Idiopathic Pulmonary Fibrosis Is a Genetic Disease Involving Mucus and the Peripheral Airways

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Abstract

Idiopathic pulmonary fibrosis (IPF) is localized to the lung, is characterized by a pattern of heterogeneous, subpleural patches of fibrotic, remodeled lung, and is associated with a median survival of 3–5 years after diagnosis. A common gain-of-function *MUC5B* promoter variant, rs35705950, is the strongest risk factor (genetic and otherwise), accounting for at least 30% of the total risk of developing IPF. The *MUC5B* promoter variant can be used to identify individuals in the preclinical phase of this progressive disease, and, in the IPF lung, we have found that MUC5B is specifically overexpressed in bronchoalveolar epithelium. Thus, MUC5B represents a key molecule to understand the mechanisms that appear to initiate the fibroproliferative process in the bronchoalveolar epithelium. Moreover, focusing on MUC5B may provide a unique opportunity to define the early molecular events that lead to, and potentially prevent, the development of IPF.

Keywords: IPF; MUC5B; idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is localized to the lung, is characterized by a pattern of heterogeneous, subpleural patches of fibrotic, remodeled lung, and has a median survival of 3–5 years after diagnosis (1). IPF affects 5 million people worldwide, disproportionately affects men, is associated with cigarette smoking (2, 3), increases with age, is inexplicably increasing in prevalence (4, 5), and is likely underdiagnosed (4, 6). Although IPF takes years to develop, most patients with IPF are diagnosed in the advanced stage, and current therapies slow disease progression with little impact on overall survival (7, 8). Earlier diagnosis of IPF will detect subjects with a lower burden of fibrotic lung disease (9, 10), and may create the opportunity to predict and prevent the progression of pulmonary fibrosis before the lung has been irreversibly compromised by extensive scarring and fibrosis. The scientific premise of this presentation is based on recent data from our laboratories and others that inform an emerging understanding of IPF pathogenesis based on the early clinical phenotype of IPF that is linked to enhanced production of the mucin MUC5B in the bronchoalveolar epithelia. Based on these findings, we now propose to focus on the interaction of MUC5B, the airway epithelia, and repair/regeneration to define the biological signatures and biomarkers that will allow us to identify pulmonary fibrosis in its preclinical phase and enable us to move toward prevention strategies for this progressive disease.

IPF is a complex, heterogeneous genetic disorder that is associated with rare and common sequence variants in many genes (*MUC5B*, *SFTPC*, *SFTPA2*, *RTEL1*, *TERT*, and *hTR* [11–16]), 11 genetic loci (17, 18), and multiple emerging epigenetic (19–23) and transcriptional (24–27) profiles. However, the *MUC5B* promoter variant, rs35705950, is the strongest and most validated risk factor (genetic and otherwise) for IPF and preclinical pulmonary fibrosis (PrePF). We have found that: *1*) a common gain-of-function *MUC5B* promoter variant rs35705950 accounts for at least 30% of the total risk of developing IPF (28); *2*) the contribution of the *MUC5B* promoter variant, rs35705950, to the risk of IPF has been confirmed in 10 independent studies (28–36), including our genome-wide association study (a standard method to interrogate the entire genome using common genetic variants; odds ratio for T [minor] allele = 4.51; 95% confidence interval = 3.91–5.21; $P = 7.2 \times 10^{-95}$) (17); *3*) rs35705950 can potentially be used to identify individuals with PrePF (37, 38), and is predictive of radiographic progression in PrePF (38); and *4*) MUC5B appears to be involved in the pathogenesis of IPF.

Specifically, MUC5B message and protein are expressed in bronchoalveolar epithelia in IPF (39, 40) and in IPF honeycomb cysts (28, 39).

Interstitial lung abnormalities (ILAs) on high-resolution computed tomography (HRCT) scans were initially reported in asymptomatic relatives of patients with familial IPF (41) and in the elderly (42). Similar to patients with IPF, ILAs in asymptomatic subjects are associated with advanced age (37, 43–46), cigarette smoking (43–49), reduced lung volume (44, 46, 47, 50), and decreased exercise tolerance (51). Moreover, the *MUC5B* promoter variant, rs35705950, is associated with a higher prevalence of ILAs on HRCT scan (37), and is predictive of radiographic progression (38). These findings suggest that ILAs on HRCT scan are a precursor of IPF. However, ILAs are not specific, and include nonfibrotic and fibrotic HRCT defects, and, consequently, the prevalence of ILAs (>5% in the general population ⩾50 yr of age [37, 43–51]) is orders of magnitude higher than the prevalence of IPF.

