Human Immunodeficiency Virus, Smoking, and Chronic Obstructive Pulmonary Disease: A Case of T Cells Stuck in the Wrong Place?

The past 20 years has seen tremendous advances in human immunodeficiency virus (HIV)–related care and survival. Though HIV infections and acquired immunodeficiency syndrome–related deaths continue to be a significant public health threat, particularly worldwide, the advent of combination antiretroviral therapies (cART) has significantly increased the number of people living with HIV (PLHIV) (1). As the number of and life expectancy for PLHIV increase, it is becoming clear that PLHIV are at an increased risk of chronic diseases, including chronic obstructive pulmonary disease (COPD) (2, 3), even when controlling for confounding comorbidities (demographics, etc.) (4, 5). Interestingly, this effect in PLHIV is still present even when controlling for tobacco use, though PLHIV are more frequently smokers (6). Increased COPD incidence has raised the question of direct HIV effects on COPD pathogenesis. Though potential mechanisms have been suggested, specific mechanisms linking HIV and COPD remain unclear. In particular, little information exists on early events in PLHIV that occur prior to the development of COPD.

In this issue of the *Journal*, Corleis and colleagues (pp. 513–520) sought to address this gap by exploring the effect of HIV and/or smoking on lung T-cell composition (7). They recruited cohorts of HIV-negative and HIV-positive individuals segregated by smoking status without evidence of lung disease. They focused on HIV-positive individuals with controlled HIV infection (cART with viral suppression for >12 mo). The cohorts underwent bronchoscopy to obtain BAL and airway brushings to define airspace phenotypes of T cells and to obtain BAL fluid for cytokine analysis.

Using flow cytometry, they determined that BAL CD4 T cells were unchanged by HIV infection but were suppressed in smokers, independent of HIV status. Alternatively, BAL CD8 cells were increased in HIV-positive nonsmokers but were suppressed in HIV-positive and -negative smokers. This suggests that HIV-positive individuals had increased BAL CD8 T cells but smoking suppressed this effect. Increased BAL CD8 T cells in HIV-positive individuals have been observed in prior studies, including cART naive HIV-positive subjects (8) and HIV-positive individuals started on cART (9). Few studies have focused on HIV-positive individuals on established ART with viral suppression, which was uniquely addressed in this study. The cumulative data support the conclusion that BAL CD8 T cells are elevated despite cART therapy. This has important implications because increased CD8 T cells are associated with COPD incidence, and animal studies suggest CD8 T-cell involvement in COPD pathogenesis. Therefore, elevated numbers of CD8 T cells in HIV could contribute to increased COPD incidence. An interesting observation not explored in this study was the extensive variation in individual BAL CD8 T-cell counts. It is possible that this is due to varied T-cell responses to cART, as interindividual variation in T-cell counts following cART administration has been described. It would be interesting to know whether individual cART responses predict BAL CD8 T-cell counts and the relationship to the risk of developing COPD.

The dominant effect of smoking on the presence of BAL CD4 and CD8 T cells independent of HIV status was another interesting observation. To explore this, the authors first asked whether there was a direct effect on T cells. They found no difference in T-cell apoptosis or proliferation among the cohorts, but the expression of lung homing receptors (CCR5 or CXCR3) was increased by smoking and HIV status. Given the lack of inherent T-cell defects, they then explored the expression of T-cell homing chemokines by determining BAL fluid CXCL10 and CCL5 concentrations. BAL CXCL10 and CCL5 were suppressed in the smokers independent of HIV status and were associated with BAL CD8 T-cell counts. To address the chemokine source, the authors focused on macrophages. Performing *in vitro* exposure of cigarette smoke extract of monocyte-derived macrophages from the cohorts, they demonstrated that the macrophages produced less CXCL10 and CCL5 following exposure to cigarette smoke extract. This was strongest for CXCL10 but was similar across the cohorts. They then went on to show a reduction in CD8 T-cell trafficking that required CXCL10 and CXCR3. This suggested that T-cell compositional alterations in smokers appear to be due to reduced macrophage-derived CXCL10 and CCL5 production, leading to reduced T-cell trafficking.

