper immune response [65]. A recent study by Shulzhenko et al reveals a bidirectional interaction between gut microbiota, mucosal epithelium and gut-associated B cells, whereby microbiota influences the balance between epithelial immune function and metabolic function. In the absence of IgA-secreting B cells, gut microbiota up-regulates epithelial immune functions (up-regulation IFN-induced genes and the complement system) at the expense of metabolic functions (down-regulation of lipid, carbohydrate, and micronutrients related genes) [2]. Similarly, probiotic *Lactobacillus casei* administration to mice increased IgA producing cells that were not specific to *L. casei* [38]. Gene expression analysis of duodenal biopsies from HIV-infected patients reveals there is an up-regulation of epithelial immune functions and down-regulation of epithelial metabolism, which could explain malnutrition and malabsorption found in HIV-infected patients [2]. Taken together, microbiota/microbiome not only regulates immune response but also nutrition and health in gut epithelium. It also modulates epithelial turnover, shedding, tight-junctions, apoptosis, and autophagy [66].

Rectal microbiome in HIV

Rectal transmission is the main route of HIV transmission in men who have sex with men (MSM). In 2010, 78% of new infections were among MSM (CDC). HIV infection is associated with a significant reduction in the diversity of microbial species in rectal mucosa however combined ART reverses this reduction to levels similar to healthy controls [14]. HIV-infected individuals have enrichment of *Fusobacteria, Anaerococcus, Peptostreptococcus* and *Porphyromonas* with a depletion of *Roseburia, Ruminococcus, Eubacterium, Coprococcus* and *Lachnospira* [14]. Analysis of metagenomic pathways demonstrated a down-regulation of genes related to amino acid, fructose/mannose metabolism and CoA biosynthesis [14]. Similarly, as infection progressed in HIV-positive MSMs, there was reduced alpha diversity and enrichment of *Fusobacteria* [67].

Fusobacteria, enriched in HIV-infected individuals [14, 67], are abundant in the colorectal adenoma and associated with an increase in the local cytokine milieu suggestive of mucosal inflammation [68]. *Fusobacterium* isolated from ulcerative colitis secrete n-butyric acid [69], a known HDAC inhibitor that can reactivate latent HIV [70, 71]. It remains to be determined

whether enrichment of butyric acid producing *Fusobacteria* in rectal mucosa could increase HIV transmission.

Vaginal and cervical microbiome

Most studies that associate HIV with alterations of vaginal microbiota are performed in women diagnosed with bacterial vaginosis (BV) [72-74], which is a clinical symptom caused by an imbalance of commensal bacteria in the female genital tract. The predominant *Lactobacillus* species in the vagina are replaced by overgrowth of anaerobic bacteria such as *Gardnerella*, *Atopobium*, *Prevotella* and several other taxa [72, 73]. A meta-analysis study comprising of 23 publications with a total of 30,739 women clearly indicates an association between BV and increased risk of HIV acquisition [1]. BV not only increases the risk HIV acquisition but also transmission. HIV positive women with BV are greater than 3-fold more likely to transmit HIV to their HIV negative male partners than HIV positive women without BV [11]. HIV MTCT was increased when there was alteration of vaginal microbiota to a *Gardnerella vaginalis* dominant species [17]. This clearly shows that the predominant community in a dysbiotic female reproductive tract alters environment facilitating HIV entry and transmission [75].

The vaginal microbiome comprises a dynamic ecosystem with important host defense capabilities that promote reproductive health. It is a kinetic ecosystem where the proportion of bacterial communities varies with hormonal changes, sexual activity, age, and race [10, 76]. Nevertheless, the vaginal microbiome can be classified into 7 community types. The majority of vaginal communities, types I, II, III, and V, are dominated by one or more species of *Lactobacillus* that constitute the majority of all sequences obtained, and are associated with low vaginal pH (pH 4.0-5.0) [77]. *Lactobacillus* dominance is lost in the type IV community, while *Gardnerella vaginalis* dominates the type VI community. Both types IV and VI are at higher risk for BV [72, 76]. The type VII community has high, approximately even proportions of *G. vaginalis* and *Lactobacillus* spp. *Lactobacilli* ferment glucose and produce lactic acid to maintain vaginal pH at an acidic state. The acidic pH environment is thought to prevent non-resident pathobionts from inhabiting and protects hosts against viral infection. H_2O_2-producing *Lactobacillus acidophillus* has an anti-HIV effect [78]. *Lactobacilllus species* do not trigger proinflammatory cytokine production in vaginal epithelial cells but non-resident skin bacteria *Staphylococcus epidermis* does [36].

