for postbronchodilator testing (8), or the different geographic location (South America), may explain some of the differences.

Overall, this study provides valuable new information, as well as the opportunity for the authors and others to initiate additional studies to examine diverse populations and settings and to determine if the findings in this study are relevant beyond Sweden. Then we will know with greater certainty whether postbronchodilator reference values should be the new norm. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Unraveling the Distal Lung Destruction in Emphysema

The landmark study by Booth and colleagues (pp. 472–486) in this issue of the *Journal* hones our understanding of the loss of the terminal conducting airways and gas exchange areas in chronic obstructive pulmonary disease (COPD) by applying single-cell analyses of lung tissue from well-phenotyped individuals (1). The investigation builds on this group's previous discovery (2) that the terminal bronchioles, the smallest conducting airways, are the early battlegrounds of tissue destruction in COPD.

The study's ambitious objective was to create a comprehensive blueprint that sheds light on the structural, cellular, and extracellular matrix changes underpinning terminal bronchiole loss in COPD. The cross-sectional evaluation of more than 200 terminal bronchioles from 109 lungs of individuals with mild to moderate COPD and 24 with severe COPD, as gauged by Global Initiative for Chronic Obstructive Lung Disease criteria, compared with 82 lungs from ex-smokers without lung dysfunction used a multifaceted approach that included stereology, micro-computed tomography, nonlinear optical microscopy, imaging mass cytometry, and transcriptomics. Their findings unveiled that in addition to a net loss, the terminal bronchioles progressively narrow as COPD severity increases, a phenomenon marked by the loss of elastin fibers within alveolar attachments. The pathology of alveolar untethering was noticeable even in the early stages of the disease in the absence of emphysematous alveolar loss, suggesting that this step is one of the first events in the hallmark distal lung destruction of emphysema. Although the concept of matrix elastin and collagen fiber degradation has been the forefront paradigm of protease–antiprotease imbalance of emphysema pathogenesis for decades (3, 4), this report refines our understanding of its spatial and temporal association with centrilobular distal lung destruction.

Furthermore, the single-cell atlas identified inflammatory and immune cells concentrated in this region of interest, with proinflammatory M1-like macrophages and neutrophils being located within disrupted alveolar attachments, whereas adaptive immune cells such as naive T cells, CD4 and CD8 T cells, and B cells were adjacent to terminal bronchiole wall remodeling. The genetic landscape was also consistent with upregulation of genes involved in both innate and adaptive immune responses, IFN response, and neutrophil degranulation. The proximity of macrophages and degranulating neutrophils to areas of matrix disruption is consistent with the mechanistic involvement of matrix metalloproteinases and neutrophil elastase and other proteinases in distal lung destruction (5–7). With our increased appreciation of the lung macrophage heterogeneity, future studies will have to build on expanding on the phenotyping of macrophages associated with disruption of alveolar tethers. Potential candidates are $CD206^{+}/CD43^{-}$ interstitial

Supported by NHLBI grant R01HL077328.

Originally Published in Press as DOI: 10.1164/rccm.202307-1198ED on July 14, 2023

macrophages, which were found to be increased in the alveolar septae of the lungs of smokers compared with nonsmokers (8). The study by Booth and colleagues indicates progressive changes in the cellular heterogeneity of terminal bronchioles, enriched in inflammatory and immune cells in milder disease with a relative paucity of these cells in more severe COPD. The finding of an apparent exuberant immune cell activity in the distal lung early in the disease course substantiates the importance of the immune response in its development (9). However, because not all individuals with mild COPD progress to severe emphysema, this cross-sectional evaluation leaves unanswered the question of whether all the herein identified immune effector cells are causal to the untethering and remodeling of the terminal bronchiole or whether they contribute to the maintenance and repair of the distal lung. Although it is remarkable that the present study of 33 cell markers enabled the mass cytometric identification of 21 cell types composing the distal lung, their functionality as well as that of other cells that have not been systematically evaluated in the present study remains to be explored in more detail by future investigations. Indeed, many of the cellular responses implicated in distal lung cell destruction and repair (10, 11), such as oxidative stress, autophagy, mitochondrial dysfunction, senescence, progenitor cell exhaustion, and various types of programmed cell death, have not been explored. Also notable is the enrichment of the terminal bronchiolar region in unique cell types that may have a role in protecting this vulnerable and critical area at the junction of conducting airways and the alveolar gas exchange surfaces, including secretory cells and various types of progenitor or reparative cells (12–15).

This report marks a significant step forward in our quest to unravel the complexities of COPD pathogenesis and underscores the urgency to better understand the mechanisms and develop strategies that target the pathological changes involving the terminal bronchiole. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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