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MINIREVIEWS

Promising new treatment targets in patients with fibrosing lung disorders

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Abstract

The processes of lung fibrogenesis and fibrotic healing are common to a number of conditions with different etiologies. The lungs are the only affected organ in some cases, whereas in others, several organ systems are involved. Therapeutic options can be discussed from various perspectives. In this review, we address the localization of therapeutic targets with regard to cell compartments, including secreted ligands, cell surface, plasma membrane-cytosol interplay, cytosol and nucleus. Complex approach using stem cell therapy is also discussed. As the prognosis of patients with these disorders remains grim, treatment combinations targeting different molecules within the cell should sometimes be considered. It is reasonable to assume that blocking specific pathways will more likely lead to disease stabilization, while stem cell-based treatments could potentially restore lung architecture. Gene therapy could be a candidate for preventive care in families with proven specific gene polymorphisms and documented familial lung fibrosis. Chronobiology, that takes into account effect of circadian rhythm on cell biology, has demonstrated that timed drug administration can improve treatment outcomes. However, the specific recommendations for optimal approaches are still under debate. A multifaceted approach to interstitial lung disorders, including cooperation between those doing basic research and clinical doctors as well as tailoring research and treatment strategies toward (until now) unmet medical needs, could improve our understanding of the diseases and, above all, provide benefits for our patients.

Key words: Interstitial lung disease; Treatment; Idiopathic pulmonary fibrosis; Connective tissue disease; Cell compartments; Signaling molecules; Signal transducers; Transcription factors

Core tip: Novel treatment targets in patients with fibrosing interstitial lung diseases are summarized. Targets are listed according to defined cell compartments. Ongoing clinical studies focusing on some of the promising targets provide insight into current progress in lung fibrosis research.

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INTRODUCTION

The processes of lung fibrogenesis and fibrotic healing are common to a number of conditions with different etiologies. The lungs are the only affected organ in some cases, whereas in others, several organ systems are involved. There are several similar features that can be observed in adult patients with fibrosing lung disorders: *e.g.*, a history of exposure to inhaled antigens (organic or

Table 1 Interstitial lung diseases with a fibro-proliferative pattern, radiologic/histologic phenotypes and new treatment modalities

Etiology	Radiologic/histopathologic phenotype	New treatment modalities studied
Lung-specific involvement		
Inhalation of organic antigens (*e.g.*, EAA)	NSIP, UIP, OP, DIP, AIP	No
Inhalation of inorganic materials (*e.g.*, asbestosis)	NSIP, UIP, OP, DIP, AIP	No
Drug and radiation toxicity	NSIP, UIP, OP, DIP, AIP	No
Idiopathic pulmonary fibrosis	UIP ± NSIP	Yes
Idiopathic nonspecific interstitial pneumonia	NSIP ± UIP	No
Systemic involvement		
ILDs associated with connective tissue diseases	NSIP, UIP, OP, DIP, AIP	Yes
Sarcoidosis and other granulomatoses	NSIP, UIP, OP, DIP, AIP	Yes

EAA: Extrinsic allergic alveolitis; IPF: Idiopathic pulmonary fibrosis; NSIP: Nonspecific interstitial pneumonia; ILD: Interstitial lung disease; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; DIP: Desquamative interstitial pneumonia; AIP: Acute interstitial pneumonia.

