Idiopathic pulmonary fibrosis – a disorder of alveolar wound repair?

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Summary

Idiopathic pulmonary fibrosis (IPF) is a chronic and usually progressive lung disorder of unknown aetiology. Conventional management of patients with IPF has been primarily based on the concept that suppressing inflammation would prevent progression to fibrosis. Although the pathogenesis is incompletely understood, it is here suggested that IPF is a disease of abnormal wound repair and remodelling in the lung rather than an inflammatory disease. Therefore, treatment strategies are no longer aimed at reducing inflammation, but rather at preventing or inhibiting the fibro-proliferative responses and enhancing efficient alveolar epithelial repair. So far, no cell-specific drugs for these purposes are clinically available. However, novel promising molecules or drugs are being studied in experimental models or ongoing clinical trials in patients with IPF. Evolving hypotheses on the pathogenesis of IPF are reviewed, focusing on possible implications for future therapies. A better understanding of the sequence of the pathogenic mechanisms that control the fibrotic response will hopefully lead to efficient therapies and finally a favourable outcome in patients with this disease.

Key words: idiopathic pulmonary fibrosis; pathogenesis; alveolar repair

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and lethal fibrotic lung disease of unknown aetiology. In a recently published consensus statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS), IPF is defined as a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with a histological pattern of usual interstitial pneumonia (UIP) [1]. The histological hallmark of the UIP pattern is patchy interstitial fibrosis, often in subpleural and/or paraseptal distribution, alternating with areas of normal lung. The fibrosis is temporally heterogeneous with architectural destruction, dense scarring with honeycombing and scattered fibroblast foci [2]. The diagnosis of IPF requires a compatible clinical history and examination, the exclusion of other known causes of interstitial lung disease (such as drug injuries, environmental exposures or connective tissue disease), abnormal lung function studies (restriction and impairment of gas exchange), basilar reticular abnormalities with minimal ground glass opacities on high resolution computer tomography (HRCT) scans and, if possible, a surgical lung biopsy showing the pattern of usual interstitial pneumonia (UIP).

Survival is poor in patients with IPF. Recent clinical series of well defined cases of IPF have identified a mean survival ranging from 2 to 4 years after diagnosis [2]. Conventional management of IPF is primarily based on the concept that suppressing inflammation prevents progression to pulmonary fibrosis. However, the response to steroids is usually poor in IPF and the use of other immunosuppressive or aggressive cytotoxic agents has largely failed to reduce the death rate in patients with IPF [3]. For significant improvements to occur in the survival of patients with IPF novel and more precisely targeted strategies have to be developed. Therefore, the cellular and molecular pathways that drive the pathogenesis of IPF have to be identified and characterised in detail.

Recent studies challenged the old concept that inflammation is the driving force in the development of IPF. In accordance with the disappointing effects of anti-inflammatory treatment, there is increasing evidence that inflammation may not be as important in the development of pulmonary fibrosis as previously thought. It has been suggested that IPF is mainly a disorder of abnormal alveolar wound repair and remodelling [4]. The current concepts of the pathogenesis of IPF are reviewed under consideration of the implications on future therapeutic strategies in this devastating lung disease.
Old and new hypothesis on the pathogenesis of IPF

The original hypothesis of the pathogenesis of pulmonary fibrosis asserts that unknown stimuli injure the lung resulting in chronic inflammation, fibrogenesis and finally end-stage fibrotic scar formation. This theory of “inflammatory fibrosis” may represent a central mechanism in the pathogenesis of a majority of interstitial lung diseases like sarcoidosis or hypersensitivity pneumonitis. However, in contrast to other interstitial lung diseases, inflammation is usually mild in lung biopsies from patients with IPF and occurs mainly in areas of collagen deposition and honeycomb changes. The role of inflammation at early stages of IPF is also not clear, although little evidence supports the concept that inflammation is more prominent in early stages of IPF/UIP [5].

These observations lead to the hypothesis that inflammation is probably not required for the development of a fibrotic response. Studies primarily in transgenic animal models indicate that the inflammatory response and the fibrotic response can be dissociated. αvβ6 integrin knockout mice, for instance, cannot activate the profibrotic cytokine transforming growth factor-β (TGF-β) from the latent to the active form and develop marked inflammation on exposure to bleomycin but fail to develop fibrosis [6]. Both overexpression of latent or active TGF-β using replication-deficient adenoviruses caused transient inflammation, however, only overexpression of the active form induced fibroblast proliferation and extracellular matrix accumulation [7]. Thus, it was hypothesized that mild inflammation in IPF may be a result of a new microenvironment caused by abnormal interaction of mesenchymal and epithelial cells in the alveolar space during alveolar repair and remodelling [8]. This hypothesis may explain the lack of effect of anti-inflammatory drugs in patients with IPF.

