
Novel Aspects of Treatment for Interstitial Lung Diseases

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Abstract

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases with a complex pathogenesis. Inflammation was noticed first to be a component of ILDs, but anti-inflammatory therapy proved effective only in a subgroup of disease entities with predominant inflammatory features such as nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP) or cryptogenic organizing pneumonia (COP). In fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF) inflammation is more limited, whereas fibrogenesis appears to be the primary disease process. Consequently, anti-inflammatory therapy has not been proven to be effective in IPF/UIP and antifibrotic therapies are currently being developed. Treatments for IPF with an antifibrotic potential that have shown positive effects in high-quality randomized controlled trials (RCTs) are N-acetylcysteine (NAC) at a high dose of 600 mg t.i.d. which significantly decreased disease progression in terms of loss of lung function after 1 year and pirfenidone which significantly decreased the number of acute exacerbations of IPF and loss of vital capacity (VC) after 9 months. Interferon- γ failed to meet primary and secondary endpoints in a large RCT. Based on pathogenetic considerations, a large number of treatment approaches currently under investigation are discussed. More effective therapies are urgently needed in a progressive disease such as IPF. Until more effective therapies are available, 600 mg NAC t.i.d. may be used to slow down disease progression but its efficacy has only been demonstrated when used in combination with prednisone and azathioprine. Alternative treatments are still

limited since pirfenidone is presently not available apart from in clinical trials. Combination therapy with prednisone plus azathioprine as recommended in the ATS/ERS consensus statement should be employed after critical risk-benefit assessment in the individual patient.

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Introduction

Treatment approaches for interstitial lung disease (ILD) are closely linked to the underlying pathophysiologic concepts. Pathophysiologic concepts are subject to changes over time. In the field of ILDs several pathophysiologic concepts have evolved recently, that primarily relate to idiopathic pulmonary fibrosis but may also have implications for other forms of pulmonary fibrosis (IPF) such as fibrotic nonspecific interstitial pneumonia or acute interstitial pneumonia (AIP). The initial hypothesis centered on the prime event being an inflammation of the alveolar wall as the result of an unidentified insult, leading to chronic inflammation (i.e. 'alveolitis') and finally inducing fibrosis by a cascade of inflammatory and fibrogenic mediators. Consequently, anti-inflammatory drugs were chosen for treatment of this condition. As this approach appeared unsatisfactory with respect to treatment effect, an alternative hypothesis focusing fibrogenesis as the primary disease mechanism was generated. According to this hypothesis, a repetitive epithelial injury leads to damage of epithelial cells and basement membranes, followed by exudation of

fibrin and focal fibroblast activation and proliferation, finally resulting in fibrotic remodeling of lung parenchyma. Consequently, drugs interfering with fibrogenesis itself appeared to be potentially more logical for treatment of these diseases. Preliminary evidence from controlled clinical trials in IPF seems to provide some encouraging signals, but definitive evidence is still lacking. Additional pathophysiological aspects that may be involved in either of the two concepts involve:

- Oxidant-antioxidant imbalance with a specific lack of glutathione (GSH) as a major antioxidant that also interferes with fibrogenesis itself.
- Impaired fibrin degradation and formation of alveolar fibrin clots as a lead structure for fibroblast chemotactic migration and proliferation.
- Exaggerated release of growth factors such as TGF- β , IGF-1, PDGF, and CTGF may play a crucial role for expansion of connective tissue in the lungs.
- Epithelial cell apoptosis, impaired epithelial regeneration and epithelial-to-mesenchymal transdifferentiation which may be closely linked to integrins and integrin signaling.
- Angiogenesis and neovascularization as an integral component of fibrotic tissue remodeling.
- Mesenchymal stem cells and circulating progenitor cells have been shown to modulate repair mechanisms after lung injury and may therefore be involved in the process of lung fibrosis.
- Mutations of the surfactant protein-C as a cause of familial ILD has shed some light on the role of genetic predisposition and genetic control of the homeostasis and repair of the lung interstitium. A number of additional potential facets of ILD pathogenesis such as fibroblast phenotype, extracellular matrix molecules and matrix metalloproteinases, arachidonic acid metabolites, surfactant proteins, etc. can be added to this list.

For each of these pathophysiologic facets involved in the pathogenesis of IPF and potentially in other forms of fibrosing lung disease, specific targets can be defined and made subject to possible therapeutic interventions (fig. 1). For some of these targets the therapeutic armamentarium is already available and experimental or clinical treatment trials are under way (table 1).