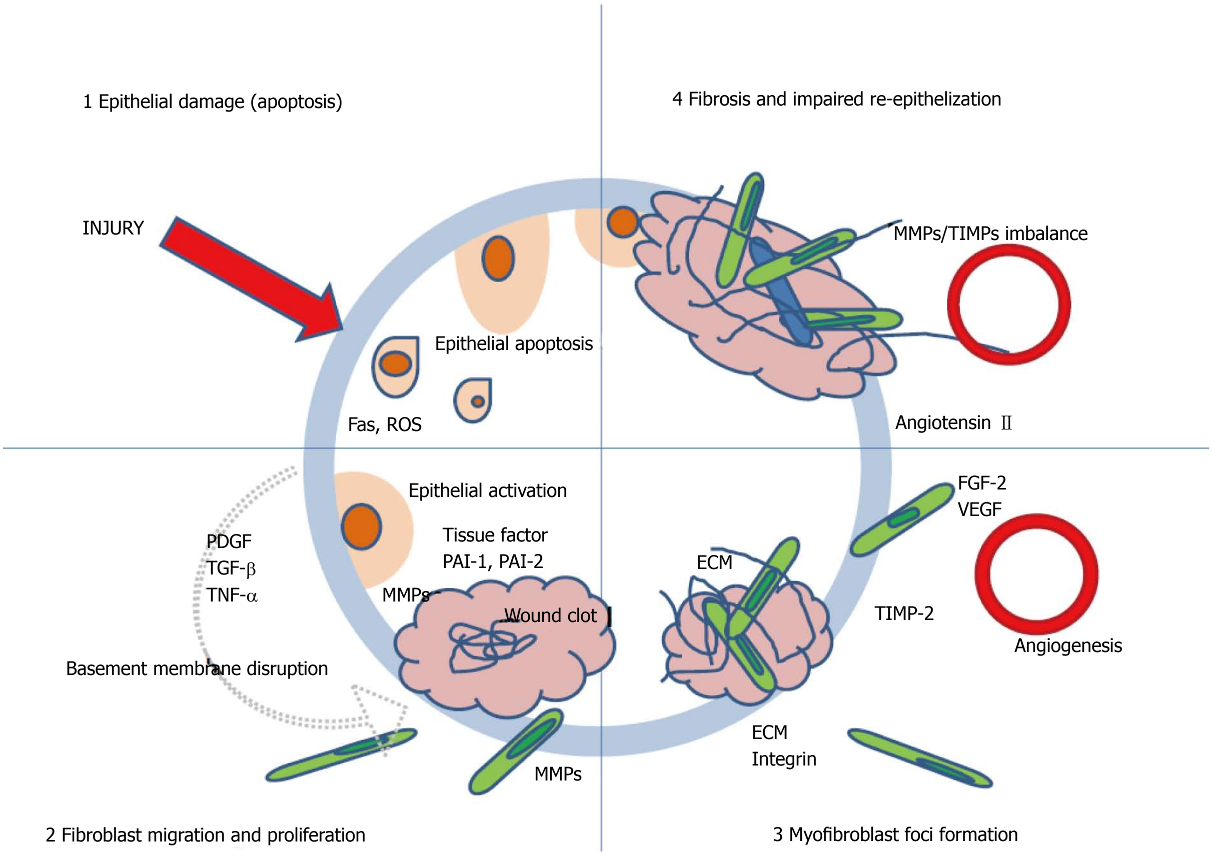

Figure 1 Suggested pathogenesis of idiopathic pulmonary fibrosis. ROS: Reactive oxygen species; PDGF: Platelet-derived growth factor; TGF-β: Transforming growth factor beta; TNF-α: Tumor necrosis factor alpha; MMPs: Matrix metalloproteases; PAI: Platelet activator inhibitor; ECM: Extracellular matrix; TIMP: Tissue inhibitor of metalloproteases; FGF: Fibroblast growth factor; VEGF: Vascular endothelial growth factor.

inorganic compounds, smoking), respiratory infections (viral), extra-esophageal reflux, impaired coagulation cascade, signs of immune system disorders with detectable autoantibodies, and genetic susceptibility[1-5]. In some patients, both fibrosis and inflammation may be observed; in contrast, in the pathogenesis of idiopathic pulmonary fibrosis (IPF), inflammation plays a relatively minor role[6].

The spectrum of interstitial lung diseases with a fibroproliferative pattern of healing is summarized in Table 1.

Until recently, most treatment options in patients with interstitial lung disorders have focused on inflammation and lung fibrosis, relying on anti-inflammatory and immunosuppressive agents[7]. However, these strategies have been found to be effective only in specific groups of patients (patients with connective tissue-associated ILD, history of inhalation of organic antigens, drug- and radiation-induced ILD, sarcoidosis or other granulomatoses). In IPF patients, as documented in the Panther study, these treatments not only failed, but they seemed to negatively impact the mortality and morbidity outcomes of patients[8].

Figure 1 depicts the hypothesized mechanism underlying the pathogenesis of IPF. Repeated micro-injuries to

Table 2 Potential treatment targets in patients with fibrosing lung disease, according to target location

Target	Potential molecular target
Signals from other cells Autocrine signals	Cytokines, survival factors, chemokines, hormones, transmitters, growth factors, extracellular matrix compounds, Wnt, Hedgehog, death factor
Cell surface	Cytokine receptors, receptor tyrosine kinase, G protein-coupled receptors, integrins, Frizzled, Patched, Fas receptor, ion channels
Plasma membrane-cytosol interface	Kinases
	miRNAs
Cytosol signal transducers	Apoptosis-related proteins
Nucleus	Transcription factors
	Epigenetic modifiers

miRNA: Micro-ribonucleic acid.

Table 3 Ongoing clinical studies in idiopathic pulmonary fibrosis patients

Target	Potential molecular target	Ongoing clinical study
Signals from other cells	Interleukin 13	Lebrikizumab NCT01872689
Autocrine signals	Connective tissue growth factor	Tralokinumab NCT02036580
		FG-3019 NCT01890265
Cell surface	Lysophosphatidic acid receptor	Lysophosphatic acid receptor antagonist-NCT01766817
	Lysyl oxidase LOXL2	Simtuzumab NCT01769196
	CD20	Rituximab NCT01969409
	Androgen receptor	Nandrolone decanoate NCT02055456
Plasma membrane-cytosol interface	Phosphoinositol kinase PI3K	Phosphoinositol kinase PI3K inhibitor NCT01725139
Cytosol signal transducers	Avβ6 integrin	STX-100 NCT01371305
Nucleus		None
Stem cells		Autologous adipose-derived adult stem cells NCT02135380
		Autologous mesenchymal bone marrow-derived stem cells NCT01919827
		Allogenic human mesenchymal stem cells NCT02013700

the alveolar epithelium seem to play a key role in the initiation of the disease. Fibroblasts are attracted to the site of injury, proliferate and eventually form fibroblast foci with exaggerated extracellular matrix production[9]. Some of the epithelial type II alveolar cells may undergo transdifferentiation into fibroblasts and become activated[10]. Developmentally active programs, including Sonic hedgehog (Shh), Notch and Wingless-related MMTV integration site (Wnt), were found to be repeated in IPF[11,12]. However, unlike in "normal" development, these pathways seem to be dysregulated, resulting in an overactive development phenotype[13].