If inflammation is not the driving mechanism in the pathogenesis of IPF, what are the key processes causing pulmonary fibrosis? Increasing evidence suggests that the changes present in IPF result from sequential alveolar epithelial injury and abnormal wound repair [4, 9]. The primary sites of ongoing injury and repair are thought to be the areas of fibroblastic proliferation, so-called fibroblastic foci (Figure 1). These small aggregates of actively proliferating and secreting fibroblasts constitute multiple sites of ongoing alveolar epithelial injury with exuberant deposition of extracellular matrix. Alveolar epithelial cell injury induces the proliferation of fibroblasts and their differentiation to myofibroblasts. Myofibroblasts are identified by the expression of α-smooth muscle actin and are generally considered to be responsible for the wound contraction and soft tissue retraction, which takes place during the development of pulmonary fibrosis [10]. Moreover, myofibroblasts are characterised by the production and secretion of collagen and a variety of cytokines, including the profibrotic TGF-β. The increased production of extracellular matrix by activated fibroblasts/myofibroblasts results in the excessive deposition of extracellular matrix with the destruction of the alveolocapillary units, leading to
pulmonary fibrosis with loss of lung function (Figure 2). In addition, myofibroblasts may induce alveolar epithelial cell death, thereby perpetuating the damage of the alveolar epithelium and inhibiting appropriate and efficient reepithelialisation [11]. The balance between anti- and profibrotic activities in the lung finally determines if restoration of normal lung architecture or fibrosis occurs.

Mechanisms of alveolar repair and remodelling

Alveolar epithelial repair

One important step is the rapid and efficient reepithelialisation of the denuded basement membrane after injury. Efficient alveolar epithelial repair can inhibit the development of pulmonary fibrosis, since the presence of an intact pulmonary epithelial layer suppresses fibroblast proliferation and matrix deposition [12]. This property of the alveolar epithelium has been confirmed in several animal models, demonstrating that delaying alveolar epithelialisation after lung injury leads to an enhanced fibrotic response [13].

Several mechanisms are involved in alveolar epithelial repair. Cuboidal alveolar type II epithelial cells represent the progenitor cells that regenerate the alveolar epithelium after injury [14–16]. Proliferation of alveolar type II epithelial cells is the most obvious event in epithelial repair in vivo, however it needs one or two days to become significant [17]. Therefore other mechanisms may contribute to early alveolar epithelial wound repair. In vitro studies using primary alveolar type II epithelial cells showed that cell spreading and migration are primarily responsible for efficient epithelial wound repair [18]. It is therefore reasonable to speculate that in vivo cell spreading and migration are the primary mechanisms during the early phase of alveolar epithelial repair, followed by cell proliferation leading to alveolar type II hyperplasia. In IPF, however, the regulation of alveolar epithelial repair seems to be disturbed. The capacity of type II alveolar epithelial cells to restore damaged type I cells is seriously altered, resulting in the presence of transitional reactive phenotypes, abnormalities in pulmonary surfactant and alveolar collapse [19].

Role of apoptosis in alveolar repair

In addition, recent evidence suggests that programmed cell death (apoptosis) may play an important causal role in the absence of appropriate reepithelialisation. In lung biopsy specimens from patients with IPF, strong labelling of fragmented DNA (a marker of apoptosis) was found in alveolar epithelial cells [20]. The apoptotic alveolar epithelial cells are detected primarily in areas immediately adjacent to underlying foci of myofibroblasts [11]. More recently, factors that kill alveolar epithelial cells were identified as angiotensin peptides. In bleomycin-induced pulmonary fibrosis, both angiotensin-converting enzyme inhibitors (captopril) or a general caspase inhibitor (zVAD-fmk) blocked alveolar epithelial cell apoptosis resulting in reduced accumulation of collagen matrix, supporting the concept that prevention of alveolar epithelial injury or efficient restoration of
the epithelial integrity may be a key event in the prevention of pulmonary fibrosis [21, 22].

However, cell-specificity is one major problem in the development of apoptosis-modulating agents. Although inhibition of fibroblast proliferation or induction of fibroblast apoptosis is desirable in patients with IPF, inhibition of alveolar epithelial cell proliferation or induction of alveolar epithelial cell apoptosis should be avoided in order to enhance alveolar epithelial repair.

**Growth factors inducing alveolar epithelial repair**

In this respect, growth factors specific for alveolar epithelial cells are of particular interest since they may specifically induce alveolar epithelial repair. Keratinocyte growth factor (KGF), also known as fibroblast growth factor-7, is one of the most potent mitogens observed for alveolar epithelial cells in vitro [23] and in vivo [24]. After bleomycin-induced lung injury elevated KGF levels were found to correlate with alveolar epithelial cell proliferation [25], indicating that KGF may induce efficient alveolar epithelial repair in vivo. These findings are supported by our alveolar wound repair studies showing that KGF increases alveolar epithelial repair in vitro [26]. KGF has impressive protective effects against a wide variety of injurious stimuli to the lung when given as a pretreatment in animal models, whereas little effect was seen when given after the injury [27, 28]. Whether this protective effect could become a treatment effect in patients with lung injury and fibrosis needs to be investigated.

