CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Revealing the Secrets of Idiopathic Pulmonary Fibrosis

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Embedded in the diagnostic term idiopathic pulmonary fibrosis (IPF) is the long-standing belief that this progressive fibrotic lung condition arises spontaneously and that its cause is unknown. Nureki and colleagues[1] have recently challenged this fundamental concept by creating a translational model that may accelerate drug discovery for IPF, a disease that often results in death within 3 to 5 years.

IPF has a complex phenotype that is manifested by clinical, etiologic, and molecular heterogeneity. In fact, heterogeneity in the radiographic and pathologic features of usual interstitial pneumonia is required for the definitive diagnosis of IPF. Rare and common variants in seven genes, including in *MUC5B*, and at least 12 loci have been associated with IPF, as have environmental exposures (e.g., asbestos and microorganisms) and autoimmune conditions (e.g., rheumatoid arthritis and scleroderma). Each of these associated factors increases the risk of the development of the radiographic and pathologic features of usual interstitial pneumonia. The more common risk factors of IPF, such as older age, male sex, cigarette smoking, and the *MUC5B* promoter variant, also confer a predisposition to the development of IPF-like disease, including rheumatoid arthritis–associated interstitial lung disease[2] and chronic hypersensitivity pneumonitis. The biologic heterogeneity of IPF is further highlighted by the multiple emerging epigenetic and transcriptional molecular phenotypes of this disease. The collective clinical, etiologic, and molecular heterogeneity of IPF suggests that this disease represents a response to recurrent environmental and endogenous injury in a susceptible host, in whom the progressive fibrotic response cannot resolve because of defects in one or several key mechanisms involved in lung homeostasis. Consequently, the integration of key risk factors (genetic susceptibility, environmental exposures, and autoimmunity) with known mechanisms of disease, such as host defense, cell senescence, bronchoalveolar cell function, and lung repair, could establish a roadmap for more effective treatment of early and established disease (Fig. 1).

Nureki and colleagues focused on pulmonary fibrosis associated with a variant in the surfactant protein C gene (*SFTPC*). *SFTPC* mutations are unusual in patients with IPF and are more commonly observed in children with interstitial lung disease or in families with a history of early onset of interstitial lung disease. Nevertheless, understanding how mutations in *SFTPC* cause pulmonary fibrosis could more generally advance our understanding of the pathogenesis of the disease. Nureki et al. introduced a missense substitution (1286T→C) into the mouse orthologue of *SFTPC* (*Sftpc*^{173T}), regulating the expression of this mutant gene in type 2 alveolar (AT2) epithelial cells, which secrete surfactant proteins. This rare gain-of-function variant is the most common *SFTPC* mutation in humans with *SFTPC*-associated interstitial lung disease. The study showed that this single missense substitution resulted in the spontaneous development of lung fibrosis, presumably caused by altered intracellular trafficking of surfactant protein C proprotein, defective proteostasis (the maintenance of protein levels through folding, trafficking, and degradation), 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 as well as fibrotic remodeling, including hyperplasia of AT2 cells, but no specific features of usual interstitial pneumonia. These findings highlight the potential role of surfactant protein C and AT2 cells in the development of pulmonary fibrosis, and by pursuing functional genomic strategies, these investi-