To address the nonspecificity of ILAs, we have defined a novel entity—PrePF. For our purposes, PrePF will be defined as: abnormalities on chest HRCT consistent with probable or definite fibrosis (e.g., bilateral subpleural reticular changes, honeycombing, or traction bronchiectasis—radiographic findings are concordant with IPF [1, 6, 52]) occurring in asymptomatic subjects of 40 years of age or older recruited from at-risk populations (first-degree relatives of patients with IPF). Our results indicate that 1.8% of the general population aged 50 years or older have PrePF (37), approximately 75% of those with PrePF progress radiographically during a 5- to 6-year period of observation (38), and radiographic progression of PrePF is associated with a decline in lung volumes and increased mortality (38). Kropski and colleagues (53) have shown that PrePF is present in 15–20% of asymptomatic relatives of families with familial IPF (⩾two family members with IPF). In aggregate, these findings suggest that PrePF is an early diagnostic sign of IPF and a harbinger of progressive fibrosis, occurring in 1.8% of the general population and 15–20% of high-risk populations of those aged 40 years or greater.

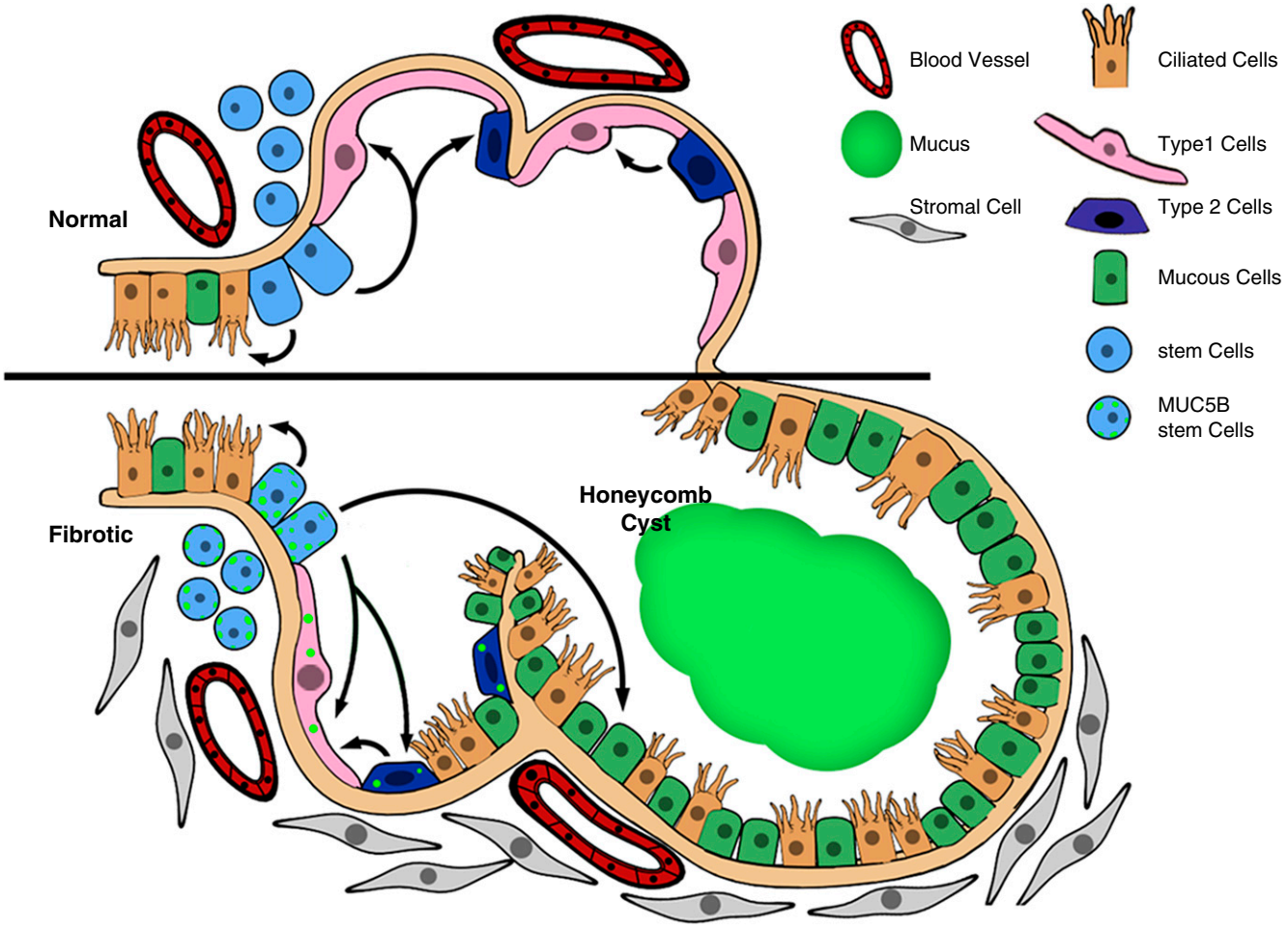

Figure 1. Model of stem cells repopulating bronchioles and alveoli under normal physiologic conditions and when challenged with increased expression of MUC5B. We hypothesize that excessive production of MUC5B by stem cells that attempt to regenerate injured bronchiolar and alveolar epithelium disrupt normal developmental pathways and hijack the normal reparative mechanisms in the distal lung, resulting in chronic fibroproliferation and honeycomb cyst formation. Adapted by permission from Reference 54.

