Lung microbiome in human immunodeficiency virus infection

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The lung microbiome plays a significant role in normal lung function and disease. Because microbial colonization is likely influenced by immunodeficiency, one would speculate that infection with human immunodeficiency virus (HIV) alters the lung microbiome. Furthermore, how this alteration might impact pulmonary complications now seen in HIV-infected patients on antiretroviral therapy (ART), which has shifted from opportunistic infections to diseases associated with chronic inflammation, is not known. There have been limited publications on the lung microbiome in HIV infection, many of them emanating from the Lung HIV Microbiome Project. Current evidence suggests that the lung microbiome in healthy HIV-infected individuals with preserved CD4 counts is similar to uninfected individuals. However, in individuals with more advanced disease, there is an altered alveolar microbiome characterized by a loss of richness and evenness (alpha diversity) within individuals. Furthermore, as a group the taxa making up the HIV-infected and uninfected lung microbiome are different (differences in beta diversity), and the HIV-infected population is more spread out (greater dispersion) than the uninfected population. These differences decline with ART, but even after effective therapy the alveolar microbiome in HIV-infected individuals contains increased amounts of signature bacteria, some of which have previously been associated with chronic lung inflammation. Furthermore, more recent investigations into the lung virome in HIV infection suggest that perturbations in lung viral communities also exist in HIV infection, and that these too are associated with evidence of lung inflammation. Thus, it is likely both microbiome and virome alterations in HIV infection contribute to lung inflammation in these individuals, which has important implications on the changing spectrum of pulmonary complications in patients living with HIV. (Translational Research 2017;179:97–107)

Abbreviations: NIH = National Institutes of Health; HIV = human immunodeficiency virus; LHMP = Lung Human Microbiome Project; ART = antiretroviral therapy; AM = alveolar macrophage; BAL = bronchoalveolar lavage; COPD = chronic obstructive lung disease; OTU = operational taxonomic unit; DNA = deoxyribonucleic acid; RNA = ribonucleic acid; PBMCs = peripheral blood mononuclear cells

INTRODUCTION

Although the lung has traditionally been thought of as a sterile organ, the use of culture-independent microbial detection methods such as 16S ribosomal RNA gene sequencing has strongly suggested that a lung microbiome is present, both in healthy[1-3] and diseased[1,4,5] populations. Recognition of the potential impact of the human microbiome on health and disease led the National Institutes of Health (NIH) to add the Human

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Microbiome Project to the NIH Roadmap in 2007. In 2009, the National Heart, Lung, and Blood Institute created the Lung human immunodeficiency virus (HIV) Microbiome Project (LHMP) to better define the lung microbiome, both in healthy individuals and those with HIV infection. This project was driven by the recognition that pulmonary complications continued to be major causes of morbidity in HIV-infected individuals even in the era of highly active antiretroviral therapy (ART).[6] Given the significant immune defects found in HIV-infected individuals, the fundamental question proposed by all sites in the LHMP consortium was whether HIV infection altered the respiratory microbiome. Almost all that is now known about the lung microbiome in HIV infection arose from work performed by investigators in this consortium, some as articles from the entire group and others as individual site research projects. In this review, we will describe what is known about the respiratory microbiome in HIV infection to date. This will include descriptions of various diversity indices in HIV-infected individuals and uninfected controls as well as the presence of over-represented or signature bacteria in the HIV-infected population. We will speculate on potential models that may explain differences in various diversity models, both between HIV-infected and uninfected individuals and changes that occur in infected individuals on ART. Finally, we will discuss how perturbations in the lung microbiome might contribute to the changing spectrum of lung complications in HIV infection in the ART era.

LUNG IMMUNE AND INFLAMMATORY ENVIRONMENT IN HIV INFECTION

Untreated HIV infection impacts all components of the pulmonary immune response.[7] In general, the alveolar environment in HIV infection is characterized by chronic alveolar macrophage (AM)[8,9] and T-cell[10,11] activation, increased concentrations of most macrophage and lymphocyte cytokines,[12] an inverted CD4:CD8 T-cell ratio in the alveolar space mostly because of an increase in HIV-specific CD8+ cells resulting in a lymphocytic alveolitis,[13-15] early preferential loss of antigen-specific memory CD4 T cells,[16-18] and high immunoglobulin concentrations[19,20] but with poor opsonic activity.[21,22]

Many of these findings are felt to be driven by the presence of HIV in the lung driving local immune and inflammatory responses. Because ART is associated with a significant decline in the lung HIV load,[23] one would expect it to have a significant impact on lung inflammation and immunity. Indeed, this is true and has been described in detail previously.[24,25] In general, ART is associated with a decrease in CD8+ lymphocytes in the alveolar space leading to a more normal CD4:CD8 ratio,[23] reduced lung T-cell activation,[26] and reduced concentrations of inflammatory cytokines and chemokines in bronchoalveolar lavage (BAL).[7,27,28] However, despite improvements in immune function, subtle defects can still be detected in HIV-infected patients on ART.[25]

LUNG MICROBIOME IN HIV-INFECTED PATIENTS WITH PNEUMONIA

Given the effect of HIV infection on pulmonary immunity, it is not surprising these individuals were susceptible to lung infections in the preantiretroviral era. In general, despite evidence of chronic macrophage and lymphocyte activation, the ability to respond appropriately to microbial challenges is impaired. As a result, before the ART era, opportunistic infections were the predominant pulmonary complication in HIV-infected individuals.[29-31] The predominance of infections in HIV-infected individuals led early lung microbiome investigators to focus on individuals with clinical pneumonia. One of the first studies compared the lung microbiome between HIV-infected individuals and uninfected controls with pneumonia undergoing diagnostic bronchoscopy with BAL.[32] Interesting findings from this study included an increased abundance of Proteobacteria in the uninfected group and increased Actinobacteria, Bacteroidetes, and Firmicutes in the HIV-infected population. Also notable was a significant increase in *Prevotella* in the HIV-infected population,[32] a finding repeatedly found in later studies. The same investigative team subsequently compared the lung microbiome in HIV-infected patients in Uganda with pneumonia to similar patients in San Francisco.[33] The major finding from this work was that the lung microbiome differed in the 2 populations, not surprising given the likely major influence of the environment on the microbiome at mucosal surfaces.[34] The San Francisco cohort lung microbiome was enriched for Firmicutes and Actinobacteria. In contrast, the Ugandan cohort was enriched for Proteobacteria. *Pseudomonas aeruginosa* was the most frequently detected pathogen in the Ugandan cohort. Not stressed was the observation that of the 2671 taxa found in the Ugandan cohort, only 33 were found in all 60 individuals. Many of these taxa belonged to the Prevotellaceae family, the second time this family of bacteria was found to be enriched in an HIV-infected population.

LUNG MICROBIOME IN HIV-INFECTED PATIENTS WITHOUT PNEUMONIA

The next series of articles examining the lung microbiome in HIV infection focused on clinically stable individuals without obvious pneumonia. Although they