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Small Airways in Idiopathic Pulmonary Fibrosis: Quiet but Not Forgotten

The quiet zone, a term coined by Jere Mead in 1970 to reference small conducting airways in the lung, denotes the fact that disease can accumulate in this anatomical region while remaining clinically silent and undetectable by either patients or their clinicians (1). Although the role played by loss of small airways in chronic obstructive pulmonary disease is widely recognized, the importance of these airways in idiopathic pulmonary fibrosis (IPF) is less well appreciated.

The current pathogenic paradigm in IPF postulates that the disease arises because of premature senescence of alveolar epithelial cells following repetitive alveolar injury in genetically susceptible individuals (2). This gives rise to an aberrant wound healing response that favors accumulation of extracellular matrix and abnormal remodeling of the lung. The alveolus and the alveolar epithelium have long been center stage in the search for the initial site of injury in IPF. Ultrastructural studies consistently report damage, necrosis, and apoptosis of alveolar epithelial cells with associated denudation of the basement membrane (3). In animal models, the selective induction of apoptosis of type II alveolar epithelial cells triggers the development of fibrosis (4). Similarly, interfering with reepithelialization of the alveolus after acute lung injury results in an exaggerated fibrotic response (5). Clinically, the absence of airflow obstruction in IPF has been taken to infer that the disease is confined to the alveolus.

More recent data have called into question the primacy of alveolar injury and disruption of the alveolar epithelium as the initial lesion of IPF. Genetic studies have identified a gain-of-function polymorphism in the promotor region of the gene for MUC5B as the most commonly occurring risk allele for IPF (6). MUC5B encodes a mucin expressed by the epithelium lining respiratory bronchioles. Although the mechanism by which excessive mucin production gives rise to IPF is unknown, it has been proposed that that accumulation in distal respiratory bronchioles leads to retention of injurious particles, resulting in focal and persistent injury, repair, and regeneration at the bronchoalveolar junction (7). Further evidence for a role of small airways in IPF pathogenesis comes from studies of single-cell transcriptomics performed on explant lungs (8). These have shown marked changes in the expression profile of numerous epithelial cell types in the fibrotic lung in comparison to healthy control lungs and identification of two unique Club-cell populations.

A recent study by Verleden and colleagues used a variety of techniques to make a detailed assessment of the full bronchial tree in IPF explant lungs (9). The authors demonstrated that small airways <2 mm in diameter show increased visibility owing to airway wall thickening and distortion of the airway lumen. At the same time, micro–computed tomography (CT) demonstrated a 60% reduction in terminal bronchioles in IPF lungs compared with healthy control lungs. This reduction was equally evident in regions of minimal fibrosis and areas of dense established fibrosis. The extent of small airway loss was not affected by pack-year smoking history.

In the current issue of the *Journal*, Ikezoe and colleagues (pp. 1048–1059) publish a further exploration of the relationship between small airway loss and fibrosis in IPF (10). Using microCT and by undertaking a systematic uniform random sampling approach within whole explant lungs, the authors were able to assess the full spectrum of disease in lungs from donors with IPF. In keeping with the prior study, Ikezoe and colleagues demonstrate that in IPF lungs compared with age-matched controls, numbers of terminal bronchioles and respiratory transitional bronchioles are significantly reduced, and terminal bronchiole airway walls thickened even in regions lacking evidence of parenchymal fibrosis. In regions of fibrosis, the terminal bronchioles have thicker walls and dilated and distorted lumens, which lead to the formation of honeycomb cysts. Although the study was performed in end-stage explant lungs, the authors took advantage of the heterogeneity of fibrosis in IPF to postulate that small airway loss occurs early in the evolution of IPF and that it appears to precede the development of fibrosis.

The study does have a number of limitations, not least of which is that the authors had to rely on explant lungs to conduct their assessment of IPF lung tissue. This is understandable given that adequate samples of lung tissue are not generally available in any circumstance apart from after lung transplant. The number of lungs studied was small, but the authors ensured, as far as possible, that these were well matched. A lack of longitudinal sampling (again challenging given the techniques involved) raises the possibility that a loss of small airways in early life may predispose to IPF development rather than necessarily representing a step in the pathogenesis of the disease. It is to be hoped that technological improvements in the resolution of CT imaging will enable these questions to be addressed in the future.

Ikezoe and coworkers are to be congratulated on providing robust evidence for an important role of the small airways in the earliest stages of the development of IPF (10). Their study has a

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number of important implications. First, from a clinical perspective, early loss of small airways helps to explain why patients with IPF usually have significant loss of D_{LCO} even when presenting with minor symptoms. This, in turn, reiterates the need for clinicians to consider early therapy given that such loss is likely irreversible. Second, their data provide potential insights into the role played by MUC5B in the pathogenesis of IPF. Third, the observation that loss of small airways is a feature of a range of respiratory diseases, including chronic obstructive pulmonary disease, cystic fibrosis, and IPF, highlights the importance of ensuring good lung health, especially during lung development. Finally, knowing that small airway loss is important in the development of IPF provides an opportunity for new therapeutic strategies.

Although the small airways of the lung can be considered the quiet zone, they should not remain a forgotten zone. Knowledge that loss of these important terminal airways occurs early in the evolution of IPF should serve as a wake-up call for the respiratory community to better understand the determinants of optimal development of small airways and to identify what can be done to prevent their premature loss in chronic respiratory disease. ■

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Breathing Hope into Directed Therapy for Pulmonary Infections

Empiric therapy for respiratory infections, including pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD), has remained the norm despite decades of promise that new diagnostic techniques and platforms would deliver clinicians accurate, timely, and affordable information on the pathogen(s). Although microbiological tests have been part of our standard of care for patients at risk of unusual or antibiotic-resistant pathogens, they have had little to no impact on initial therapy. As each successive pneumonia guideline has pointed out (1, 2), there is no evidence that traditional diagnostic offerings from the laboratory have any meaningful impact on patient outcomes or clinician behavior in usual settings. Equally, in the setting of acute exacerbations of COPD, it is well recognized that although viral pathogens are extremely frequent, there is substantial overuse of antibiotics owing to clinical uncertainty over the pathogen(s). Although recently some small gains had been made, such as the use of rapid-diagnostic platforms to screen for methicillin-resistant *Staphylococcus aureus* (3), the sense of promise molecular methods engendered in the 1990s still remained to be realized.

Then, along came coronavirus disease (COVID-19) and changed the world's perspective on the importance of having the ability to rapidly determine the pathogen(s) in play. In the last 18 months, we have seen a massive uplift in the capability of "ordinary" hospitals to rapidly process respiratory samples, driven by clinical need and

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