Given the above considerations and the emerging understanding of the pathogenesis of IPF, there are at least two related concepts that link enhanced production of MUC5B in the bronchoalveolar region of the lung to the development of pulmonary fibrosis (54). One line of reasoning focuses on the *intracellular* relationship between overexpression of *MUC5B*, metabolic/stress-responsive changes in MUC5B-producing cells, the involvement of the respiratory bronchiole, microscopic honeycomb cyst formation, and repair/regeneration of the distal airspace in IPF (55–58). Based on these considerations, as stem cells attempt to regenerate injured bronchiolar and alveolar epithelium, excess expression of *MUC5B* may disrupt normal developmental pathways and hijack the normal reparative mechanisms in the distal lung, resulting in chronic fibroproliferation and honeycomb cyst formation (Figure 1). A second line of reasoning focuses on the possibility that IPF is a mucociliary disease caused by recurrent injury/repair at the bronchoalveolar junction, which is initiated and exacerbated by overexpression of MUC5B leading to *extracellular* effects of reduced mucociliary clearance, retention of particles, and enhanced lung injury. Based on the relationship between the *MUC5B* promoter variant, rs35705950, and excess production of MUC5B specifically at the bronchoalveolar junction (40), too much MUC5B may impair mucociliary function (59–61), cause excess retention of inhaled substances (air pollutants, cigarette smoke, microorganisms, etc.), and, over time, the foci of lung injury may lead to scar tissue and persistent fibroproliferation that expands and displaces normal lung tissue (Figure 2). Lastly, we have recently found that lung tissue samples from approximately 40% of patients with IPF are highly enriched for transcripts of cilium genes, *MUC5B*, and

