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IDIOPATHIC PULMONARY FIBROSIS: A DISORDER OF EPITHELIAL CELL DYSFUNCTION

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Abstract

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive dyspnea, interstitial infiltrates in lung parenchyma, and restriction on pulmonary function testing. IPF is the most common and severe of the idiopathic interstitial pneumonias (IIPs), with most individuals progressing to respiratory failure. Multiple lines of evidence reveal prominent roles for alveolar epithelial cells (AECs) in disease. Our current disease paradigm is that ongoing or repetitive injurious stimuli in the presence of a genetic or acquired dysfunctional type II AEC phenotype results in increased AEC injury/apoptosis, deficiencies in regeneration of normal alveolar structure, and aberrant lung repair and fibroblast activation, leading to progressive fibrosis. While the nature of injurious events and processes involved in aberrant repair of the alveolar epithelium are not well understood, ongoing investigations provide hope to better understand mechanisms by which AECs maintain homeostasis or contribute to fibrosis. These strategies may hold promise for developing novel treatment approaches for IPF.

Keywords

alveolar epithelial cell; familial interstitial pneumonia; idiopathic pulmonary fibrosis; lung

Idiopathic Pulmonary Fibrosis: An Overview

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease that is characterized by progressive dyspnea, decreased exercise tolerance, interstitial infiltrates in the lung parenchyma, and restriction on pulmonary function testing.¹ IPF is estimated to have a prevalence of approximately 20 per 100,000 males and 13 per 100,000 females,² with current figures suggesting that approximately 50,000 individuals in the US suffer from the disease. Most individuals with IPF progress to respiratory failure within a period of 3 – 5 years.² Unfortunately, short of lung transplantation, no effective therapies are available for

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this disease. The clinical definition of IPF requires exclusion of other known causes of interstitial lung disease (ILD), and its diagnosis requires characteristic changes on high-resolution computed tomography (HRCT), restriction on pulmonary function testing, impaired gas exchange, and/or histologic appearance of usual interstitial pneumonia (UIP) on surgical lung biopsy (Figure 1).²

IPF is the most common and severe form of Idiopathic Interstitial Pneumonia (IIP). The current classification of Idiopathic Interstitial Pneumonia (IIP) includes seven entities: IPF/UIP, nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia (LIP).^{3,4} Since IPF represents approximately 70% of IIP cases, it is the form most often targeted in clinical trials.

The current clinical emphasis regarding the specific pathologic subsets of IIP by consensus panels carries the implicit presumption that each subset comprises a different disease.³ In contrast, in families with Familial Interstitial Pneumonia (FIP), in which two or more relatives have an IIP, multiple pathogenic subsets can be seen within the same family.^{5,6} This observation suggests phenotypic heterogeneity in which different subsets of IIP may actually represent different manifestations of a common underlying pathogenic process.

Progression of Ideas Regarding IPF Pathogenesis

For many years, it was believed that chronic inflammation in the lungs led to the progressive fibrosis noted in IPF. However, failure of the disease to respond to anti-inflammatory treatment strategies combined with insights from histological assessment of patient samples and animal models have resulted in reformulation of ideas regarding IPF pathogenesis by the medical and scientific community.^{1,7} Over the past 15 years, a new concept has emerged in which repeated injury to lung epithelial cells leads to an aberrant wound healing response with subsequent tissue fibrosis.¹

Multiple cell types likely contribute to the pathogenesis of IPF, but over the past two decades, the lung fibroblast has been the most analyzed cell in studies of pulmonary fibrosis. Multiple lines of evidence implicate the fibroblast, particularly the myofibroblast, as a principal effector cell responsible for the deposition of collagen and other extracellular matrix components during tissue fibrosis.⁸ Analysis of UIP lung biopsies demonstrates the presence of fibroblasts (and myofibroblasts) in fibroblastic foci, one of the hallmark pathologic findings in this disease, which are thought to be the leading edge of active fibrosis.^{9,10}