In contrast to KGF, hepatocyte growth factor (HGF), another potent mitogen for alveolar type II cells in vitro [29] and in vivo [30], was shown to reduce bleomycin-induced lung fibrosis if administered after lung injury [31]. It might therefore represent a novel and promising molecule that specifically improves alveolar wound repair after injury, thereby reducing the development and progression of pulmonary fibrosis. However, the clinical studies to date have not explored the mechanistic role of HGF in human lung injury and fibrosis nor have there been any therapeutic trials so far [32].

**Coagulation and fibrinolysis**

The turnover of the provisional fibrin matrix in the alveolar space is critical in the development of pulmonary fibrosis. Organised and efficient resolution of the fibrin matrix in the alveolar space promotes the restoration of the normal alveolar architecture after injury. Dysregulated coagulation and persistent fibrin deposition, however, may contribute to pulmonary fibrosis [33]. The balance of procoagulatory, fibrinolytic and antifibrinolytic activities in the lungs determines whether fibrin will be deposited and organised or resorbed (Figure 2).

Increased procoagulant and anti-fibrinolytic activities have been found in bronchoalveolar lavage fluid from patients with IPF [34, 35], suggesting that fibrin removal is slow in IPF lungs. The enhanced procoagulant activity was mainly ascribed to enhanced tissue factor (TF) production, whereas the reduced fibrinolytic activity is due to an imbalance between urokinase plasminogen activator (uPA) and its inhibitor, plasminogen activator inhibitor (PAI-1) [35, 36]. TF is a cell membrane-associated protein that initiates the coagulation cascade by binding to factor VIIa, leading to thrombin and fibrin generation. In immunohistochemical studies from patients with IPF, TF activity was mainly observed in macrophages and on regenerating alveolar epithelial cells at areas of fibroblast foci [37]. Recent data support the hypothesis that TF may not only serve as a local initiator of the coagulation cascade, but also as a regulator of epithelial resolution by induction of epithelial cell adhesion, cell spreading and cell migration [38, 39].

The fibrinolytic system is active during wound repair to cleave a path for epithelial cell migration. The plasmin/plasminogen activator cascade is a key component in tissue remodelling that accompanies the repair process. Urokinase plasminogen activator (uPA), especially when bound to its specific receptor uPAR, promotes plasmin generation, inducing local fibrinolysis. Alveolar epithelial cells produce both uPA and its receptor, uPAR [40, 41]. The proximity of the two molecules greatly accelerates the rate of plasminogen activation on the alveolar epithelium and clearance of fibrin from the intact lung [42, 43]. The importance of the functional uPA/uPAR system in the prevention of the development of pulmonary fibrosis is supported by experiments performed with animals that received bleomycin intratracheally causing pulmonary fibrosis. Bleomycin-treated mice deficient for plasminogen or uPA showed enhanced pulmonary fibrosis compared to controls [44], whereas adenovirus-mediated transfer of uPA to a bleomycin-treated lung showed reduction in pulmonary fibrosis [45], indicating a protective role of uPA in the development of pulmonary fibrosis. Overexpression of the naturally occurring inhibitor of uPA, plasminogen activator inhibitor-1 (PAI-1), in bleomycin-treated mice resulted in enhanced pulmonary fibrosis [46], indicating a profibrotic role of PAI-1. PAI-1 is strongly induced by TGF-β and may be in part responsible for TGF-β-mediated fibrosis [33]. Although it has to be emphasized that the bleomycin model does not fully represent the pathological changes observed in patients with IPF, PAI-1 was also strongly expressed by alveolar epithelial cells in patients with IPF [56]. However, if PAI-1 is causally related to the development of fibrosis in patients with IPF or merely acts as a marker of disease activity is not known.
Epithelial-fibroblast cross-talk

Alveolar epithelial and mesenchymal cells signal each other bidirectionally, either by direct contact or the release of soluble mediators in a paracrine fashion. Alveolar epithelial cells, particularly after injury, release growth factors that regulate proliferation, migration, apoptosis and matrix protein deposition by fibroblasts and vice versa. The epithelial-fibroblast crosstalk is most critical in determining whether the ultimate outcome of wound healing responses to lung injury is pulmonary fibrosis.