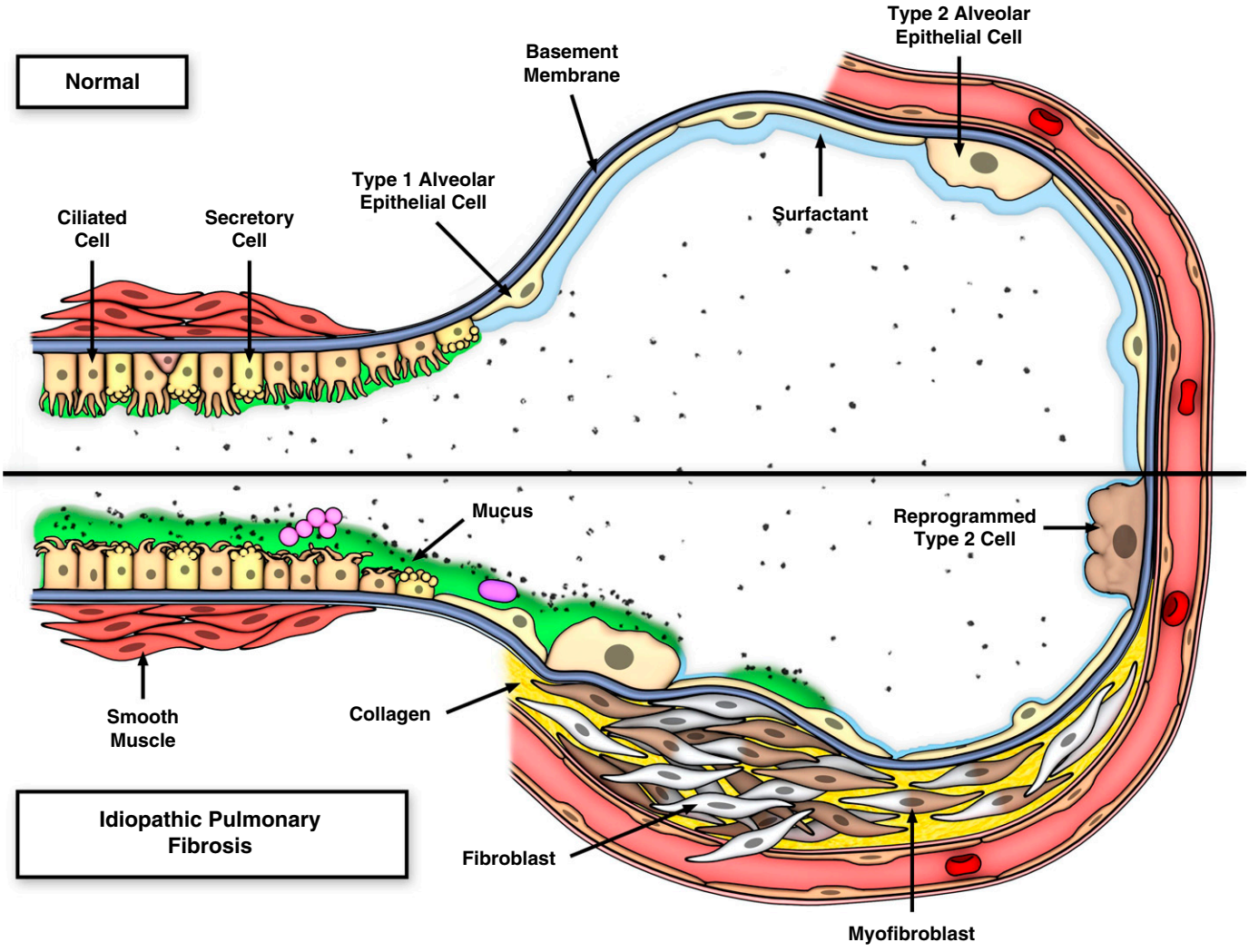

Figure 2. Model of recurrent injury/repair at the bronchoalveolar junction that is initiated and exacerbated by overexpression of MUC5B, retention of inhaled particles, and enhanced lung injury. The upper panel is the normal bronchoalveolar region and the lower panel represents a bronchoalveolar region affected by idiopathic pulmonary fibrosis (IPF). We hypothesize that IPF is a mucociliary disease that is caused by recurrent injury/repair at the bronchoalveolar junction that is initiated and exacerbated by overexpression of MUC5B leading to reduced ciliary function, retention of particles, and enhanced injury. Reprinted by permission from Reference 54.

MMP7 (27), and this molecular phenotype is associated with the expression of keratin 5^{+} cells, supporting a role for MUC5B in abnormal repair and aberrant regeneration. Thus, we postulate that: IPF is caused by recurrent injury/repair/regeneration at the bronchoalveolar junction secondary to overexpression of MUC5B, mucociliary dysfunction, retention of particles, ER stress, and disruption of normal reparative and regenerative mechanisms in the distal lung.

Patients with IPF are usually diagnosed when the fibroproliferative process has caused permanent and extensive lung parenchymal damage. Given the irreversible nature of this disease, even approved treatments for IPF (pirfenidone [7] and nintedanib [8]) only modestly slow progression and have not been shown to alter the 3- to 5-year median survival after diagnosis. However, several common risk factors (age, sex, smoking, and *MUC5B* promoter variant) and clinical features (physiology, HRCT findings, and disease progression) shared by PrePF and IPF indicate that PrePF may be a harbinger of IPF. The gain-of-function *MUC5B* promoter variant is the strongest risk factor (genetic and otherwise) for both PrePF (10, 37) and IPF (17, 28–36), and the radiographic features of PrePF and IPF are concordant (10). Moreover, we have recently found that, during a 5- to 6-year period of observation, approximately 75% of subjects with PrePF progressed radiographically, and that radiographic progression of PrePF is associated with a greater decline in forced vital capacity (P = 0.0001) and an increased risk of death (hazard ratio = 3.7 [95% confidence interval = 1.3–10.7]; P = 0.02) (38). Thus, the emerging clinical phenotype of PrePF (⩾40 yr of age, asymptomatic → mild respiratory symptoms, and HRCT features of IPF) creates a window of opportunity to identify at-risk individuals with preclinical stages of pulmonary fibrosis before the injury/repair/regenerative process has permanently damaged substantial lung parenchyma (Figure 3). Identification of patients with early or preclinical stages of IPF would allow for the treatment of disease before significant, irreversible loss of functional lung parenchyma has occurred. In addition, the identification of biological pathways active in early stages of IPF will provide important mechanistic clues about the critical pathogenic events involved in the early phases of this complex disease.

