Looking Higher: Is It Prime Time for the Oral–Lung Axis in HIV-related Lung Disease?

The natural history of HIV has shifted from a devastating infectious disease characterized by immunosuppression and opportunistic infections to a chronic disease dominated by comorbid conditions more commonly seen in advanced age, such as chronic obstructive pulmonary disease (COPD) and lung cancer. The immune reconstitution achieved with current antiretroviral therapy is certainly the main culprit in this change. However, the causes of the increased prevalence of many comorbid conditions in the current HIV era are not clear. For example, COPD is predominantly associated with chronic cigarette smoke exposure and primarily affects individuals >50 years old. However, HIV is an independent risk factor for COPD (1), and HIV-infected individuals with COPD are phenotypically different from the general population of individuals with COPD, being characterized by the presence of lower D_{LCO} values and 6-minute-walk test scores (2). It is now well accepted that the pathogenesis of COPD in HIV-infected individuals likely differs from that in persons without HIV. For example, studies have associated HIV-related COPD with different molecular profiles, such as PARC/CCL-18 (3), chitinase 1 (4), and alpha-1 antitrypsin (5), to name just a few. With the growth of culture-independent approaches that allow characterization of the microbiota, it seems pertinent to explore the potential role of the respiratory microbiome in HIV-related lung disease.

Probably because of the initial natural history of HIV-related lung disease, which is dominated by the immune-suppressive state and opportunistic infections, most initial investigations sought to identify distinct features of the lung microbiota in HIV-infected versus non–HIV-infected subjects. Contrary to what was initially expected, the lower-airway microbiota in HIV-infected subjects did not differ dramatically from that in control subjects. Yes, one study reported enrichment of Tropheryma *whipplei* in the lower-airway microbiota of some HIV-infected subjects (6), and another reported enrichment in oral commensals (7); however, the significance of these findings in relation to HIV-related lung disease has not been clarified yet. It may be rather naive to think that only microbes that are present in the lung mucosa are important for the pathogenesis of lung injury in this disease. It is now apparent from many models of respiratory disease that the gut microbiota can play a very significant role in lung inflammation through the conceptualized "gut–lung axis." This stems from the idea that niche (mucosa)-specific interactions between the microbiota and host may exert different effects on the host immune phenotype and, through a variety of possible mechanisms, impact the lung in different ways.

In a study presented in this issue of the *Journal*, Yang and colleagues (pp. 445–457) explored two different microbial niches to search for associations with lung function abnormalities in subjects with and without HIV who were enrolled from one participating institution in a multicenter AIDS cohort study (8). The authors evaluated the microbiota composition of two different mucosae, the oral cavity and the lower gastrointestinal tract, from which samples were obtained noninvasively. This allowed them to ask a fundamental question: Do characteristics of the microbiota in these two different mucosal niches associate with abnormalities in lung function seen in subjects with HIV? To answer this question, the authors analyzed saliva and stool samples from 75 HIV-infected subjects and 93 control subjects.

An evaluation of the oral microbiota showed significant differences between HIV-infected subjects and non–HIV-infected control subjects. Saliva samples from HIV-infected subjects had overall lower diversity but were enriched in *Veillonella*, *Rothia*, and *Streptococcus*. The authors also noted a significant effect of smoking (particularly active smoking) on the oral microbiota, as was shown in previous studies (9, 10), and this covariate was properly included in a multivariate analysis. In contrast, there were few differences in gut microbiota characteristics between HIV-infected subjects and non–HIV-infected control subjects that did not hold in the multivariate analysis.

Importantly, there were significant associations between the oral microbiota and abnormalities in lung function in HIV-infected subjects. Specifically, the presence of airflow obstruction or low D_{LCO} in HIV-infected subjects was associated with compositional differences in the oral microbiota, which was characterized by lower α diversity, and enrichment with *Veillonella*, *Streptococcus*, and *Lactobacillus*. Interestingly, the relative abundance of these three genera had a direct correlation with the plasma levels of three inflammatory biomarkers (TNF-α, endothelin-1, and MIP-1β) that were also associated with lower lung function measures. Once again, no significant associations were found between lung function abnormalities and the gut microbiota.

In this study, Yang and colleagues move away from a sole focus on microbiome differences between subjects with and without HIV, and start exploring for associations with chronic inflammatory processes that affect patients with HIV in the current era. Although we could not expect that the cross-sectional nature of this research design would allow for conclusive causal inference, the authors take the first step toward embracing the fact that we need to thoughtfully consider compartmentalization in our human microbiome studies. In doing so, we may gain a more comprehensive picture of microbiota–host interactions, both within and outside the respiratory tract, that shape immune phenotypes and potentially impact pathophysiologic mechanisms in chronic lung diseases.

Based on the current findings, it seems likely that other factors also contribute to the pulmonary dysfunction seen in subjects with HIV. Among the possible causal scenarios, it is easy to consider the oral mucosa as the microbial gateway to the lower airways, where microbes could exert direct effects on lung immune tone (11, 12) and possibly induce a low-level lung injury. Interestingly, the identified differences in oral microbiota were quite consistent across the

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reported comparisons: when adjusted for HIV-infected status, and when adjusted for current smoking, reduced FEV_1/FVC, or reduced D_{LCO} within HIV-infected subjects, saliva samples were less diverse and were enriched with three or four main bacterial genera. Although the authors adjusted for smoking in their multivariate analysis, the potential effect of active smoking cannot be fully discounted, given its direct impact on airway dysfunction and mucosal inflammation. Moreover, cigarette smoke can induce intestinal inflammation and has been associated with altered intestinal microbiota patterns (13–15) (somewhat surprisingly, the latter was not observed here, which may relate to insufficient statistical power). Nonetheless, returning to the oral cavity, it is important to consider the oral mucosa as an immunologically very active interface. Thus, dysbiotic oral microbiota signatures could exert significant distant effects, constituting a potential "oral–lung axis." Although more experimental work will be needed to discern these causal scenarios, the current investigation invites us to consider that when we look for pulmonary disease, we should think beyond a single site of microbial–host interaction. ■

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Against the Odds: Risk Stratification with Cardiac Magnetic Resonance Imaging in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare, heterogeneous disease characterized by a distinct microvascular remodeling with a concomitant increase of pulmonary arterial pressure and resistance (1). As a central pathophysiological element, the right ventricle eventually reacts to the increased load, leading from adaptation to maladaptation and beyond as eventually failure ensues (2). The state-of-the-art therapeutic strategy to address this pathophysiological progression is based on individual risk stratification (3). This risk assessment integrates pulmonary hemodynamics, symptoms, functional capacity, laboratory values, and echocardiographic parameters to classify the patient

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