In pulmonary fibrosis a variety of profibrotic factors like platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), connective tissue growth factor (CTGF), TGF-α and TGF-β are produced by alveolar epithelial cells and fibroblasts. Several lines of evidence suggest that TGF-β is a central regulator of pulmonary fibrosis. Several animal models over expressing TGF-β showed extensive progressive fibrosis but limited inflammation, indicating that TGF-β may play a predominant role in the progression of pulmonary fibrosis [7, 47]. Therapeutic efforts are therefore focusing on inhibition of TGF-β activity, for instance by anti-TGF-β1 antibodies, or modulators of TGF-β1 such as pirfenidone. Pirfenidone inhibits TGF-β1 gene expression in vivo resulting in inhibition of TGF-β1-mediated collagen synthesis and appears to slow progression of IPF in patients [48]. Other novel, promising antifibrotic agents include relaxin (inhibits TGF-β1-mediated overexpression of collagen and increases collagenases), suramin (inhibits growth factors), prostaglandin E2 (inhibits collagen production) and lovastatin (blocks formation of granulation tissue by induction of fibroblast apoptosis) [2].

Extracellular matrix accumulation and remodelling

Fibroblasts and myofibroblasts play a central role in synthesis, deposition and remodelling of the extracellular matrix. Increased deposition of extracellular matrix is the hallmark of the aberrant tissue remodelling in IPF. The loss of a regulated turnover of extracellular matrix mainly involves two families of proteins, matrix metalloproteinases (MMP) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). Recent evidence suggests that a local imbalance between MMP and TIMP expression in IPF may create a non-degradative lung microenvironment, leading to the accumulation of extracellular matrix in the interstitial space [4]. In particular, the four TIMPs (TIMP 1–4) are strongly expressed and widely distributed in the lung of IPF patients [49]. TIMP-2, for instance, is expressed by myofibroblasts within the fibroblast foci and may locally inhibit matrix degradation. In addition to its enzymatic inhibitory effect, TIMP-2 may be related to the stimulation of fibroblast proliferation within fibroblastic foci. In contrast, MMP-1 and MMP-2 are upregulated in regenerating alveolar epithelial cells, but are virtually absent in the interstitial compartment [49].

Role of endothelin-1 in pulmonary fibrosis

Several lines of evidence also suggest a possible pathogenetic role of endothelin-1 (ET-1) in IPF. ET-1 is a 21-amino-acid peptide that is synthesized from biologically inactive precursors known as preproendothelin (212 amino acids) and proendothelin, also called big endothelin (38 amino-acids). Beside its potent vasoconstrictor activities, it has been shown to stimulate fibroblast chemotaxis, proliferation and collagen synthesis [50]. ET-1 RNA expression, ET-1 immunoreactivity and ET-1 converting enzyme (ECE-1) activity are increased in lung tissue of patients with IPF [51, 52]. ET-1 activity is mainly upregulated in macrophages, the airway epithelium and in proliferating alveolar type II epithelial cells, particularly in those migrating over the fibrinous matrix, indicating a possible role in alveolar repair and remodelling [52].

Data from animal models indicate that ET-1 may play a role in the pathogenesis of pulmonary fibrosis. In a model of ET-1 transgenic mice, ET-1 overexpression results in the development of pulmonary fibrosis [53]. In bleomycin-induced pulmonary fibrosis in the rat, the increase of ET-1 precedes the increase in collagen content [54].

Several in vitro and in vivo data indicate that the ET receptor antagonist bosentan may have antimitogenic and antifibroproliferative properties. Administration of the ET receptor antagonist bosentan reduced pulmonary fibrosis in bleomycin-induced lung fibrosis [55]. Blocking the endothelin pathway with bosentan may therefore represent a promising novel therapeutic approach in patients with pulmonary fibrosis that is presently being studied in a randomised, placebo-controlled multicentre trial in patients with IPF.
Imbalance of Th1/Th2 cytokines

Recent experimental and clinical studies suggest that a persistent imbalance in the expression of Th2 versus Th1 cytokines in the lung represents an additional possible mechanism for the progression of pulmonary fibrosis. In lung tissue of patients with IPF, the presence of Th2 cytokines predominated over the expression of Th1 cytokines, in particular interferon-γ (IFN-γ) [56]. Whereas Th2 cytokines (IL-4, IL-9, IL-13) activate fibroblasts and induce the production of extracellular matrix, Th1 cytokines (INF-γ) have suppressive effects on fibroblast proliferation and the production of extracellular matrix such as collagen and fibronecctin. It was therefore hypothesized that an imbalance between IFN-γ and the Th2 cytokines IL-4 and IL-13 that favours IFN-γ may be beneficial in inhibiting pulmonary fibrosis. This hypothesis is supported by a recent clinical study of 18 patients with pulmonary fibrosis of unknown aetiology treated with IFN-γ [56]. Whereas the potential efficacy of INF-γ in the treatment of IPF is now being performed in order to determine the potential efficacy of INF-γ in the treatment of IPF.

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