Anti-Inflammatory Therapy

Based on the so-called 'alveolitis hypothesis', anti-inflammatory drugs have historically been recommended

as first-line treatment in ILD. Apart from corticosteroids, a number of cytotoxic and immunosuppressant substances have been used, including azathioprine, cyclophosphamide, cyclosporine-A, mycophenolate mofetil, and methotrexate. A major shortcoming in this area is the fact that sufficiently powered controlled clinical trials to confirm or refute the efficiency of these drugs have never been performed. However, there is a strong belief and empirical knowledge that corticosteroids in combination with azathioprine or cyclophosphamide are effective treatment in nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated ILD (RB-ILD), and eosinophilic pneumonia mimicking ILD. All of these ILDs are characterized by histopathologic patterns that may occur in isolation (idiopathic) or in the context of connective tissue diseases or other precipitating triggers (e.g. hypersensitivity pneumonitis, infections, drugs). Recently, results from the scleroderma lung study have been reported. In this randomized placebo controlled clinical trial, oral cyclophosphamide at a dose of 2 mg/kg/day showed positive effects on decline of vital capacity, SF-36 vitality score, dyspnea score, and skin score as compared to placebo after one year in a total of 162 scleroderma patients with active fibrosing alveolitis (based on BAL or HRCT criteria) [1]. This finding suggests that cyclophosphamide is active in NSIP, which is the histologic pattern that is found in the majority (approximately 80%) of scleroderma patients with lung involvement.

Whereas inflammation is a prominent feature of NSIP, especially in the cellular and mixed subgroups, it is scarce in IPF characterized by the usual interstitial pneumonia (UIP) pattern. Since sufficiently powered controlled clinical trials of corticosteroids or combination therapy with corticosteroids plus cytotoxic/immunosuppressive drugs (e.g. azathioprine, cyclophosphamide) are lacking, it remains unknown whether these drugs are effective or ineffective in IPF. The validity of older studies suggesting at least some effect of this approach in 20–30% of patients with IPF is doubtful, because the patient populations investigated might have included a considerable number of NSIP patients who responded, whereas UIP patients might have had no benefit from this therapy. Despite this unclear situation, but in the absence of any better options, the ATS/ERS consensus statement on the management of IPF recommended combined anti-inflammatory therapy with prednisone (initial dose 0.5 mg/kg/day) plus azathioprine (2 mg/kg/day) or plus cyclophosphamide (2 mg/kg/day) in patients with active disease [2].

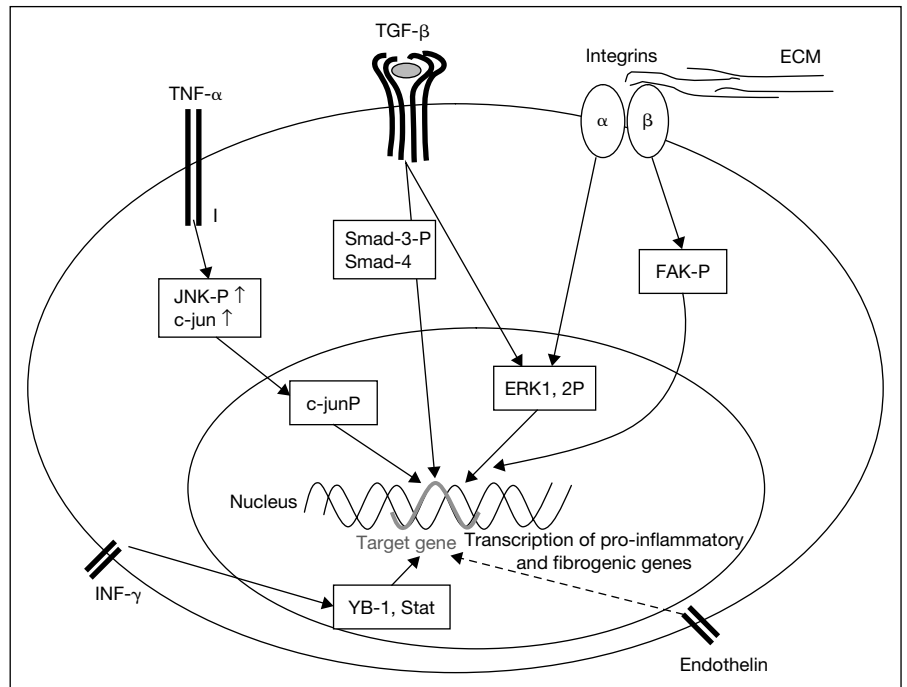


Fig. 1. Anti-fibrotic treatment targets comprise among others TNF- α , TGF- β , integrins, Smad-3, and other cytoplasmic transcription factors. On a cellular level these activation pathways seem to be closely linked and interrelated suggesting at least partial redundancy in the respective activation mechanisms.

Antifibrotic Therapy

Colchicine inhibits collagen secretion and fibroblast proliferation *in vitro* and has been studied in IPF. Retrospective and prospective nonrandomized studies and one good-quality, randomized, controlled trial did not confirm efficacy of this drug.

D-Penicillamine inhibits cross-linking of collagen molecules thus inhibiting collagen maturation, turnover, synthesis, and deposition. Despite extensive use of this drug in IPF there are no RCTs available and nonrandomized uncontrolled trials failed to show any benefit of this drug in IPF.

