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Viruses, Aging, and Chronic Lung Disease

The antiretroviral era has heralded a significant shift in lung complications recognized in the HIV-infected population. Opportunistic infections have been replaced by an increased prevalence of chronic lung diseases, including chronic obstructive lung disease, cancer, and pulmonary hypertension (1). Much of this improvement has been attributed to the immune reconstitution that comes with control of systemic viremia. As a result, patients with HIV infection now have nearly normal life spans (2). However, in this issue of the *Journal*, we are reminded that despite medical successes in the management of HIV infection, lung disease continues to be a significant cause of morbidity in this population.

In a carefully performed study, Collini and colleagues (pp. 1604–1615) examined the effect of HIV infection on intracellular killing of pneumococci by macrophages (3). They first demonstrated that infecting monocyte-derived macrophages with HIV *in vitro* resulted in significantly lower late killing of ingested pneumococci through mitochondria-mediated cell apoptosis, without altering initial pneumococci uptake and phagolysosomal killing. This was mediated through a decreased ability of pneumococci to downregulate the antiapoptotic protein Mcl-1 in HIV-infected cells, which resulted in decreased caspase 3/7 expression. Second, all of these findings were recapitulated in alveolar macrophages from HIV-infected subjects on antiretroviral therapy (ART). Third, the investigators demonstrated the persistence of viral proteins in the lungs of many patients on ART, and that exposure of monocyte-derived macrophages to gp120 alone resulted in all of the pneumococcal phagocytic and apoptotic defects seen in macrophages after exposure to whole virus. Finally, a comparison of transcriptional activity in alveolar macrophages from HIV-infected subjects and healthy volunteers showed no significant differences, although the latter result is limited significantly by the low number of subjects studied in these experiments (HIV, $n = 8$; healthy, $n = 5$).

The findings from this study are sobering on several fronts. First, the median time on ART in their study was 75 months. One would think that this is more than enough time to ensure adequate immune reconstitution, especially considering that pulmonary viral control and improvements in BAL cell CD4 counts can be seen as soon as 6 months

after starting ART (4). Second, this study is a reminder that infections are still a significant cause of morbidity in the HIV-infected population. Finally, the ability to detect viral proteins in the lungs of patients who have received more than 6 years of ART suggests there is intermittent ongoing low-level replication. It is striking that 30% and 45.5% of asymptomatic subjects on ART had detectable p24 and gp120, respectively, in BAL, especially since this is just a snapshot in time. It is likely that the ability to detect HIV proteins in the lungs waxes and wanes, increasing during times of active HIV replication such as might occur during a lung infection.

The persistence of HIV RNA and HIV proteins in the lung has significant implications for lung disease in patients with HIV. HIV infection is characterized by chronic inflammation (5), and most of the pulmonary and vascular complications that HIV-infected subjects develop in the ART era are also associated with chronic inflammation (1, 6). In fact, these are the same diseases seen in elderly populations, and HIV infection has been viewed as a model for accelerated aging (7, 8). HIV-infected subjects, including those on ART, demonstrate accelerated immunologic aging characterized by accumulation of terminally differentiated lymphocytes with reduced proliferative and immunologic function, a state frequently referred to as immunosenescence (5, 7, 8). Paradoxically, senescent lymphocytes secrete an inflammatory cytokine profile (7, 8). As a result, tissues that contain abundant senescent immune cells should be characterized by chronic inflammation.

The major driving factor in immunosenescence is chronic antigenic stimulation. With each replicative cycle, lymphocytes demonstrate telomere shortening, ultimately resulting in exhausted terminally differentiated lymphocytes with a limited ability to proliferate (9). In the presence of immunodeficiency, many persistent pathogens could promote chronic antigenic stimulation. Viruses, including HIV itself, are the most likely candidates because of their capacity to establish a latent infection in the host. Evidence linking persistent viral infections to chronic inflammation and disease is rapidly accumulating (10–12). Herpes viruses are especially prominent in this regard, with links between many chronic conditions and multiple herpes species. One could easily envision the immunodeficiency associated with HIV infection predisposing to the acquisition of many viral species. Along with HIV, these viruses could then persist in the lung and elsewhere, leading to chronic antigenic stimulation, chronic inflammation, and, ultimately, diseases now

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associated with HIV infection. In work from our lab, we have seen a significant increase in the total virome burden in the lungs of asymptomatic HIV-infected individuals compared with healthy control subjects, with various herpes virus species being a major driver of this difference (unpublished results, H. Twigg III and colleagues), and we are in the process of linking the lung virome to local inflammation and evidence of lung disease.

Not all of the news is bad. In the article by Collini and colleagues, there is a strong positive association between the BAL CD4:CD8 ratio and the ability of alveolar macrophages to undergo apoptosis after pneumococcus exposure. This suggests that pulmonary immune reconstitution can return alveolar macrophage function toward normal. Furthermore, individuals with the greatest concentrations of gp120 in BAL had the lowest peripheral blood CD4 counts. In this regard, it is notable that the mean nadir peripheral blood CD4 count in the subjects on ART was 216 cells/mm³. This in fact is a potential limitation of the study by Collini and colleagues, as CD4 levels this low are not commonly encountered these days, when early treatment with ART is the standard for HIV-infected subjects (13). Thus, the subjects in the study by Collini and colleagues demonstrated a more profound immune defect at the time of HIV diagnosis, which is known to impact an individual's ability to recover normal immune function even in the presence of good viral control (14).

The longer we live, the more likely we are to acquire viruses, many of which are capable of establishing a latent or persistent infection. Any immunodeficiency can accelerate this process. Most clinicians are already cognizant that many viruses, once acquired, are almost impossible to eradicate, including herpes viruses and papilloma viruses. For now, until the NIH HIV Cure initiative reaches its goals, so is HIV. The inability to detect viruses in blood or tissues at any one time is not synonymous with cure. Successful approaches to curing viral infections will involve not only controlling active replication but also eradicating viral stores, wherever they may lie. Only in this way can we finally get rid of potentially pathologic viruses and their proteins, and hopefully along the way abrogate the chronic inflammation that leads to disease in both HIV-infected and aging populations. ■

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Generic Respiratory Symptoms and Branded Lung Diseases Same Difference?

From time immemorial, the learned have known that most things in the universe exist along a continuum. Lesser mortals and clinicians must contend with deviations from the normal arc, and consensus thresholds for normality and the diagnosis of disease.

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In this issue of the *Journal*, Kalhan and colleagues (pp. 1616–1624) blur the boundaries of normal health and lung disease (1). There is a growing awareness that lung function later in life is substantially influenced by early life exposures, starting almost from the time of conception (2). Airway branching is complete in late pregnancy, and the branching pattern can significantly influence the likelihood of lung disease later in life (3). Airway caliber and function are influenced by early life exposures, and *in utero* exposures to environmental pollution, cigarette smoke, toxins, and stress have