In summary, these findings indicate that: *1*) the gain-of-function *MUC5B* promoter variant, rs35705950, is associated with an elevated risk of developing IPF, accounting for at least 30% of disease risk; *2*) in the IPF lung, MUC5B is specifically overexpressed in the bronchoalveolar epithelium; *3*) the MUC5B promoter variant can be used to identify individuals in the preclinical phase of this progressive disease; *4*) MUC5B represents a key molecule to understand the mechanisms that initiate the fibroproliferative process in the bronchoalveolar epithelium; and *5*) focusing on MUC5B may provide a unique opportunity to define the early molecular events that lead to the development of IPF. However, the role of MUC5B (or other genetic variants) in identifying early or more

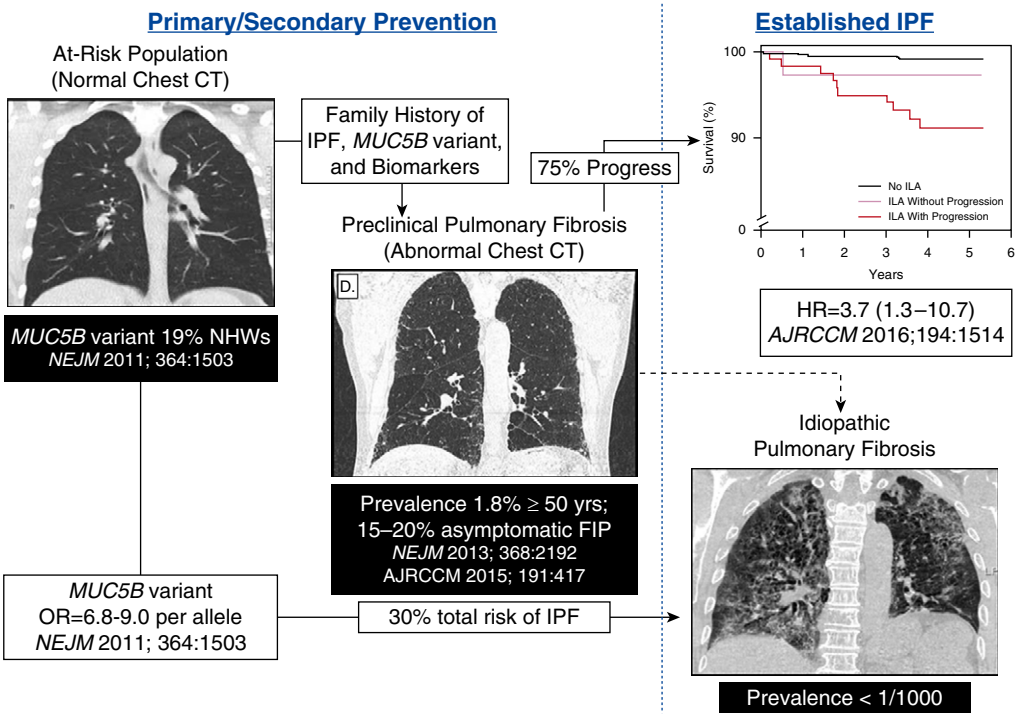

Figure 3. Our overall concept is that family history of idiopathic pulmonary fibrosis (IPF), the *MUC5B* variant, and biomarkers can identify individuals at high risk for preclinical pulmonary fibrosis (PrePF), establishing the opportunity for primary and secondary prevention of IPF. The "at-risk" population (family history of IPF) and the population with PrePF is large, and the yield of PrePF will be enriched by family history of IPF, the *MUC5B* variant, other genetic variants, and biomarkers that we discover in this program. Recent findings (38) indicate that PrePF (detected via chest CT scan) is associated with a poor prognosis, suggesting that PrePF may be a harbinger of IPF. CT = computed tomography; FIP = familial interstitial pneumonia; HR = hazard ratio; ILA = interstitial lung abnormality; NHWs = non–Hispanic white individuals; OR = odds ratio. Adapted by permission from Reference 54.

treatable stages of IPF has not been studied, and thus the clinical utility of genetic variants in IPF has yet to be defined. Although most patients with IPF are detected when the disease is advanced, the process takes at least 10 years to develop, and an earlier diagnosis of IPF will detect patients with a lower burden of lung disease (9, 10, 53), providing an opportunity for secondary prevention of this progressive disease. Thus, the overall concept that we propose is that understanding the role of MUC5B in the early molecular stages of lung fibrosis and defining the predictive and prognostic biomarkers in preclinical stages of pulmonary fibrosis will, in aggregate, establish the scientific basis to ultimately prevent the progression of IPF. ■

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

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