Interferon- γ 1b (IFN- γ -1b) has antifibrotic properties *in vitro* as it inhibits fibroblast proliferation and collagen synthesis and may therefore be regarded as an antifibrotic drug. The effects of IFN- γ are, however, much more complex as it also interferes with inflammatory mediators from phagocytes and has been shown to downregulate angiogenic biomarkers (CXCL11, epithelial neutrophil-activating protein-78). After positive signals from a randomized, prospective pilot study a pivotal RCT on 330 IPF patients was performed, which did not show a positive effect on the primary endpoint – progression-free survival [3]. However,

exploratory post hoc analysis of the data showed a significant survival benefit in a subgroup of patients with less advanced disease at baseline (FVC >62%, DLco >35%). This finding prompted a subsequent study (INSPIRE trial), including more than 800 patients in earlier disease states and using mortality as the primary outcome variable. This RCT was recently completed and showed that IFN- γ -1b is not effective in IPF.

Pirfenidone is a pyridone compound with antifibrotic properties essentially due to inhibition of effects of TGF- β 1. Positive effects on lung function parameters (FVC, DLco) have been reported in an open label study of IPF patients suggesting a potential role in the treatment of this condition. A recent RCT using pirfenidone vs. placebo in 109 IPF patients (2:1 randomization) was stopped prematurely because of a significant accumulation of acute exacerbations in the placebo group and absence of acute exacerbations in the pirfenidone group ($n = 5$ vs. $n = 0$, $p < 0.0031$); it was considered ethically not justified to withhold active therapy from the placebo treated patients. The primary endpoint, difference of minimal oxygen saturation during a 6-min timed walk test at 9 months vs. baseline, showed a trend in favor of pirfenidone, but statistical significance was not met ($p = 0.07$), potentially due to the premature end of the study.

Table 1. Drugs employed in recent, ongoing, and future clinical trials in IPF

Substance	Mechanism	Trial-status
Acetylcysteine	antioxidant, glutathione ↑	phase II–III completed (IFIGENIA)
Bosentan	endothelin receptor antagonist	phase II completed (BUILD-1) phase III planned (BUILD-3)
Etanercept	TNF- α -antagonist	phase II completed
FG-3019	CTGF-antagonist	phase I–II ongoing
Heparin (inhaled)	anticoagulant	phase II ongoing
Imatinib mesylate	PDGF-receptor antagonist	phase II ongoing
Interferon- γ	fibroblast inhibition, immunomodulating	phase II completed (GIPF-001) phase III ongoing (INSPIRE)
Pirfenidone	fibroblast inhibition, TGF- β -antagonism	phase II completed phase III starting (PIPF-003)
Rapamycin	antiproliferative, immunosuppression	phase II ongoing
SD-208	orally active TGF- β receptor-I-kinase inhibitor	phase I–II ongoing
Integrin- $\alpha v \beta 6$ -mab	inhibition of integrin-mediated TGF- β activation	in vitro and animal models

A significant positive effect was, however, observed on the decline of FVC ($p = 0.03$) reconfirming a potential treatment effect [4]. Despite the premature termination of the study, pirfenidone seems to be active in IPF, but confirmation of this study in a new RCT is under way. Although pirfenidone is well tolerated when given orally, a relatively high percentage of photosensitization and gastrointestinal side effects were noted during the clinical trial [4].

Miscellaneous other compounds have been shown to have antifibrotic effects in vitro, including statins and angiotensin-converting enzyme inhibitors. Good-quality clinical trials investigating the potential effect of these substances in IPF are, however, lacking.

Antioxidant Therapy

Excessive oxidative stress has been shown to occur within the lungs of IPF patients and systemically, whereas

