Does Current Knowledge Explain the Pathogenesis of Idiopathic Pulmonary Fibrosis?

A Perspective

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The cause of idiopathic pulmonary fibrosis (IPF) remains unknown. Although the observed biologic and biochemical processes associated with the disease are consistent with a fibrotic process, they are not necessarily unique to IPF. Furthermore, the importance of these observations will not be apparent until a directed therapy alters the natural history of the disease. There are essentially no studies that explain the unique histologic features of this disease. As mechanistic data accumulates, it is our opinion that these data should pass the test of explaining the clinical histologic features of the disease before it can be assumed that these features are unique for IPF.

Keywords: fibrosis; injury; repair

Although a number of biologic and biochemical processes have been associated with the development of pulmonary fibrosis in animal models, few, if any, can clearly be applied to the development of idiopathic pulmonary fibrosis (IPF) and its underlying histology, usual interstitial pneumonia (UIP), in humans. The difficulty in translating discoveries in animal models to human subjects is explained by the fact that no animal model faithfully replicates the UIP histology of IPF (1). The only conclusion to be drawn is that the environment that would be expected is present in patients with IPF: this includes the presence of relevant profibrotic growth factors; evidence for myofibroblast proliferation, with subsequent collagen deposition, as well as production of other matrix proteins; evidence for epithelial cell injury and proliferation; the generation of proteolytic enzymes; and other factors that may contribute to remodeling of the lung (2–7). It is our opinion, however, that one should not definitely conclude that these biologic alterations are causally associated with the lung injury and/or fibrosis until a directed therapy alters the natural history of the disease or a genetic process is identified that strongly supports the role of these biologic and biochemical changes in the pathogenesis of the disorder. In addition, there should be unique findings that differentiate IPF from other fibrotic lung disorders. One genetic change, the mutation in the surfactant protein C (SP-C) gene, has been identified that appears to explain the development of a fibrosing interstitial lung disease in a small number of patients, but not all patients have findings consistent with the histology of IPF (8, 9).

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We can, however, make two simple assumptions: (*1*) there must be some type of initiating injury and (*2*) there is an explanation for the continuous abnormal repair that follows. The dysregulated repair response could occur because the injury is too extensive for normal recovery, the agent causing the injury persists (i.e., asbestos fibers), or there is an underlying genetic factor, like the mutation in SP-C that consistently alters the expected repair process (8, 9). Even this well-described genetic alteration, however, appears to require an initial injury to the lung.

An assumption that is often made is that the presence of profibrotic mediators, such as transforming growth factor β and other cytokines known to be associated with fibrosis, relates to the pathogenesis of this disorder (10–12). Although these observations may be consistent with ongoing fibrosis in the lung, they really do not demonstrate, with any certainty, that they are necessarily important and unique features to this lung disease. In this regard, the presence of these mediators may mean nothing more than that healing (scarring), in the case of uncontrolled IPF, is occurring in the lung. The appearance of these mediators occurs with many injuries undergoing the repair process and have been identified in many organs and disorders undergoing healing or fibrosis (13). It would be necessary to demonstrate that there is abnormal regulation of the fibrotic process in the IPF lung. To date, this has not been the case.

If the biologic milieu of the IPF lung is the explanation for the development of the fibrotic changes, this setting should also explain some of the unique features of this disease. The recognizable feature of IPF, both on lung computed tomography (CT) and histology, is the presence of a patchy fibrosis that is subpleural in location (14–16). Moreover, IPF demonstrates only modest inflammation, consisting of occasional interstitial lymphoplasmacytic cells and intraalveolar macrophages and the presence of fibroblastic foci. Fibroblastic foci are believed to represent of the site of recent injury that initiates the repair process (17–19). One belief is that IPF results from repeated episodes of acute injury to discrete peripheral areas of the lung that eventually result in fibrosis and collagenous remodeling of the involved area (20). Over time, the sum of these discrete episodes of injury leads to progressive fibrosis and remodeling of larger areas of lung. However, recent evidence suggests that, although fibrotic foci are the leading edge of the fibrotic process, they are connected in a complex reticulum extending from the pleura inward, further suggesting that individual foci may not represent discrete cites of injury (21). Another unique feature of IPF is that, after its discovery, in most patients it moves at a relatively fast pace (i.e., $\sim$ 50% of patients die within 2–3 yr after diagnosis or 4–5 yr after the onset of symptoms) (22, 23). What is not known is whether this injury accumulates at a constant rate or if there are discrete repetitive episodes that cause progression. Most likely, the latter is at least partially the case as evidenced by

episodes of acute exacerbation that often result in a rather severe loss of lung function and often accelerated mortality (24–27).

A unique feature that remains unexplained relates to the subpleural location of IPF and its appearance early on in the fibrotic process. This can be detected on lung CT scans as peripheral honeycombing and/or reticulation. IPF can occur simultaneously with nonspecific interstitial pneumonia (NSIP) (28, 29). The implication is that the initiating injury or trigger of the disease is limited to the periphery of the lung and, even with concurrent NSIP, there is a peripheral pattern of involvement on lung biopsy. These observations suggest that an insult that initially involves the lung diffusely eventually results in a predominant peripheral pattern of involvement. This further suggests that there are features of the peripheral airways in patients with IPF that make it more accessible to injury, possibly due to an inability to reexpand or repair itself in a normal fashion after the insult. The reasons for this distribution are unknown; however, any attempt to explain the pathogenesis of IPF should include this disease feature.