It is not clear how BV increases HIV acquisition and transmission but it has been shown that BV increases viral shedding, increases the abundance of target cells, promotes the production of pro-inflammatory cytokines, and disrupts membrane integrity [3, 15, 79-81]. BV results in an increase in inflammatory cytokines [15] which remains present even during immunosuppressive states such as pregnancy [80]. Also, high levels of inflammatory cytokines such as IL-1β, IL-6 and IL-8 in cervicovaginal lavages (CVL) correlates with reduction of CD4 T cells [79]. Furthermore, high concentrations of proinflammatory cytokines in CVL increased HIV-1 RNA levels and viral shedding [81]. *Atopobium vaginae*, not *L. inners* nor *L. crispatus*, induce proinflammatory cytokines, antimicrobial peptides, and disrupt the mucosal barrier [13]. To summarize, vaginal dysbiosis in the setting of an

inflammatory condition such as BV could increase HIV transmission by increasing target cells at the site, disrupting the mucosal barrier, and increasing viral shedding.

Penile microbiome in HIV

Male circumcision reduces the incidences of urinary tract infection [6] and HIV acquisition [82]. Although the underlying mechanism remains to be defined, it is thought that penile foreskin, which is removed during circumcision, can trap HIV virions during sexual intercourse, increasing the opportunity for infection [6]. Additionally, the foreskin is lined with moist mucosal epithelium that provides an ideal environment for pro-inflammatory anaerobic bacteria and immune cells such as Langerhans cells (LC) and CD4 T cells, target cells for HIV infection [83]. Foreskin inflammation manifested by massive infiltrates of CD4 and CD8 T cells increases HIV infection [84]. Male circumcision significantly reduces the bacterial load, prevalence of some but not all anaerobic bacteria, and reduces microbiota diversity and composition [85, 86]. Studies have clearly shown that circumcision reduces the risk of HIV acquisition and bacterial and viral sexually transmitted infections (STIs) [87, 88]; however, the underlying mechanism remains to be defined.

Lung microbiome in HIV

Bacterial pneumonia is frequently observed in HIV-positive patients [89]. Opportunistic infections in HIV-infected patients have been attributed to their state of immunosuppression. Bacterial rDNAs are detectable in lungs of HIV-infected individuals with no respiratory symptoms [89]. Broncheoalveolar lavage of HIV-infected patients with pneumonia (from the San Francisco area) has greater a number of taxa including *Actinobacteria*, *Firmicutes*, *Cyanobacteria*, *Bacteroidetes*, and *Chloroflexi* when compared to non-HIV patients with pneumonia [90]. On the other hand, HIV-infected patients (from Uganda cohort) showed a enrichment in members of *Lachnospiraceae* and sulfur reducing bacteria (*Desulfovibrionaceae* and *Desulfuromonadaceae*) and exhibited even more diverse bacterial communities than the western cohort [91]. *Pseudomonas aeruginosa* pathogen was associated with pneumonia in the Uganda HIV cohort [91]. A metabolomics study of BAL from HIV-positive patients demonstrated increased levels of pyochelin metabolite, a by-product of *P.aeroginosa*, which was not observed in healthy individuals [92]. HIV-infected patients have a high abundance of *Tropheryma whipplei*, the causative agent of Whipple's disease, in the lung, which is significantly reduced by ART [4].

Diversity in lung microbiome between different cohorts of HIV-infected patients can be attributed to factors such as antimicrobial therapy, clinical status, ethnicity (genetics), diet and environmental exposure [91, 93]. Germ-free mice upon challenge with ovalbumin exhibited exaggerated airway eosinophilia with increased production of IgE and Th2 cytokines compared to pathogen-free mice [93]. The contribution of environmental microbial exposures to HIV pathogenesis remains to be explored.

Conclusion

HIV infection alters microbial communities in various mucosal compartments that may contribute to microbial translocation and immune activation during HIV disease progression.

Conversely, microbiomes in the genital or rectal mucosa can impact the local immune response and HIV transmission. The bidirectional cross-talk between microbiome and the immune response may influence HIV transmission and pathogenesis. Further studies delineating the interplay between microbiome and immunity will offer insight into the development of a better strategy for HIV prevention and treatment.

Acknowledgments

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Key points

- HIV infected individuals have altered microbiome associated with immune activation that impact the consequence of disease progression.
- Genital and rectal microbiome may modulate immune response and affect HIV transmission.