the major pulmonary antioxidant, GSH, is lacking in the epithelial lining fluid as well as intracellularly in BAL cells. This pro-oxidative condition has been linked to pro-inflammatory as well as fibrogenic mechanisms including fibroblast proliferation and collagen turnover. Moreover, GSH – a tripeptide consisting of γ -glutamyl-cysteinyl-glycine – is a multi-task compound which, besides its antioxidant properties, also inhibits fibroblast and lymphocyte proliferation and differentiation, it is involved in detoxification and protein synthesis. N-acetylcysteine (NAC) at a high dose of 600 mg t.i.d. has been shown to be able to replenish GSH levels in the epithelial lining fluid as well as intracellularly in IPF patients. Potential modes of action of NAC therapy and consequent GSH replenishment are summarized in figure 2. Moreover, in one pilot study over 12 weeks, NAC 600 mg t.i.d. was reported to positively influence lung function in a mixed group of patients with IPF or fibrosing alveolitis due to systemic sclerosis [5]. Based on these and other findings a RCT, in 155 IPF patients using NAC 600 mg t.i.d., given together with prednisone and azathioprine vs. placebo together with prednisone and azathioprine, was performed showing significant beneficial effects on the decline of vital capacity (VC) and diffusing capacity (DLco) after 1 year [6]. There was an absolute difference of 180 ml of VC and 0.75 mmol/min/ kPa of DLco in favor of the NAC group as compared to placebo after 1 year, representing a relative difference between both groups of 9% for VC and 24% for DLco. A significant survival benefit was not observed in this study, which, however, was not powered nor designed to investigate survival [6]. As for the primary endpoints – change in VC and DLco after 1 year – this study was clearly positive. The clinical relevance of the findings reported is, however, still under debate. Categorical analysis of the lung function data applying the criteria given in the ATS/ERS statement [1] showed stabilization or improvement in VC (i.e. no decline of VC >10% from baseline) in 61% of patients in the NAC group compared to only 49% in the placebo group; similarly stabilization or improvement of DLco (i.e. no decline of DLco >15% from baseline) was observed in 57% of NAC treated patients and in 49% within the placebo group; both differences were in favor of NAC treatment but statistically not significant ($p = 0.22$ and $p = 0.17$ respectively), and were also not prespecified endpoints of the study [6]. At this time it seems fair to conclude that the available evidence supports the use of high dose NAC (i.e. 600 mg t.i.d.) together with prednisone and azathioprine in IPF patients in an attempt to slow down loss of lung function. Although the treatment effect was seen with high-dose NAC vs. placebo it remains unclear whether a similar effect could be

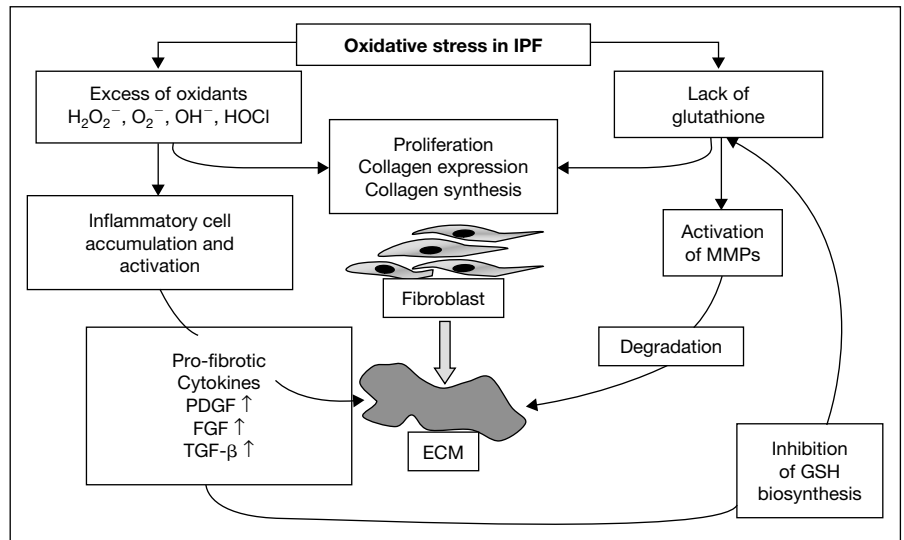


Fig. 2. Role of oxidants and antioxidants (e.g. glutathione) in the pathogenesis of idiopathic pulmonary fibrosis and sites of interaction with NAC therapy.

achieved with NAC alone since prednisone plus azathioprine therapy were administered equally in both groups and a combinatorial effect cannot be excluded. The absence of major side effects with this therapy also allows its broad use in IPF. Whether NAC therapy translates into a clinical benefit for the patients in terms of exercise tolerance, quality of life or survival has not yet been demonstrated and is subject to controversial discussion.

Anticoagulant and Fibrinolytic Therapy

Fibrinogen exudation and formation of intra-alveolar fibrin clots is described histologically in patients with ILD and pulmonary fibrosis and is interpreted as a direct consequence of an insult to lung parenchyma and/or an inflammatory reaction to lung injury. Impaired fibrinolytic activity within the lungs has been described in IPF patients and contributes to a lack of clearance of fibrin, which itself functions as a lead structure for chemotactic fibroblast migration into the alveolar wall and air spaces and allows focal fibroblast proliferation thus contributing to the fibrotic remodeling process. Moreover, formation of fibrin clots interferes with physiologic surfactant function and favours alveolar collapse and development of atelectasis. Based on these observations, a pragmatic approach is to shift coagulant/anticoagulant balance toward anticoagulation or fibrinolysis using heparin or fibrinolytic substances; both can be administered topically to the lungs via the inhaled route. In animal experiments using the bleomycin model in rabbits, it has already been

demonstrated that inhaled heparin and inhaled urokinase-type plasminogen activator are able to improve compliance and reduce fibrosis even when therapeutic intervention started 14 days after bleomycin administration [7]. A clinical phase II study is also under way, but there are no data available yet.