Another intriguing finding seen in the IPF lung is the remodeling of pulmonary blood vessels (30–34). A significant number of patients with IPF have elevated pulmonary artery pressures, either at rest or with exercise (35, 36). Because a significant amount of the pulmonary vasculature (40%) must be involved to account for pulmonary hypertension, this suggests that vascular involvement begins early on. What is not known is if the vascular disease occurs as a result of the ongoing fibrotic process in the lung or, in part, whether it somehow drives the uncontrolled fibroproliferation. The latter is not necessarily the case because in primary pulmonary arterial hypertension there is no fibrosis of the lung parenchyma. Therefore, if vascular involvement is a primary driving force of the fibrotic process, there must be unique biologic alterations that affect the pulmonary vessels in the setting of IPF. A recent study suggested that *in situ* pulmonary artery thrombosis might be an important feature of this disorder, especially during acute exacerbations of IPF (37). It would be interesting to know if anticoagulation early in the course of this disorder might alter the natural history of the disease. As an aside, our ability to detect vascular abnormalities occurs late in the course of the disease. Therefore, newer methods of detection to indicate early vascular remodeling would be desirable and would have specific therapeutic implications.

It is assumed that there is epithelial dysfunction in patients with IPF. It has been shown that epithelial cells are undergoing apoptosis at an accelerated rate, suggesting ongoing lung cell injury or, alternatively, they have a preexisting biologic abnormality (38). Clearly, once remodeling has occurred, the epithelium is altered, but this is likely a result of the initial injury and then the response to repair. What is not clear is if the epithelium is altered in some way, thereby giving certain individuals a susceptibility to developing IPF.

A preexisting abnormality in epithelial function could result in increased permeability and/or the inability to clear fibrin from the alveolar surface (39, 40). These observations are relevant to IPF because it has been shown that the fibrotic process is associated with fibrin deposition on the alveolar surfaces, which leads to fibrosis and remodeling in the area of injury. This could also occur if the epithelium was more susceptible to injury and/or could not repair areas of injury rapidly, as expected in the normal lung. In the small subset of patients with mutations in the SP-C gene, the epithelial injury likely follows epithelial cell SP-C protein accumulation (8, 9). It is known that this interferes with protein folding.

It has been suggested that the proliferating fibroblast (myofibroblasts) are themselves abnormal and responsible for the disease after injury. However, no study to date conclusively demonstrates that their function differs from fibroblasts involved in the normal repair process, other than the fact that they remain under the influence of the profibrotic milieu and continue to proliferate (41).

Although IPF can develop in patients who are lifetime nonsmokers (33%), there is a clear association between cigarette smoking and the development of the disease (42). Recent studies have also identified cigarette smoking as an important environmental cofactor in patients with familial pulmonary fibrosis consistent with earlier observations pointing to cigarette smoking as an important determinant of the development of lung fibrosis (43). A number of patients with IPF develop symptoms of IPF after discontinuation of smoking. Although it is possible that patients stop smoking because of symptoms from IPF, it is unlikely because this is a frequent occurrence. This clinical observation could be consistent with a hypothesis that cigarette smoking causes lung cell injury but active smoking inhibits the IPF pattern of fibrosis. Once patients stop smoking, the IPF pattern of healing/fibrosis is expressed. It is of interest, in this regard, that there seems to be a unique pattern of fibrosis that develops in active smokers. It is often associated with other features of smoking-related disease, such as emphysema and ground glass changes and centrilobular nodules on lung, representing respiratory bronchiolitis–associated interstitial lung disease (44–46). At a minimum, these observations suggest that smoking is associated with fibrosis, as well as emphysema and inflammation in the lung.

The role of inflammation in the development of IPF remains another unresolved issue. Histologically, there is modest evidence to support this. In addition, CT ground glass densities in IPF are unusual, except during acute exacerbations. In other clinical settings, however, inflammation can lead to fibrosis. There is an interesting subset of patients with IPF who simultaneously exhibit histologic features of both NSIP and UIP (28). Although it is possible that these patients have two distinct, unrelated histologies from different injuries, it is likely that there is a close association between NSIP and UIP in some patients. Perhaps, in some cases, NSIP (which often is associated with inflammation) does precede the development of what we recognize as IPF. Moreover, in familial pulmonary fibrosis, NSIP and UIP occur and have similar gene expression profiles in the same families; and in patients with connective tissue diseases and hypersensitivity pneumonitis, both histologies occur (47, 48).

Can more than one type of injury initiate IPF in the same patient? An assumption has been made that this is a disorder that occurs in response to a specific insult in a genetically or otherwise susceptible patient. It is as likely, however, that this disease simply occurs in a patient who has a vulnerable lung with the inability for normal repair. Therefore, a variety of environmental insults, such as subclinical aspiration, viral infection, or environmental dust or drug exposures, could result and perpetuate IPF (49, 50). This would be consistent with the observation that lung function often declines in a stepwise manner, and in some instances, the declines are large and in others are more gradual with prolonged survival. Furthermore, this would not be inconsistent with the fact that many individuals with IPF are ex-smokers, predisposing the lung in these susceptible patients to develop fibrosis in response to another injury. It is important to consider this possibility because, if true, the natural history of this disorder might be altered by preventative measures that protect the lung from further injury.

A final issue for consideration is that IPF may be a biphasic disease in some affected subjects. The early phase is represented by the injury that initiates the fibroproliferation. This could result in a critical loss of lung units sufficient enough that the lung disease then progresses independently of the initial injury (the perpetuation phase). Observations that support this hypothesis

are those that show that, once lung fibrosis (NSIP or UIP) occurs in other fibrosing lung diseases, such as hypersensitivity pneumonitis, the disease continues despite antigen avoidance (47).

IPF remains an investigative and therapeutic challenge. We still do not have a treatment that alters the natural history, nor do we understand how the lung disorder develops or progresses. As mechanistic data accumulates, it should pass the test of explaining the clinical features of the disease before it is assumed to be unique to IPF.

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