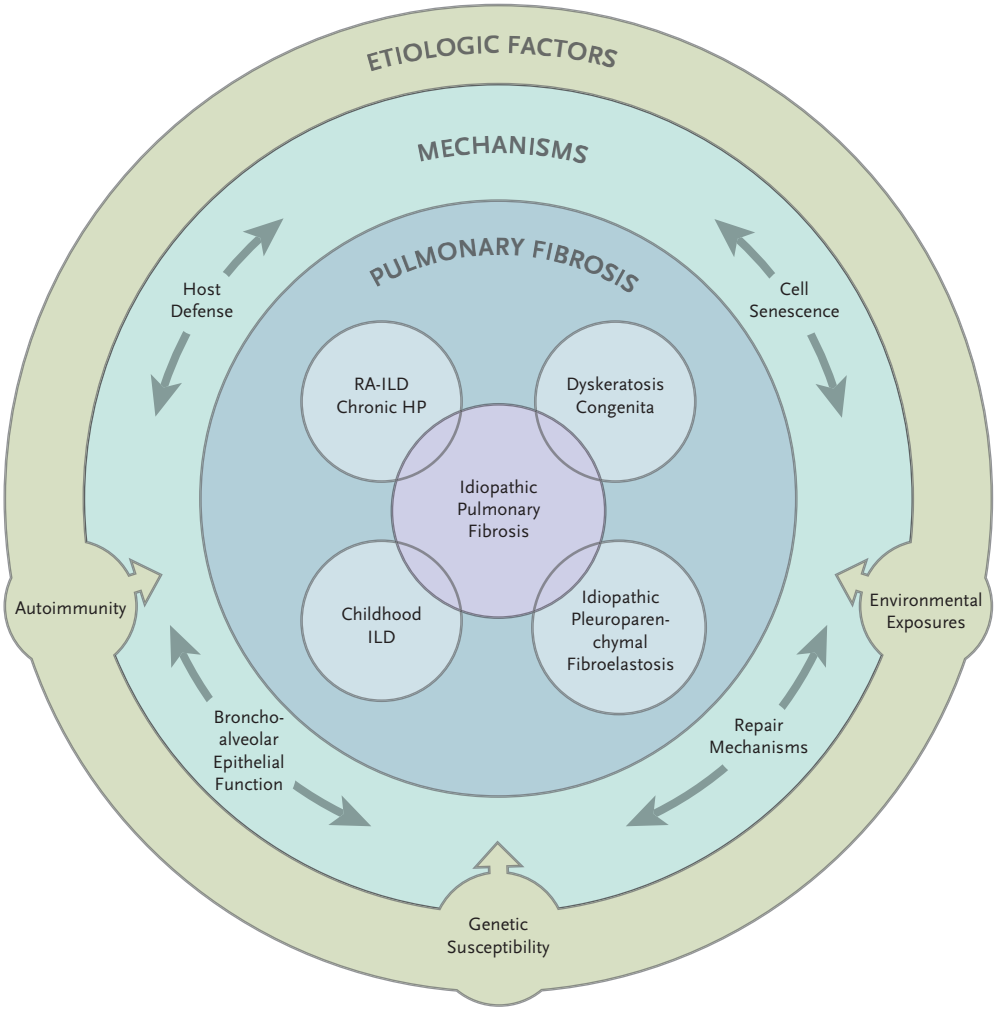

Figure 1. Toward an Understanding of Idiopathic Pulmonary Fibrosis (IPF), a Multifactorial Disease.

IPF, a heterogeneous disease, is caused by abnormalities in host defense, cell senescence, bronchoalveolar cell function, and lung repair, all of which are affected by autoimmunity, genetic variants, and environmental exposures. Although each of these biologic processes can fail substantially and result in unique types of lung fibrosis (rheumatoid arthritis–associated interstitial lung disease [RA-ILD], chronic hypersensitivity pneumonitis [HP], childhood interstitial lung disease [ILD], dyskeratosis congenita, or idiopathic pleuroparenchymal fibroelastosis), most cases of IPF probably occur in patients with mild defects in these mechanisms of lung homeostasis, resulting in ineffective repair and cumulative fibrosis of the lung that worsens over time.

gators 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 functions related to its ability, in the presence of appropriate phospholipids, to lower surface tension at low lung volumes by facilitating the spreading and adsorption of the phospholipids extant at the air–liquid interface. The protein inserts itself into the phospholipid monolayer as a function of surface tension, facilitating respreading of surfactant after alveolar compression at low volumes and promoting surfactant recycling. Many investigators have suggested that alveolar collapse and collapse induration are involved in the pathogenesis of pulmonary fibrosis, and both alveolar collapse and collapse induration will increase in the absence of normally functioning

surfactant or impaired AT2 cell production or the recycling of surfactant. The chronic physiologic and bronchoalveolar stress from cyclical opening and closing of atelectatic alveoli or from overdistention of alveoli adjacent to areas of collapse induration is more pronounced in the peripheral and lower lobes of the lung and, consequently, may explain the distribution of the fibrotic lesions in IPF.

The intriguing work of Nureki and colleagues has solidified some of the basic concepts in pulmonary fibrosis and created a translational model of fibrotic lung disease; this work underscores the importance of genetic targets in understanding the causes and pathogenesis of this disease. Of note, their research has reinforced the importance of AT2 cell injury in the initial stages of pulmonary fibrosis. As emphasized by Blackwell,[3] the work of Nureki et al. also shows that endogenous defects in cellular function, as well as defects induced by environmental exposures, can cause recurrent microscopic injury to the alveolar space, and poorly functioning AT2 cells can serve to initiate and perpetuate the fibroproliferative process. Although no murine model has yet fully recapitulated the complex heterogeneity and pathogenesis of IPF, the spontaneous model of *SFTPC*-associated interstitial lung disease created by Nureki and colleagues will most likely prove valuable in understanding the biology of pulmonary fibrosis and developing new drugs for this progressive disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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