Antifibrogenic Therapy

A number of profibrogenic mediators and growth factors has been claimed to be involved in the pathogenesis of ILDs and especially IPF. An overview of cytokines and signal transduction pathways in fibrogenesis is shown in figure 1.

Endothelium-derived endothelin-1 (ET-1) is not only a pulmonary vasoconstrictor but also a potent mitogen to endothelial cells, vascular smooth muscle cells, myofibroblasts, and fibroblasts. ET-1 also increases synthesis and deposition of collagen and thus may contribute significantly to pulmonary remodeling. Since elevated ET-1 levels and increased expression of ET receptors in lung tissue have been demonstrated not only in pulmonary hypertension (PH) but also in pulmonary fibrosis without PH, it is hypothesized that ET-1 is involved in the pathogenesis of ILDs and especially of IPF. Consequently, the use of the dual ET-receptor antagonist bosentan, which is already approved for treatment of pulmonary arterial hypertension, might positively influence the fibrogenic process and the course of IPF. This hypothesis is presently tested in a randomized placebo-controlled multicenter trial using

bosentan at a dose of 125 mg b.i.d. in IPF patients. A media release by the manufacturer of bosentan on November 28th 2005 states that this study did not meet the primary endpoint, which was exercise improvement as measured by the 6-min walk test. Positive trends were, however, noted in pre-defined secondary endpoints such as the combined incidence of death or treatment failure (i.e. worsening pulmonary function tests or acute decompensation of IPF) at 12 months (36.1% in the placebo group vs. 22.5% in the bosentan group; $p = 0.076$; 95% CI 0.37, 1.05), representing a relative risk reduction of 38%. Since publication of these data is still pending, a more detailed interpretation is not possible at present.

Tumor necrosis factor- α (TNF- α) is known as a proinflammatory but also fibrogenic mediator. TNF- α antagonists are presently approved for the treatment of rheumatoid arthritis, psoriasis arthritis, and ankylosing spondylitis (M. Bechterew). Anecdotal reports and small case series imply that TNF- α antagonists may also be beneficial in cutaneous and therapy-resistant pulmonary sarcoidosis. Increased amounts of TNF- α have been found in the lungs of patients with IPF. On the basis of these findings, blockade of TNF- α using the fully human soluble TNF- α receptor etanercept at a dose of 25 mg s.c. twice a week over a 48-week period was used in a randomized controlled trial. Eighty-seven patients with IPF were included in this trial and were randomized to receive etanercept or placebo (1:1); patients with severe disease (FVC <45% predicted and/or DLco <25% predicted) were excluded. Preliminary results of this study were reported during the ACCP conference in Montreal 2005 and are published as an abstract [8]. The primary endpoints – i.e. change of FVC, DLco, and P(A-a)O₂ gradient vs. baseline – were not met in this study, but there was a small positive trend in favor of etanercept therapy. Moreover, post hoc analysis of disease progression or death as a combined endpoint showed an advantage for etanercept of borderline statistical significance ($p = 0.052$). Given these positive signals, TNF- α antagonism may prove effective in IPF, but additional studies are necessary.

Tyrosine kinase activation is another common pathway of fibrogenesis that has been shown to be involved in bone marrow fibrosis; imatinib mesylate is an inhibitor of the tyrosine kinase and also inhibits bone marrow fibrosis. Moreover, imatinib is also an inhibitor of the platelet-derived growth factor (PDGF) receptor and PDGF has been found to be one of the major fibrogenic growth factors in IPF [9]. PDGF inhibition, therefore, may be beneficial in IPF patients. A phase II randomized, placebo-controlled, study with imatinib mesylate administered orally in IPF patients is currently under way, but results are not yet

available. Interestingly, a recent case report in a patient with progressive pulmonary arterial hypertension suggests that imatinib may be effective in this disease. In agreement with this human case report, partial reversal of vascular remodeling by imatinib has been demonstrated in two different animal models of PH [10]. Based on these positive effects, it is possible that imatinib may also be active in IPF, but studies to support this hope objectively are still pending.

Another potential treatment approach is provided by the monoclonal antibody FG-3019 directed against connective tissue growth factor (CTGF), which is of crucial importance for the secretion of collagen and fibronectin. A phase I study of limited duration (1 month) in patients with IPF was initiated, and further development of this novel approach is already scheduled.

Rapamycin is a macrolide molecule with profound immunosuppressive properties, which are currently exploited by use of this substance in solid organ transplantation. However, rapamycin – also known as sirolimus – also has potent antiproliferative effects especially on mesenchymal cells and may, therefore, be of potential interest for treatment of ILDs and especially IPF. There are numerous reports of positive effects of rapamycin in animal models of lung fibrosis. In Australia, an open-label randomized study has been initiated in IPF patients to receive sirolimus at a dose to achieve trough levels of 5–8 ng/ml plus prednisone 10 mg o.d. or standard therapy with the primary endpoint being absence of disease progression.