In addition to the critical role of the lung fibroblast, studies have revealed a prominent role for alveolar epithelial cells (AECs) in the pathogenesis of IPF. In IPF lung biopsies, epithelial cell abnormalities are common, including bronchiolar-like epithelial cells and hyperplastic type II AECs lining areas of honeycomb fibrosis.¹¹ Furthermore, AECs produce key pro-fibrotic mediators including connective tissue growth factor (CTGF), platelet derived growth factor (PDGF), and transforming growth factor β (TGF β).¹²⁻¹⁴ AEC apoptosis has also been implicated in disease pathogenesis with IPF lung biopsies having prominent AEC apoptosis in areas adjacent to active remodeling and heavy myofibroblast activity.^{15,16} AEC apoptosis is a prominent event in the experimental model of bleomycin induced pulmonary fibrosis,^{17,18} and inhibition of apoptosis has been shown to attenuate fibrosis in this model.^{19,20} In addition, AEC apoptosis appears to be a critical step in the development of fibrosis in other animal models, including TGF β 1 induced lung fibrosis.²¹ Recently, Sisson et al. used a transgenic mouse model in which human diphtheria toxin receptor is expressed in type II AECs to show that induction of cell death by treatment with

diphtheria toxin is sufficient to produce pulmonary fibrosis.²² Perhaps the most convincing evidence for a prominent role of AECs in pulmonary fibrosis comes from studies in the past decade linking genetic mutations in surfactant protein C (*SFTPC*) to cases of FIP.^{6;23} Surfactant protein C is expressed exclusively in type II AECs in the lung. Thus, taken together, compelling evidence indicates that AECs are central to the pathogenesis of IPF, and AECs impact lung remodeling and fibrosis through multiple mechanisms.

Assimilating the current available data suggests that the response of type II AECs to injury is a key determinant of initiation and progression of lung fibrosis in IPF (and FIP). Our working model is based on the idea of the “vulnerable AEC” (Figure 2). In this scenario, we hypothesize that ongoing or repetitive injurious stimuli in the presence of a genetic or acquired dysfunctional type II AEC phenotype results in: 1) increased AEC injury/apoptosis, 2) deficiencies in regeneration of the normal alveolar structure, and 3) aberrant lung repair and fibroblast activation. The result of these pathobiological changes is progressive lung fibrosis. While this is an attractive model to consider, there are still many unanswered questions that need to be addressed by ongoing and future investigations.

Critical Unanswered Questions in IPF

While many questions still exist regarding the pathogenesis of IPF, we highlight and discuss 4 important unanswered questions.

1) What initiates the cycle of injury and aberrant repair?

Toxic exposures have long been suspected as instigators of epithelial injury with investigations demonstrating an increased risk of disease in smokers.⁵ Although other occupational or environmental insults are likely to be involved in disease progression and acute exacerbation, the nature of these insults has been elusive. Infection is another possible cause of epithelial injury in IPF. A large number of IPF patients express herpesvirus antigens in AECs,²⁴ but it is unclear if these viruses are involved in disease pathogenesis or are seen because of advanced architectural lung distortion. Alternatively, endogenous abnormalities in AECs may lead to epithelial injury and death. Cases of FIP linked to mutations in *SFTPC* and *SFTPA2* suggest the possibility that aberrant surfactant protein processing could be a primary abnormality in IPF.^{6;25} Some of these *SFTPC* mutations have been shown to induce endoplasmic reticulum (ER) stress, which can induce apoptosis of AECs.^{24;26;27} The search for inciting events in IPF is an important area of investigation since identification of these processes holds much promise for better defining the pathogenesis of disease.

2) What are the factors that determine whether injured alveoli repair normally or progress to fibrosis?

In other diseases with severe AEC injury, such as the acute respiratory distress syndrome,²⁸ the lungs have a remarkable ability to regenerate architecturally and functionally intact alveoli. In addition, most animal models of IPF show resolution of lung architecture over time,^{29–31} yet in IPF progression of fibrosis is the rule. Cases of FIP linked to mutations in the telomerase complex raise the possibility that impairment in AEC regeneration is central to disease pathogenesis. Mutations in telomerase components that result in reduced telomere length occur in some families with FIP, suggesting that AEC senescence and impaired ability to re-epithelialize injured alveoli may be a critical disease component.^{32;33} At present, it is uncertain whether other genetic or acquired abnormalities in AECs and/or stem cell populations could limit the reparative capacity of alveolar structures.

3) From what origins do lung fibroblasts arise and how are they regulated?

While fibroblasts are clearly the cells most responsible for extracellular matrix deposition, their origins and behavior still require much further delineation. In disease states, lung fibroblasts likely arise from multiple origins, including resident interstitial cells, bone marrow precursors (fibrocytes), and through transition from other cell populations including epithelium and endothelium by the process of epithelial (or endothelial) to mesenchymal transition (EMT).³⁴ The relative importance of these sources of effector fibroblasts and the mechanisms by which site of origin impacts fibroblast phenotype and function requires further investigation.

