Table 15-5 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Connective tissue disease-associated
Pneumoconiosis
Drug reactions
Radiation pneumonitis
Granulomatous
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic
Smoking Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis-associated interstitial lung disease
Other
Langerhans cell histiocytosis
Pulmonary alveolar proteinosis
Lymphoid interstitial pneumonia

characteristic radiologic, pathologic, and clinical features. The histologic pattern of fibrosis is referred to as usual interstitial pneumonia (UIP), which can often be diagnosed based on its characteristic appearance in CT scans. The UIP pattern can also be seen in other diseases, notably connective tissue diseases, chronic hypersensitivity pneumonia, and asbestosis; these must be distinguished from IPF based on other clinical, laboratory, and histological features.

Pathogenesis. While the cause of IPF remains unknown, it appears that the fibrosis arises in genetically predisposed individuals who are prone to aberrant repair of recurrent alveolar epithelial cell injuries caused by environmental exposures (Fig. 15-13). The implicated factors are as follows:

- *Environmental factors*. Most important among these is cigarette smoking, which increases the risk of IPF several fold. IPF incidence is also increased in individuals who are exposed to metal fumes and wood dust, or who work in certain occupations, including farming, hairdressing, and stone-polishing. It is hypothesized that exposure to environmental irritants or toxins in each of these contexts causes recurrent alveolar epithelial cell damage. Gastric reflux has also been recently implicated.
- *Genetic factors*. The vast majority of individuals who smoke or who have other environmental exposures linked to IPF do not develop the disorder, indicating that additional factors are required for its development. Chief among the suspects are inherited genetic variants. One group of genetic lesions of particular interest is germline loss-of-function mutations in the *TERT* and *TERC* genes, which encode components of telomerase. You will recall that telomerase is an enzyme that maintains the ends of chromosomes (the telomeres) and thereby prevents cellular senescence. Up to 15% of familial IPF is associated with telomerase gene defects, and up to 25% of sporadic IPF cases are associated with abnormal telomerase shortening in peripheral blood lymphocytes; the cause of this shortening is currently unknown, and it is not yet known whether such individuals also have telomere shortening in their alveolar epithelial cells. Other, rare familial forms of IPF are associated with mutations in genes encoding components of surfactant; these mutations create folding defects in the affected proteins, leading to activation of the unfolded protein response in type II pneumocytes. This in turn appears to make pneumocytes more sensitive to environmental insults, enhancing the consequent cellular dysfunction and injury. Finally, roughly one-third of IPF cases are associated with a common genetic variant that greatly increases the secretion of MUC5B, a mucin that may make alveolar epithelial cells susceptible to injury or exaggerate downstream events that lead to fibrosis.
- *Age*. IPF is a disease of older individuals, rarely appearing before the age of 50 years. Whether this association stems from aging-related telomere shortening or from other acquired changes associated with aging is unknown.

It is easy to imagine how some of the factors cited herein might combine to exacerbate alveolar epithelial cell damage and senescence, which seems to be the initiating event

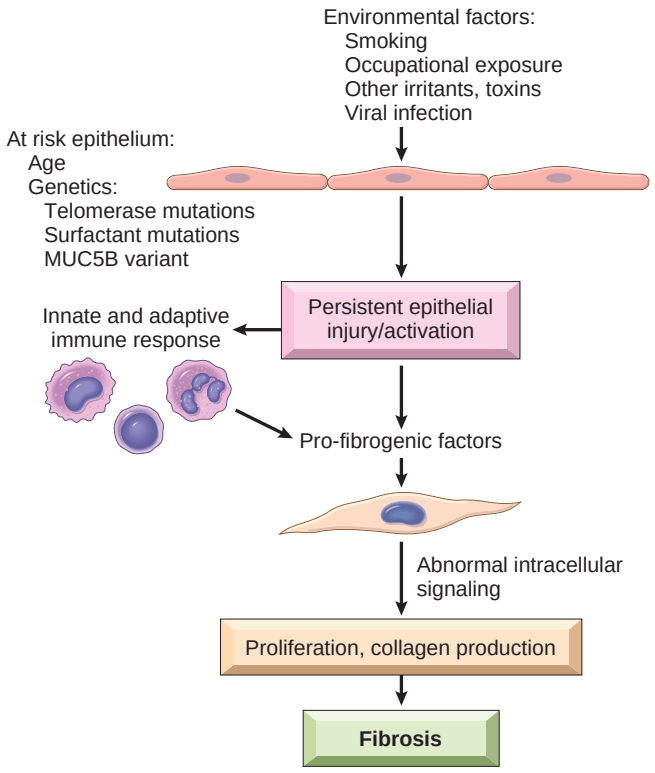

Figure 15-13 Proposed pathogenic mechanisms in idiopathic pulmonary fibrosis. Environmental factors that are potentially injurious to alveolar epithelium interact with genetic or aging-related factors that place epithelium at risk to create a persistent epithelial injury. Factors secreted from injured/activated epithelium, possibly augmented by factors released from innate and adaptive immune cells responding to "danger" signals produced by damaged epithelium, activate interstitial fibroblasts. There is some evidence that these activated fibroblasts exhibit signaling abnormalities that lead to increased signaling through the PI3K/AKT pathway. The activated fibroblasts synthesize and deposit collagen, leading to interstitial fibrosis and eventual respiratory failure.