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REVEALING THE SECRETS OF IDIOPATHIC PULMONARY FIBROSIS

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Embedded in the diagnosis of Idiopathic Pulmonary Fibrosis (IPF) is the long-standing belief that this progressive fibrotic lung condition arises spontaneously and its cause is unknown [1]. While the exceptional work of Nureki and colleagues [2] chips away at this fundamental concept, these investigators have also created a translational model that may accelerate drug discovery for a disease that often results in death within 3-5 years [1].

IPF is a complex phenotype, typified by clinical, etiologic, and molecular heterogeneity. In fact, the radiographic and pathological features of usual interstitial pneumonia (UIP) require heterogeneity to definitively diagnose IPF [1]. Gene variants (rare and common sequence variants in 7 genes [*MUC5B*, *TERT*, *TERC*, *RTEL1*, *PARN*, *SFTPC*, and *SFTPA2*; [3-11]] and in at least 12 novel loci [12,13]), environmental exposures (asbestos and microorganisms), and immune conditions (rheumatoid arthritis and scleroderma;[14]) place individuals at risk of developing the radiographic and pathological features of UIP. The more common risk factors, such as age, male sex, cigarette smoking, and the *MUC5B* promoter variant predispose individuals to develop phenocopies of IPF [3], including rheumatoid arthritis associated interstitial lung disease (RA-ILD) [15] and chronic hypersensitivity pneumonitis [16]. The heterogeneity of IPF is highlighted further by the multiple emerging epigenetic [17] and transcriptional [18-20] profiles reported in this disease. The collective clinical, etiologic, and molecular heterogeneity of IPF suggests that this disease represents a nonspecific response to recurrent environmental and endogenous injury in a susceptible host that is unable to resolve the progressive fibrotic response due to defects in one or several key mechanisms involved in lung homeostasis. Consequently, integrating key etiologic attributes (genetic susceptibility, environmental exposures, and autoimmunity) with known mechanisms of disease, such as host defense, bronchoalveolar cell function, cell senescence, and lung repair could establish a roadmap for more effective treatment of early and established disease (Figure 1).

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Competing Interests

D.A.S. is the founder and chief scientific officer of Eleven P15, a company focused on the early diagnosis and treatment of pulmonary fibrosis. D.A.S. has patents awarded (US Patent no: 8,673,565) and submitted (US Patent application no: 62/250,390, US Patent application no: 62/525,087, and US Patent application no: 62/525,088) for the treatment and diagnosis of fibrotic lung disease. D.A.S. serves on the scientific advisory boards of Apellis Pharmaceuticals, NuMedii, and Pliant Therapeutics, and has consulted for Arrowhead Pharmaceuticals and Pieris Pharmaceuticals.

To understand further the mechanisms that induce pulmonary fibrosis, Nureki and colleagues [2] focused on surfactant protein C gene (*SFTPC*) -associated pulmonary fibrosis. While *SFTPC* mutations are unusual in patients with IPF, they are more often observed in children with interstitial lung disease (ChILD) or families with early onset of interstitial lung disease [9,21-27]. Nevertheless, understanding how mutations in *SFTPC* cause pulmonary fibrosis could more generally advance our understanding of the etiology and pathogenesis of IPF. Nureki pursued this research by introducing a missense substitution (1286T>C) of the surfactant protein C gene ($SFTPC^{I73T}$) into mice and regulating the expression of this mutant gene in type II alveolar epithelia (AT2). This gain-of-function rare variant involves the C-terminal or BRICHOS domain of proSP-C, and is the most common *SFTPC* mutation in humans with *SFTPC*-associated ILD. Their results demonstrate that this single missense substitution results in the spontaneous development of lung fibrosis, presumably caused by altered intracellular trafficking of surfactant protein C proprotein, defective proteostasis, impaired mitophagy, and enhanced macroautophagy (but not apoptosis) of AT2 cells. These molecular events were associated with the spontaneous development of acute alveolitis with overexpression of IPF biomarkers (SP-D, MMP-7, OPN, and IL-6), and fibrotic remodeling, including hyperplasia of AT2 cells but no specific features of UIP. Hence, Nureki and colleagues [2] have demonstrated the potential role of surfactant protein C and AT2 cells in the development of pulmonary fibrosis, and by pursuing functional genomic strategies, these investigators have developed a spontaneous model of interstitial lung disease that may prove useful as a translational platform for IPF.

