The Airway in Idiopathic Pulmonary Fibrosis: Protecting the Lung or Promoting Disease?

Idiopathic pulmonary fibrosis (IPF) is a progressive and often fatal disease characterized by the histologic presence of usual interstitial pneumonia in the absence of identifiable associated exposures or conditions (1). Current paradigms propose that IPF results from chronic alveolar epithelial cell injury coupled with excessive fibroblast activation (1). The last decade has seen a remarkable change in the understanding and management of IPF. Basic scientists have expanded the understanding of epithelial injury to include mitochondrial dysfunction and aging (1, 2). Groundbreaking translational work has facilitated new insight into the role that mechanotransduction and epigenetics might play in fibroblast activation (3). High-throughput transcriptomics (4) and genetic profiling combined with pharmacogenomics (5) have renewed appreciation of the putative contribution of innate and adaptive immune responses to pathologic remodeling. Perhaps most importantly, the indefatigable efforts of the IPFnet and industry investigators have culminated in the cessation of potentially harmful treatments and the U.S. Food and Drug Administration approval of two new antifibrotic agents (6).

One particularly surprising advancement is the increasingly recognized association of airway epithelial biology with IPF. For example, variants of *MUC5B*, a gene encoding the mucin-producing protein mucin-5B, confer both a higher risk of IPF and a more indolent clinical course (7). Additionally, PLUNC is overexpressed in lung biopsy samples from patients with progressive IPF (8), differential expression of cilium genes may lead to the development of microscopic honeycombing (9), and the recapitulation of certain developmental pathways has been observed in the IPF airways (10). However, to date, the putative mechanism through which the airway might be involved in IPF—an entity that is defined by a relative lack of bronchocentricity (1)—has remained obscure.

In this issue of the *Journal*, Mathai and colleagues (pp. 1151–1160) shed light on this area in their studies of the Desmoplakin (*DSP*) gene in IPF (11). DSP is an essential protein for desmosome functions, including cell adhesion, wound closure, and epithelial integrity, that is expressed by airway epithelial cells in the mammalian lung (12). In a prior genome-wide association study conducted by this group, they had demonstrated variants in introns 1 and 5 of the *DSP* locus to be associated with IPF. In this study they sequenced the *DSP* locus in a discovery cohort of 230 IPF samples and 228 control samples and identified five single nucleotide polymorphisms that were genotyped in a large validation cohort, where the intron 1 variant rs2744371 was protective against IPF and the intron 5 variant rs2076295 conferred an increased risk for IPF. Using samples from the Lung Tissue Research Consortium, they evaluated *DSP* mRNA and immunolocalization, where, relative to control lungs, the IPF lung showed increased *DSP* expression that localized to airway epithelial cells and cystic structures within fibrotic regions. Interestingly, unlike control lungs, *DSP* expression in the IPF lung did not decrease with age. When exploring *DSP* expression among variants, only the intron 5 variant rs2076295 was accompanied by decreased *DSP* expression in both IPF and control lungs, with a higher number of copies of the minor allele associated with lower expression. When viewed in combination, this study suggests that differential expression of *DSP* by airway epithelial cells, especially intron 5 variant rs2076295, is associated with IPF pathogenesis.

Although important, this manuscript leaves many unanswered questions regarding the relationship of *DSP* and IPF. Because overall expression of *DSP* was higher in disease, but the intron 5 mutation resulted in lower expression, further work is required to understand the role of *DSP* and its mutations in IPF, particularly whether *DSP* mutations are causative. In fact, the increased expression of *DSP* noted in IPF might simply reflect relative persistence of the airway in the context of parenchymal obliteration. Because aging is a risk factor for this disease, it was interesting that the authors did not discern a relationship between *DSP* expression and age in their IPF cohort. In addition to the development of *ex vivo* modeling systems to study the contribution of *DSP* to disease, molecular studies could help characterize how this intronic mutation might result in the altered detection of mature protein in the IPF lung. It will also be important to determine whether abnormal *DSP* promotes fibrosis, as is believed for *DSP* mutations in the clinical settings of right ventricular dysplasia and certain skin disorders (12), or is a protective response, as has been recently proposed in the clinical setting of lung cancer, where DSP protein appears to possess tumor-suppressive functions (13). In terms of clinical management, correlating *DSP* variants with clinical outcomes might impact both lung transplant allocation and/or pharmacogenomic approaches to antifibrotic therapy. Last, it would be worthwhile to conduct studies of *DSP* variants in other interstitial lung diseases, similar to those performed in scleroderma-associated interstitial lung disease and sarcoidosis that have helped delineate *MUC5B*'s potential specificity to IPF (14).

The study by Mathai and colleagues (11) also informs the paradigm of IPF pathogenesis, supported by previous ultrastructural studies of IPF lungs and biomarker studies, that suggests the initial injury to the lung occurs in the alveolar epithelium (1, 2). The finding of mutations in a gene expressed predominantly in the airway indicates that this tissue compartment may either participate in repair of the injured alveolus or contribute to disease. The potential validity of these hypotheses is supported by studies demonstrating recapitulation of the developmental pathways in the airways of patients with IPF (10) and could be further verified in immunodetection studies of DSP colocalized with markers of lineage, injury, and repair. It is also possible that the airways participate in fibrosis via additional processes including, but not limited to, the orchestration of inflammatory and immune responses, the paracrine production of soluble secretory mediators, and/or the recruitment and activation of fibroblasts. Considering the increasingly recognized overlap between chronic obstructive pulmonary disease and IPF (15), it will be important to understand the mechanisms through which the airways and the alveoli interact in the setting of pathologic lung remodeling in both its inadequate and excessive forms.

In conclusion, Mathai and colleagues (11) support both the concept of genetic heterogeneity in IPF as well as the potential role

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of the airway in diffuse parenchymal lung disease. Defining the role of *DSP* variants in these contexts may significantly impact our understanding of whether the airway protects against, or in part promotes, the development of IPF. ■

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Mortality Related to Surgical Lung Biopsy in Patients with Interstitial Lung Disease

The Devil Is in the Denominator

When a patient with interstitial lung disease (ILD) needs a definitive diagnosis, a histopathologic pattern obtained by surgical lung biopsy (SLB) is frequently required. However, similar to any diagnostic procedure, the decision to pursue SLB requires a careful weighing of its risks and benefits. The risks of SLB typically include morbidity, as well as in-hospital and 30-day mortality. With the advent of video-assisted thoracoscopic SLB in the 1960s and its widespread adoption in the following decades, the risks associated with SLB have been felt to be quite low, although good data that are generalizable to a broad population of patients have been difficult to identify. The available data are almost entirely retrospective, limited by lack of uniform inclusion criteria and systematic characterization of the patient population, and often missing in details on characteristics

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