Premature Aging of the Airway Epithelium in Chronic Obstructive Pulmonary Disease in People Living with HIV

Epidemiologic, retrospective, and prospective cohort data show an increased frequency of chronic obstructive pulmonary disease (COPD) and emphysema in people living with HIV (PLWH) at an earlier age than in HIV-negative individuals with COPD (1–3). Why PLWH are more susceptible to the effects of tobacco smoke even when HIV replication is completely suppressed is incompletely understood. After the initial HIV infection, lung BAL cytokine concentrations remain elevated for months after complete viral suppression in the peripheral blood has been achieved, suggesting an ongoing inflammatory process (4). Moreover, airway basal cells isolated from virologically suppressed PLWH spontaneously elaborate increased concentrations of cytokines (5). This inflammatory process could result in increases in lung proteases, aggravating abnormal protease and antiprotease balance, leading to emphysematous lung destruction (6). This latter mechanism is targeted in a recently funded phase II clinical trial to determine if the antibiotic doxycycline, which is also U.S. Food and Drug Administration approved as a protease inhibitor, will slow emphysema progression in PLWH (UG3 HL154944; NCT05382208).

What is driving the ongoing inflammatory process in the lung? Despite control of viral replication, a reservoir of HIV DNA remains integrated in the host genome in susceptible cells. Is there stimulation of inflammation by low-level production of HIV gene products in the absence of viral replication (7)? There could also be defects in the ability of the immune system to shut down the inflammation via Tregs and other antiinflammatory cell types. Alternatively, antiretroviral therapy itself might have unintended adverse effects on lung cells that could accelerate COPD pathogenesis (8, 9).

Another possibility is that HIV infection and/or its treatment result in epigenetic changes in lung cells, particularly in the airways, that alter global gene expression. These DNA modifications affect gene expression at the transcriptional level and are important in chronic disease processes, including aging. The most well studied epigenetic alteration is methylation of the DNA. There is evidence of altered DNA methylation in whole lung tissue in COPD, which also correlates with disease severity (10–13), as well as in small airway epithelium (14). COPD has also been characterized as a disease of accelerated lung aging (15). Aging is closely associated with epigenetic alterations to the cellular DNA and with methylation in particular. A consequence of airway cells undergoing a premature aging process is an impaired ability of airway basal cells to differentiate into a mature airway epithelium (16). Importantly, there is evidence of accelerated aging in small airway epithelium and impaired basal cell differentiation potential in small airways of PLWH (17).

On the basis of this background, it is logical to ask if airway epithelial DNA methylation is altered in COPD in PLWH. To address this question, in this issue of the *Journal*, Hernández Cordero and colleagues (pp. 150–160) analyzed DNA methylation in small airway epithelial cells obtained from bronchoscopic endobronchial brushings performed in a cohort of PLWH with well-controlled HIV infection (18). They found major alterations in the methylation pattern of airway epithelial cells, which differed from the pattern observed in HIV-negative individuals with COPD (18). The methylation patterns correlated with estimation of aging based on estimated telomere length, gene expression, and lung function. An important control group included PLWH who were never-smokers. In comparison with HIV-negative never-smokers, PLWH have an altered methylation profile even in the absence of cigarette smoking. In addition, smoking significantly altered both the methylation and gene expression patterns in PLWH. These profiles were distinct from those of HIV-negative individuals with COPD, suggesting that COPD in PLWH may have a unique pathogenesis. Several of the significant differentially expressed genes in HIV COPD airway epithelium are involved with cellular structure, function, and development, plausibly associated with airway remodeling (18). Taken together, these observations support the concept that the accelerated COPD pathogenesis in PLWH is accompanied by premature aging in airway epithelial cells (18). These findings are even more striking in that the control participants were chronologically older than the PLWH groups. They also highlight on a molecular level why smoking cessation is of great importance in PLWH.

The study has some limitations that may limit the generalizability of the conclusions. It was a single-center study. Bronchoscopic studies by their invasive nature tend to be smaller than in other types of biological research. The number of women in the study was also relatively small, reflecting their proportion in the population of PLWH.

Increased understanding of the cell and molecular biology of lung abnormalities in PLWH who smoke is crucial to develop new targets for therapy to improve outcomes in COPD and emphysema in PLWH. Despite the limitations, the work of Hernandez Cordero and colleagues is an important step forward in this effort (18). ■

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What COVID-19 Has Taught Us
Ventilator-associated Pneumonia Is Back!

Ventilator-associated pneumonia (VAP) has been a common source of ICU infection, morbidity, and mortality for many years, but recently, the use of "ventilator bundles" and other prevention efforts has led to the belief that "zero VAP" is an achievable goal, and that many episodes of VAP are the result of medical error (1). However, since coronavirus disease (COVID-19) became a reality in our ICUs, we have seen once again high reported rates of VAP (typically 40%), and in one study, VAP was associated with a higher 28-day mortality rate in patients with COVID-19 than in those with influenza or no viral infection (2, 3). In another study of 774 patients with COVID-19, 46% had hospital-acquired infections, of which VAP was the most common (4). These data make it clear that during COVID-19, "VAP is back", and many questions have emerged (5). Was VAP ever really gone, or is COVID-19 changing its epidemiology? In the COVID-19 pandemic era, does VAP occur as often in patients without COVID-19 as in those with COVID-19? And finally, what are the mortality implications of VAP in patients with COVID-19? Specifically, is VAP a terminal event, or does it independently add to the risk of death for both individual patients and the population as a whole?

Many of these issues are addressed in a study in this issue of the *Journal* by Vacheron and colleagues (pp. 161–169) using the REA-REZO French ICU Surveillance network, including over 70,000 patients: 64,816 control patients before COVID-19, 7,442 patients in the COVID-19 pandemic without COVID-19, and 1,687 patients with COVID-19 (5). Their goal was to study VAP in each population and

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