Surfactant protein C is a hydrophobic peptide with a number of biologic functions related to its ability to lower surface tension at low lung volumes, including facilitating the spreading and adsorption of the phospholipids comprising surfactant at the air/liquid interface, variably inserting into the phospholipid monolayer as a function of surface tension, facilitating re-spreading of surfactant following alveolar compression at low volumes, and promoting surfactant recycling. Numerous investigators have noted that alveolar collapse and collapse induration are involved in the pathogenesis of pulmonary fibrosis [28], and both alveolar collapse and collapse induration will increase in the absence of normally functioning surfactant or impaired AT2 cell production or recycling of surfactant. The chronic endoplasmic reticulum stress resulting from cyclical airspace opening and closing of atelectatic alveoli, and/or from over-distension of alveoli adjacent to areas of collapse induration may explain the peripheral, heterogeneous distribution, and the progression of the fibrotic lesions in IPF.

The intriguing work of Nureki and colleagues [2] has solidified some of the basic concepts in pulmonary fibrosis, created a translational model of fibrotic lung disease, and reinforced the importance of genetic targets in understanding the etiology and pathogenesis of this disease. More specifically, their research has reinforced the importance of AT2 cell injury in the initial stages of pulmonary fibrosis. As emphasized in the associated editorial [29], their research also demonstrates that endogenous defects in cellular function, as well as those induced by environmental exposures, can cause recurrent microscopic injury to the alveolar space, and poorly functioning AT2 cells can serve as initiating, and perhaps recurrent events in the fibroproliferative process. Although no murine model has yet recapitulated the complex heterogeneity and pathogenesis of IPF, the spontaneous model of *SFTPC*-

associated ILD created by Nureki and colleagues [2] will undoubtedly prove valuable in understanding the biology of pulmonary fibrosis and developing novel drugs for this progressive disease.

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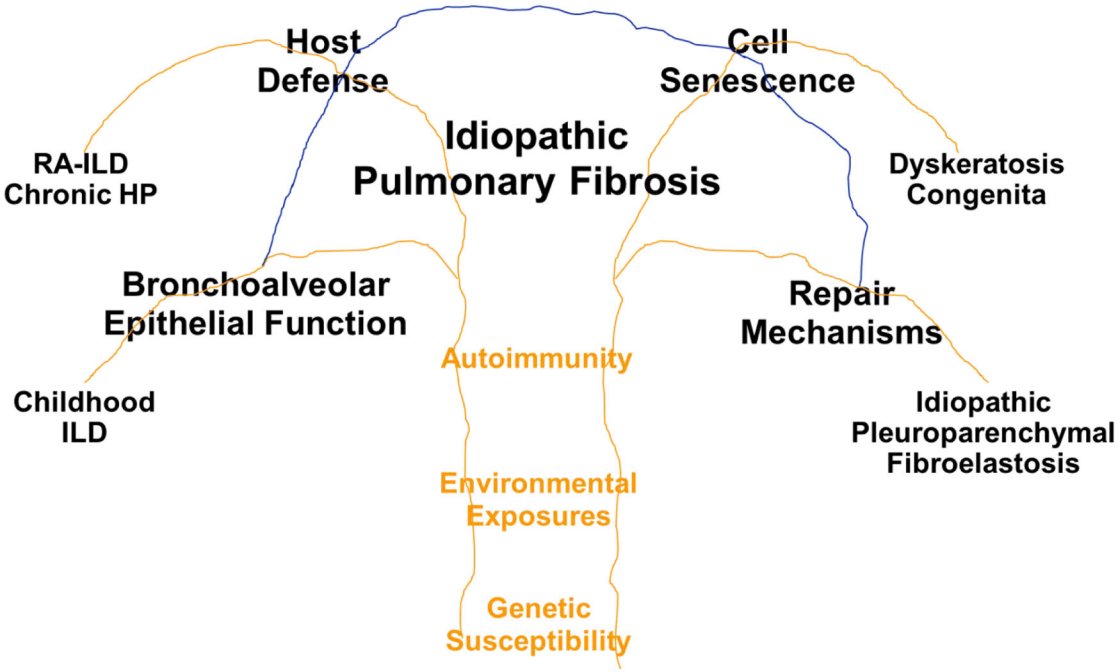

Figure 1.

IPF is a heterogeneous disease, caused by abnormalities in host defense, bronchoalveolar cell function, cell senescence, and lung repair, all of which are affected by genetic variants, environmental exposures, and autoimmunity. While each of these biological processes can fail substantially and result in unique types of lung fibrosis (ChILD, RA-ILD, chronic HP, dyskeratosis congenital, or idiopathic pleuroparenchymal fibroelastosis), it is likely that most cases of IPF occur in those with mild to modest defects in one or several of these key mechanisms of lung homeostasis.