Epithelium to Mesenchyma Cross-Talk

The new hypothesis of the pathogenesis of (idiopathic) pulmonary fibrosis includes a crucial role for the interaction of epithelial and mesenchymal cells. Observations from various investigators suggest that epithelial cell apoptosis and a lack of epithelial regeneration may allow unregulated proliferation of interstitial fibroblasts. These observations from animal models resemble human UIP and AIP in histologic and ultrastructural findings. The presence of epithelial necrosis and apoptosis with denuded basement membranes in widely scattered foci that are characterized histologically by loosely aggregated interstitial fibroblasts, so called ‘fibroblast foci’, are the histologic hallmark of UIP, whereas AIP is characterized by more generalized fibroblast proliferation [11]. Based on these observations, focal or extensive acute lung injury is thought to be the cause of these changes, with an increasing number of fibroblast foci being associated with an adverse prognosis in UIP. In addition, experimental studies suggested that

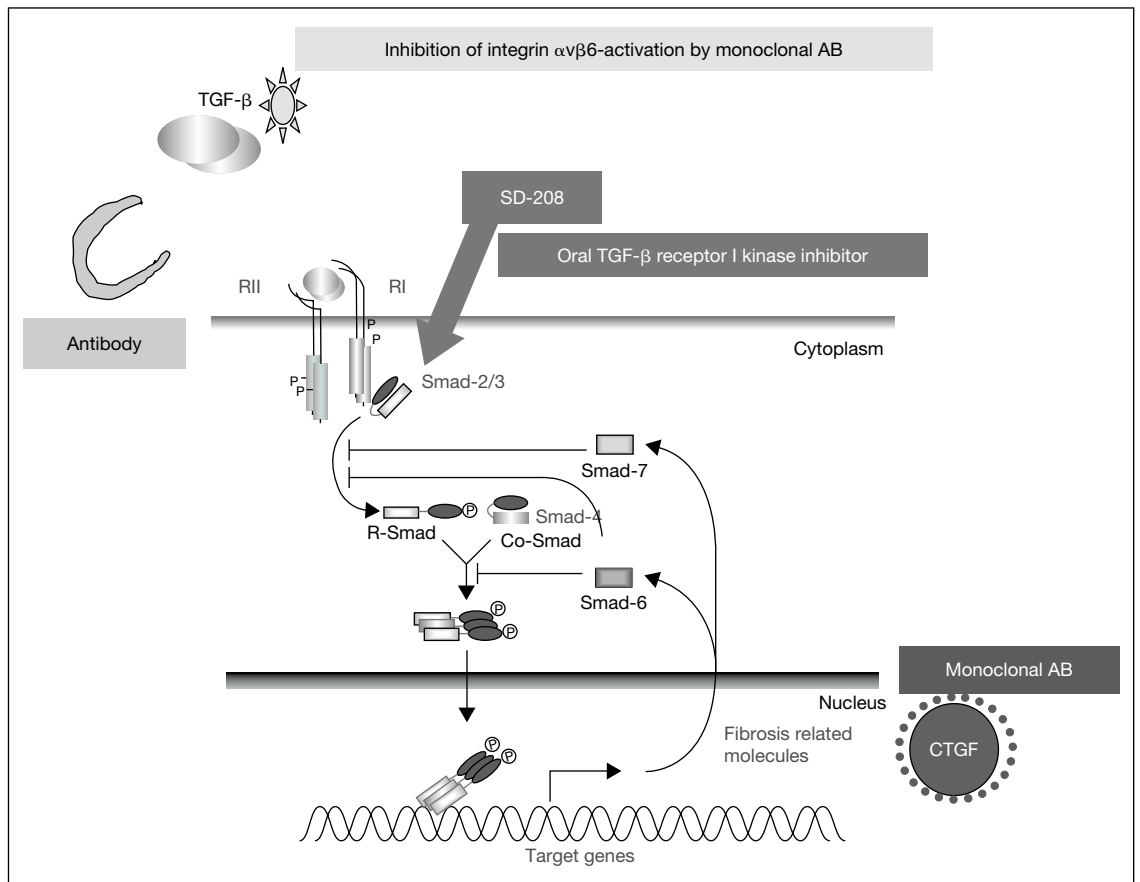


Fig. 3. Treatment approaches with respect to epithelial mesenchymal interaction and transdifferentiation aiming at inhibition of integrin and TGF- β activation, and intracellular Smad signaling.

