Microbiome in Human Immunodeficiency Virus Infection

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KEYWORDS

• Microbiome • HIV transmission • HIV pathogenesis • Immune activation
• Microbial translocation

KEY POINTS

- Individuals infected with the human immunodeficiency virus (HIV) have altered microbiome associated with immune activation that impacts the consequence of disease progression.
- Genital and rectal microbiome may modulate the immune response and affect HIV transmission.

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 (ie, 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 communities in health and diseased states. With this came an explosion of information shedding light on the important role of 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 indicate that microbiome plays a crucial role in HIV transmission

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and pathogenesis.[11–13] Alteration of vaginal and rectal microbiome may influence HIV acquisition[11,14–16] and mother-to-child transmission (MTCT).[17] The microbiome and immune response coevolve in response to 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 summarizes the recent progress on microbiome in HIV transmission and pathogenesis. Although microbes are composed of bacteria, fungi, protozoa, and virus, the authors primarily focus on bacteria because of the availability of published data.

CHRONIC IMMUNE ACTIVATION IN HUMAN IMMUNODEFICIENCY VIRUS 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 are associated with increased age-related diseases, such as cardiovascular, kidney, diabetes mellitus, and bone fracture, in patients with HIV.[20,21] Immune activation and inflammatory markers decline with antiretroviral therapy (ART) but always remain high compared with 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 and, 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 was elevated in HIV-infected patients and associated with an increase in plasma interferon α (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 on HIV-specific CD8+ T cells (marker also elevated in cytomegalovirus and Epstein-Barr virus 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 disease process 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]). Although 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 that prevents natural colonization by microbiota, have increased mortality, bacteria burden on challenge, and susceptibility to infection compared with their counterparts raised in a conventional environment,[7,37] indicating the beneficial effects of early bacterial exposure on shaping host immunity.