To confirm evidence of altered T-cell trafficking, the investigators defined the T-cell composition of the airway mucosa from airway epithelial brushes. In the most interesting and provocative part of the study, they determined that, in contrast to the BAL, CD8 T cells were increased in the airway mucosa of smoking and HIV-positive cohorts. In fact, the highest CD8 T-cell counts—particularly effector memory CD8 T cells—were found in the HIV-positive smoker cohort. Furthermore, this increase in CD8 T cells was associated with lung computed tomography scan abnormalities that, in turn, are associated with inflammation and remodeling. This suggests that the reduced BAL CD8 T cells in smokers could be a result of reduced trafficking that leaves T cells "stuck" at the mucosal surfaces (Figure 1). These intriguing data certainly require confirmation and a more detailed exploration. For example, the exact structural location of these T cells (i.e., within the mucosa or adherent to the airway epithelial surface) is not clear. Furthermore, the mechanism driving increased proportions of CD8 effector memory T cells in the HIV-positive smokers was also not defined. In particular, is this effect additive or synergistic, and what is the mechanism? The answers to these questions will be critical to defining how increased amounts of mucosal CD8 T cells could lead to an increased risk of COPD in PLHIV and how cigarette smoking affects that risk.

This epithelial brushing dataset provides novel insight into potential associations between PLHIV and increased COPD incidence, but it also has broader implications for our understanding of

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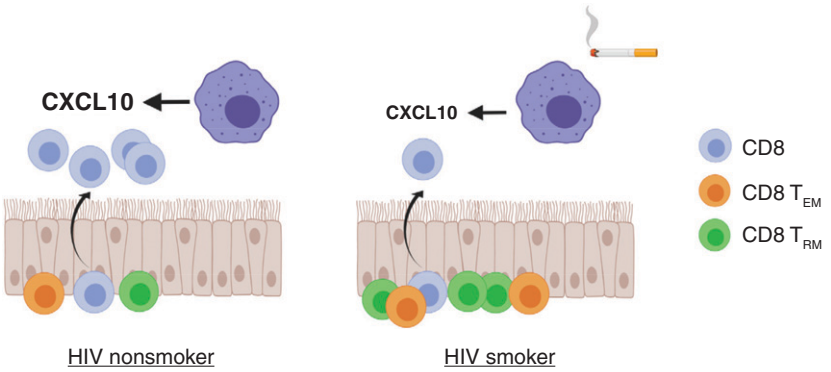

Figure 1. Overview of CD8 T-cell locations in human immunodeficiency virus (HIV)$^+$ individuals and the effect of smoking. HIV$^+$ individuals on combination antiretroviral therapy have evidence of increased BAL CD8 T cells (CD8, blue) driven by macrophage-derived CXCL10. In the airway mucosa of HIV$^+$ individuals, there are CD8 effector memory (CD8 T_{EM}, orange) cells and CD8 tissue resident memory (CD8 T_{RM}, green) cells. In HIV$^+$ smokers, numbers of BAL CXCL10 and CD8 T cells are reduced. This is associated with an increase in CD8 T_{RM} and T_{EM} in the airway mucosa. The curved line refers to the movement of the CD8 T cells (blue) into the airspace. The straight arrows refer to the production of CXCL10 by macrophages (reduced in the HIV smokers when compared to the HIV nonsmokers). The graphic was created with BioRender.com.

mechanisms directing chronic airway disease. Research continues to support the idea that immune responses are regulated within specific cellular niches and that these cellular niches can be distinct and highly specialized within tissues. These complex interactions have been highlighted by the use of increasingly complex cell culture models, including "lung on a chip," 3-D organoids, and precision lung cut slices (10). Ultimately, this research and data from new culture models suggest that we have to consider local interactions to understand the complex biology of lung disease. This has only been furthered by single cell technology and advanced bioinformatics that allow investigators to explore the "interactome" of cell–cell interactions. In the end, we may be moving to a time in which it will be insufficient to consider a whole lung cellular response as representative of the biology of that organ. Rather we must consider individual regional cellular responses and the signals they are receiving from the underlying matrix or other cells. This will become the only way to consider the origins of complex lung disease and the mechanisms that lead to their initiation, propagation, and exacerbation.

In total, this study expands on our understanding of T-cell responses in PLHIV and interactions with cigarette smoke. Future studies will need to expand on these observations, particularly as increasing numbers of PLHIV develop chronic lung disease. Most critically, this initial study begs for a prospective study to determine whether the observed BAL and mucosal T-cell changes in individuals without lung disease are predictive and causative of future incident COPD. This could allow for the identification of "at-risk" individuals and the development of targeted interventions for this group. ■

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