there is also the possibility that epithelial cells may under certain circumstances transform or differentiate into mesenchymal cells, i.e. fibroblasts or myofibroblasts, an observation called epithelial to mesenchymal transdifferentiation (EMT). This intriguing process can be induced by TGF- β and is mediated by a complex process involving the nuclear transcription factor Smad-3 [12]. In this context integrins, a family of heterodimeric transmembrane receptor proteins, may also play a crucial role as they provide cell specific binding to matrix proteins and adaption of cell phenotype to changes in matrix environment [13]. As a consequence programmed cell death (apoptosis) may even occur when appropriate signals from the environment (outside-in-signaling) are not present. Of special interest in this context is the epithelial cell specific $\alpha\beta6$ integrin, which binds to several ligands including fibronectin, tenascin-C, and vitronectin. It has been demonstrated that activated $\alpha\beta6$ integrin induces TGF- β secretion thus initiating a profibrotic signal [13]. Interestingly, integrin- $\beta6$ -deficient

mice were resistant to bleomycin induced fibrosis but developed an exaggerated inflammatory response and blockade of various integrins – $\beta2$, $\alpha1$, $\alpha1\beta1$, $\alpha\beta6$ – has shown promising antifibrotic effects in animal experiments. Anti-integrin antibodies or pharmacologic integrin inhibitors, therefore, may provide new antifibrotic treatment options in the future. Alternative approaches to this ‘epithelium-to-mesenchyma’ pathway include direct inhibition of TGF- β by monoclonal antibodies or inhibition of down-stream signalling, e.g. inhibition of Smad-3. All of these new potential therapeutic targets are presently under investigation, but clinical application is not yet in sight (fig. 3).

Antiangiogenic Therapy

The formation of new blood vessels is a ubiquitous, complex and fundamental process of tissue repair after injury and requires coordinated regulation of matrix proteolysis and

endothelial cell migration. Angiogenesis and neovascularization have become an issue in the pathogenesis of pulmonary fibrosis since a net pro-angiogenesis imbalance of angiogenic and angiostatic chemokines was noted in animal models of lung fibrosis and in IPF patients [14]. Interestingly, within the fibroblast foci vascularization is diminished, whereas the surrounding areas show increased angiogenic activity. This observation prompted the interpretation that angiogenesis is part of the temporal heterogeneity in UIP and may precede the fibrotic process. Alternatively, angiogenesis may also help to conserve the lung structure by facilitating an appropriate repair [15]. A number of angiogenic mediators such as interleukin-8 (IL-8), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), epithelial neutrophil-activating protein-78 (ENA-78) and angiostatic mediators such as gamma interferon inducible protein-10 (IP-10) are involved in the process of angiogenesis. Additionally, the presence of proteolytic enzymes, e.g. matrix metalloproteinases (MMPs), is critical for local degradation of vascular basement membrane and surrounding interstitial extracellular matrix proteins to allow endothelial chemotactic migration and sprouting of new capillaries. Again this process of local proteolysis is limited and tightly regulated by tissue inhibitors of metalloproteinases (TIMP) and some MMPs also mediate angiostatic effects by converting plasminogen to angiostatin.

Obviously, angiogenesis is a complex and highly regulated process and its role within the pathogenesis of pulmonary fibrosis is not yet completely defined. However, some studies in human IPF and in animal models of lung fibrosis suggest that aberrant angiogenesis contributes to an enhanced fibrotic response prompting the hypothesis that anti-angiogenic therapy may be beneficial in this condition. Indeed, interferon- γ and the endothelin receptor antagonist bosentan may have some anti-angiogenic properties which are potentially clinically relevant. New promising targets for anti-angiogenic treatment approaches include inhibitors of angiogenic factors such as VEGF or b-FGF as well as inhibitors of specific MMPs.

Stem Cells

The origin of fibroblasts in pulmonary fibrosis is assumed to be intrapulmonary. This assumption has been challenged recently by observations that in animal models of pulmonary fibrosis mesenchymal stem cells and bone-marrow derived progenitor cells traffic to the injured lung, where they settle and differentiate into fibroblasts and myofibroblasts, thus contributing to the fibrotic response [16, 17].

However, bone marrow-derived stem cells may also adopt an epithelium-like phenotype, which favors regeneration and ameliorates the fibrotic response [18]. The circumstances leading to differentiation into fibroblast or epithelial phenotype are, however, not yet identified. Nonetheless, these observations add a novel aspect to the traditional views of fibrotic lung disease. The potential treatment implications are speculative at present, but stem cell research is developing rapidly and it may be a reasonable vision that stem cells primed to differentiate into epithelial cells might be used to support re-epithelialization and parenchymal regeneration after lung injury thus avoiding fibrotic reactions.