4) How can the cycle of injury/repair be interrupted to limit or reverse fibrosis?

For patient care, this is the most pressing question for the field of pulmonary fibrosis. Unfortunately, despite many recent pharmaceutical trials, we still do not have interventions that limit or reverse disease progression. At present, it appears that a better understanding of IPF pathogenesis will be required in order to devise new, specifically targeted therapeutic strategies.

Significant barriers exist to these and other questions about IPF. Unfortunately, when it comes to studying IPF in human subjects, we are too often faced with late diagnoses; biopsies or explants usually show end-stage fibrosis, and it is difficult to determine the primary inciting events as opposed to the overwhelming response to the injury. Although animal models are valuable in studying IPF, there are a number of obstacles to translating information from animal models to humans with IPF. Issues with current animal models of lung fibrosis include: inconsistencies with disease progression and persistence, the lack of exposure to relevant environmental stimuli, and the inability to recapitulate key pathologic features such as fibroblastic foci.²⁹ Development of better animal models is essential to validate new therapeutic agents and approaches.

Using FIP to Understand IPF

A potential way forward in investigating IPF involves the use of families with FIP, where IIP is present in two or more family members.³⁵ FIP accounts for at least 2–4% of IPF cases, and pedigrees suggest it is inherited as an autosomal dominant trait with incomplete penetrance.³⁵ The clinical characteristics, radiographic studies, and histology are indistinguishable from the sporadic form of the disease, except the disease often presents at a younger age, with an average age of onset that is 10 years younger in FIP compared to sporadic IPF.³⁶ These FIP families serve as a unique population at increased risk of developing disease, and are a valuable resource to study the pathogenesis of lung fibrosis.

FIP families provide a resource from which genetic links to disease can be discovered. To date, four well defined genes have been identified that are associated with FIP. Mutations in genes for surfactant proteins (*SFTPC*, *SFTPA2*)^{6;25} and telomerase components (telomerase reverse transcriptase - *TERT*, telomerase RNA component - *TERC*)^{32;33} have been linked to FIP. However, mutations in these four genes explain only 15% of FIP, suggesting that other important genetic causes of the disease can be identified.

In addition, FIP families represent a unique population in which at-risk family members can be evaluated for early stages of disease. Screening individuals for pre-symptomatic disease is not feasible in a general population given the low prevalence of disease, but in an FIP family, such screening becomes feasible since of first degree relatives of an affected individual would be predicted to have genetic risk for disease. Once identified as having pre-symptomatic disease, such individuals would be a valuable resource for identifying factors at play in the early stages of disease, as well as a group of individuals in which the natural

progression of disease processes could be followed over time. Demonstrating the feasibility of such a screening approach, our group recently reported a case of a man diagnosed with UIP/IPF at age 58 with a known *SFTPC* mutation.^{37;38} Two of his three children also had the *SFTPC* mutation but were asymptomatic with normal physical examinations and pulmonary function tests. The father and one daughter (age 39) were also found to have a variation in the gene encoding for ATP-binding cassette A3 (*ABCA3*). This daughter was found to have mild interstitial thickening on high-resolution computed tomography (HRCT) of the chest, and underwent bronchoscopy with transbronchial biopsies which showed multiple foci of interstitial fibrosis and a fibroblastic focus, a histologic hallmark of UIP.³⁸ This case demonstrates that radiographic and histologic changes consistent with fibrotic lung remodeling can be found in asymptomatic individuals at increased risk of disease, and that studying families with FIP is a feasible and potentially fruitful way to better understand IPF.

Conclusions

IPF remains a challenge both clinically and scientifically. Treatment options are limited and little progress has been made to improve disease morbidity and mortality. A substantial amount of information supports the idea that AEC dysfunction is central to IPF pathogenesis. While the exact injurious events and processes involved in aberrant repair of the alveolar epithelium are not well understood, ongoing investigations provide hope to better understand the mechanisms by which AECs either maintain homeostasis or contribute to fibrosis. These strategies may hold promise for developing novel treatment approaches for IPF.

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Figure 1. Hematoxylin and eosin (H&E) stained section from a lung biopsy showing findings of usual interstitial pneumonia (UIP). Hallmark findings of UIP are noted, including areas of dense fibrosis (white arrow) adjacent to areas of normal lung (striped arrow), fibroblastic foci (black arrow), and hyperplastic epithelial cells lining areas of fibrotic remodeling (black arrowhead).

Figure 2. Schematic for IPF pathogenesis based on the dysfunctional (vulnerable) alveolar epithelial cell.