Idiopathic Pulmonary Fibrosis — A Sticky Business

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Pulmonary fibrosis comprises a spectrum of disease phenotypes, including familial and idiopathic forms. Current research suggests that pulmonary fibrosis is a "two-hit" disease: a genetic predisposition to abnormal alveolar epithelial-cell regulation of the cell cycle and apoptosis combined with environmental stressors, including exposure to known fibrogenic materials (e.g., asbestos, silica, and cigarette smoke).[1] Indeed, the identification of mutations in genes expressed in alveolar epithelia in association with pulmonary fibrosis — such as the surfactant proteins A and C (*SPA* and *SPC*, respectively)[2,3] — and genes associated with cell stability — such as telomerase[4] (*hTERT* and *hTER*) — have reinforced the notion that the genetic contribution to pulmonary fibrosis reflects abnormalities in the homeostasis of alveolar epithelial cells. Hence, it comes as a surprise that the linkage and fine-mapping data reported by Seibold et al. in this issue of the *Journal* show that a variant single-nucleotide polymorphism (SNP) in the promoter region of an airway mucin gene (*MUC5B*) is associated with greatly increased production of MUC5B — and with pulmonary fibrosis.[5]

If MUC5B is a mucin secreted into the airway and pulmonary fibrosis reflects a lack of cellular homeostasis in alveolar epithelia, how do we connect these observations? Surprisingly little is known about the communication between the alveolar and terminal bronchiolar surfaces, because this juncture resides deep in the lung and is difficult to study. It is likely that surfactant moves off of alveolar surfaces and onto bronchiolar surfaces and that alveolar macrophages migrate onto bronchiolar surfaces. However, whether inhaled soluble toxins — or indeed, alveolar surface liquids — are normally cleared from alveolar surfaces and transferred to bronchiolar surfaces is not known. Also unknown is whether there is normally retrograde flow of airway mucins into alveoli, although biophysical analyses suggest that this is unlikely.

Even with these uncertainties, however, there are ways to conceive of bronchiolar–alveolar interactions in pulmonary fibrosis. First, as suggested by Seibold et al., increased secretion of MUC5B may lead to bronchiolar plugging, producing a chronic inflammatory and toxic burden on the alveolar surface. Indeed, recent biophysical studies suggest that increased concentrations of mucin (4 to 6 times the normal concentration) destabilize the mucus clearance system and promote mucus stasis. Second, MUC5B contains hydrophobic domains that organize a host defense complex of 40 to 100 proteins, and it is possible that hypersecretion of MUC5B with this protein complex leads to a persistent host–defense imbalance favoring excessive inflammation and alveolar damage. Clearly, however, this is not the whole story, because the mucus plugging caused by MUC5B in chronic obstructive pulmonary disease and cystic fibrosis is not associated with a pulmonary fibrosis phenotype.

An intriguing alternative possibility that may link a dysfunction of airway secretory cells with alveolar cells is the unfolded-protein response, which is initiated by diverse stimuli that together can produce proinflammatory and proapoptotic states. The mutations in *SPC* and *SPA* that are associated with pulmonary fibrosis lead to dysfunction in alveolar type II cells that is probably caused by misfolded proteins, endoplasmic-reticulum retention, and unfolded-protein responses.[6] Recent data have shown that the metabolic pathway for an unfolded-protein response, which is dependent on the inositol-requiring enzyme 1β, is up-regulated consequent to increased mucin biosynthesis.[7] Hence, it is conceivable that different genetic defects affecting airway cells and alveolar cells collectively produce a chronic unfolded-protein response in the alveolar–bronchiolar zone. Indeed, one study provided strong evidence for the importance of a chronic unfolded-protein response and a proapoptotic state in the lungs of patients with familial pulmonary fibrosis or idiopathic pulmonary fibrosis.[8]

Superimposed on the multiple genes that feed into genetic predisposition may be multiple pathways that are affected by environmental stressors. Clues to the nature of these environmental stressors are revealed in the heterogeneity of disease in the lung with pulmonary fibrosis. Cigarette smoke is a risk factor for pulmonary fibrosis and produces heterogeneous disease in chronic obstructive pulmonary disease, reflect-

ing, in part, the heterogeneity of distribution of inhaled toxicants. Microaspiration and viral infection also typically produce heterogeneous lung disease. Indeed, there is strong evidence that microaspiration contributes to the risk of pulmonary fibrosis and produces heterogeneous injury in bronchiolar—alveolar units.[9] Similarly, viral infections may trigger the pulmonary fibrosis phenotype in patients with defined underlying genetic causes of pulmonary fibrosis (e.g., mutations in *SPC*).[6] Intriguingly, viruses produce unfolded-protein responses in healthy cells, and viral infection of cells expressing *SPC* variants associated with pulmonary fibrosis produced synergistic unfolded-protein–apoptotic responses, suggesting that viruses trigger an unfolded-protein response that crosses the threshold required to produce the pulmonary fibrosis phenotype.[10]

Like many successful genomewide linkage studies, the report by Seibold et al. provides a provocative stimulus for broadening our understanding of the pathogenesis of pulmonary fibrosis. It is likely that the "two-hit" hypothesis — one from genetic variation and one from environmental stressors — is generally correct but not complete. It must be modified to account for additional genetic and environmental influences. A better understanding of the pathogenesis of pulmonary fibrosis now may also require an understanding of the normal commerce between alveolar and bronchiolar surfaces. This study will stimulate investigations of the effects of the *MUC5B* variant on secretion rates of MUC5B in quantitative cell systems, the ectopic expression of *MUC5B* in alveolar epithelia in patients with this genetic variation, goblet-cell unfolded-protein responses in patients with and without this polymorphism, and other genes or environmental stressors that produce pulmonary fibrosis phenotypes in patients who do not express the variant SNP. In addition, the study dictates that we broaden our vision of pulmonary fibrosis therapeutics, particularly given the absence of satisfactory clinical responses to immunosuppressants and corticosteroids. Thus, agents in clinical development that may regulate the unfolded-protein response may be worthy of early trials in pulmonary fibrosis. Similarly, agents that reduce *MUC5B* transcriptional activity in vitro should be tested for activity in vivo, including in subjects expressing the variant genotype. Thus, the study by Seibold et al. may have "unstuck" our thought processes with respect to a disease that has frustrated both patients and their physicians.

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

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Truly Emerging — A New Disease Caused by a Novel Virus

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Contrary to predictions of the mid-20th century, infectious diseases are on the rise, threatening human and animal health on both local and global scales. Multiple factors are contributing to the emergence or reemergence of infectious diseases, including increasing human intrusion into the natural environment, with behavioral changes associated with expanding economic