Genetic Predisposition

A fast growing body of evidence supports the view that genetic predisposition plays a role in pulmonary fibrosis not only in a small percentage of familial forms of ILD but also in the context that interstitial remodeling and fibrogenesis itself may be governed by genetic factors. Mutations of the surfactant protein C gene have been found to be associated with familial idiopathic interstitial pneumonia [19, 20]. Interestingly, in the affected families there is not only a cohort of IPF patients, but other ILDs are also observed, especially in children, including non-specific interstitial pneumonia and DIP. Recently, mutations of ABCA3, an ATP binding transmembrane carrier for a wide range of substrates including proteins and lipids, have been described in association with pediatric ILD and fatal surfactant deficiency in full-term neonates [21]. These examples illustrate that specific mutations may lead to different forms of ILDs which seem to involve similar pathways of inflammation and fibrogenesis. A number of gene polymorphisms including surfactant proteins, TGF- β , IL-1, IL-6, TNF- α , angiotensin-converting enzyme, and complement receptor-1, have been discussed in association with the pathogenesis of ILDs [22]. Although the specific role and contribution of these genetic factors within the complex pathogenesis of pulmonary fibrosis remains to be defined, it is already obvious that genetic predispositions once identified will allow new treatment targets to be defined and, in the long run, gene therapy may even be considered to be a future treatment approach.

Conclusion

ILDs comprise a heterogeneous group of complex diseases with variable responsiveness to treatment and variable prognosis. As a rule, ILDs with predominant

inflammatory features such as cellular nonspecific ILD (NSIP), DIP, and cryptogenic (or associated) organizing pneumonia, are responsive to anti-inflammatory therapy comprising corticosteroids alone or in combination with cytotoxic agents (azathioprine or cyclophosphamide). New immunosuppressive drugs with additional antiproliferative properties such as mycophenolate mofetil or rapamycin may offer some advantages, but experience is too limited to allow recommendation of these substances outside of controlled clinical trials.

In diseases with predominant fibrogenic features such as IPF (histologic pattern of UIP) and AIP (clinical presentation as Hamman-Rich syndrome) treatment is far less effective and elusive. The role of anti-inflammatory therapy employing corticosteroids and cytotoxic agents (azathioprine or cyclophosphamide) in IPF is still unknown and controlled clinical trials to settle this issue should be undertaken. However, the simultaneous presence of NSIP and UIP patterns in different biopsies from the same lung in up to 15% of patients suggests that there may be at least a limited response to anti-inflammatory therapy in some patients, which is in line with clinical experience in a small minority of IPF patients. Therefore, anti-inflammatory therapy should not be discarded completely in IPF patients until clear evidence shows that it is ineffective. It should also be noted here that there are close relations between inflammatory and fibrogenic pathogenetic pathways and available therapies are not specific in this respect but affect inflammation, fibrogenesis, and even angiogenesis to a variable extent.

Recent results from well designed high-quality randomized controlled clinical trials in patients with IPF/UIP suggest that N-acetylcysteine at a dose of 600 mg t.i.d., given with prednisone and azathioprine, significantly slows down disease progression in terms of loss of lung function and pirfenidone at a dose of 600 mg t.i.d. significantly reduces the frequency of acute exacerbations and functional deterioration. However, whether these effects suffice to improve survival and change the natural course of the disease remains to be elucidated.

Preliminary data on the endothelin receptor antagonist bosentan and the TNF- α soluble receptor etanercept in IPF

indicate interesting effects on secondary endpoints but the primary endpoints were missed.

New treatment approaches targeting fibrin break down, inhibition of PDGF, TGF- β , Integrins, transcription factors (Smad), angiogenesis are under investigation and may eventually be tested in clinical trials.

Genetic predisposition, genetic control of lung parenchymal remodeling, and stem cell engraftment of injured lungs have been described and may represent a basis for the development of future treatment concepts.

Practical Recommendations

In patients with NSIP, DIP, RB-ILD, or COP either as an idiopathic disease or in association with other diseases or exposures such as collagen vascular diseases (e.g. systemic sclerosis), exposure to organic dusts (hypersensitivity pneumonitis), inhaled cigarette smoking (DIP, RB-ILD), recommended treatment after elimination of a potential causal factor are systemic corticosteroids (usually prednisone at an initial dose of 0.5 mg/kg o.d. tapered after 6–12 weeks). If resolution of the disease is not achieved despite a course corticosteroid monotherapy over 12 weeks combination with azathioprine (2 mg/kg o.d.) or cyclophosphamide (2 mg/kg o.d.) is recommended.

In IPF patients (UIP pattern) N-acetylcysteine at a dose of 600 mg t.i.d. has proven effective in reducing disease progression and should be recommended for all patients who do not wish or qualify to participate in a clinical trial. Prednisone (initial dose 0.5 mg/kg o.d.) plus azathioprine (2 mg/kg o.d.) or plus cyclophosphamide (2 mg/kg o.d.) as recommended by the ATS/ERS consensus statement on IPF should be added. Pirfenidone is currently not available outside clinical trials. Since available therapies for IPF are still unsatisfactory as they usually do not restore lung function to normal or near normal it has to be emphasized that the major interest should be to include these patients in controlled clinical trials to find more effective treatment strategies; a number of promising approaches in this respect have been discussed in this chapter.

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