These clinical observations as well as new insights into the pathogenesis of fibrosing lung diseases have led to a vigorous search for alternative treatments. Potential targets for the treatment of fibrosing ILD are listed in Table 2. Table 3 presents ongoing clinical studies in IPF patients.

SECRETED LIGANDS (SIGNALS FROM OTHER CELLS, AUTOCRINE SIGNALS)

Cytokines, chemokines, growth factors and their receptors have been widely investigated in patients with various fibrosing lung diseases. These molecules play a role in inflammation, fibrogenesis and angiogenesis, and most of them have been found to be somehow involved in the pathogenesis of fibrosing lung disorders[14]. Although *in vitro* studies and experiments using mouse models have provided promising results suggesting that blocking certain chemokines or cytokines could prevent the progression of lung fibrosis, results from clinical studies have not been convincing. For instance, although tumor necrosis factor alpha (TNF-alpha) inhibitors were found to be useful in the management of connective tissue diseases (CTDs) and sarcoidosis, they were demonstrated to have no benefit in patients with marked lung fibroproliferation, such as in IPF patients[15,16]. Moreover, in patients with pulmonary involvement due to CTDs, the role of TNF-alpha inhibitors has yet to be established[17]. Other agents, such as interleukin-13 (IL-13) inhibitors, chemokine (C-C motif) ligand 2 inhibitors, connective tissue growth factor (CTGF) inhibitors, transforming growth factor (TGF) inhibitors and (beta 1 isoform) lysyl oxidase-like (LOXL) 2 inhibitors, are currently the subject of clinical studies[18]. TGF beta is considered an important mediator of fibrotic processes. It plays a role in in wound healing, extracellular matrix production and angiogenesis. However, it is also involved in inflammatory responses and can exhibit both pro-inflammatory and anti-inflammatory properties. TGF beta also plays an ambiguous role in oncogenesis: it can inhibit the growth of some tumor cells while enhancing migration and growth in others[19]. As the fibrogenic properties of TGF beta have been known and extensively studied, an anti-TGF beta antibody (fresolimumab) has already been tested in IPF patients. Current strategies are directed mostly at downstream mediators, which are thought to have fewer harmful effects on tissue homeostasis[20].

Oxidative stress is considered to be a key mediator in IPF pathogenesis. It is not known whether this is due to the overproduction of reactive oxygen species (ROS) or to the diminished scavenger capacity of various cells[21]. NADPH oxidase (NOX) is one of the ROS-generating enzyme systems expressed by alveolar epithelial cells, endothelial cells, macrophages, neutrophils, mesenchymal cells and smooth muscle cells. Several isoforms of NOX have been characterized, with NOX-1, NOX-2 and NOX-4 appearing to be the most relevant in IPF pathogenesis. Specific NOX inhibitors may prove to be effective drug targets in IPF[22].

CELL SURFACE

Pirfenidone was found to inhibit the synthesis of TGF beta and TNF alpha, even though the underlying mechanism has yet to be elucidated. Compared to placebo, pirfenidone delays the progression of IPF and mortality, and it is currently the only registered molecule for IPF treatment in some countries[23].

Lung fibrosis with distortion of vessel architecture is accompanied by enhanced coagulation. The primary function of the coagulation cascade is to promote hemostasis and limit blood loss in response to tissue injury. However, coagulation also plays a pivotal role in inflammatory and tissue repair responses, including lung fibrosis[24]. Hyperplastic alveolar epithelium in patients with fibro-proliferative lung disorders might be an important source of several coagulation-promoting factors. There have been several studies on the potential therapeutic role of warfarin, but these resulted in a strong recommendation against the use of warfarin in IPF treatment. Further studies have shown that other components of the coagulation cascade can be targeted. Proteinase-activated receptor 1 (PAR-1) is a major high-affinity receptor for thrombin and its activation leads to a number of pro-fibrotic events, including the proliferation of fibroblasts and their differentiation into myofibroblasts[25]. PAR-1 has been suggested as a major player in endothelial-epithelial barrier disruption. Atopaxar and vorapaxar inhibit PAR-1 and may represent possible options in IPF treatment[26].

Given that fibroblast proliferation and extracellular matrix production are the hallmark of fibrotic lung diseases, huge efforts have been made to investigate fibroblast biology and signaling[27]. Lung fibroblasts derived from IPF patients have enhanced motility compared to their normal counterparts. This hypermotile phenotype of fibroblasts is thought to be driven by ligation of urokinase with its receptor (uPAR), which leads to the formation of unique lipid raft platforms. Blocking fibroblast migration *via* uPAR represents one possible future treatment option for IPF patients[28].

Another therapeutic approach may involve blocking signaling mechanisms in cells that are common to multiple pathways. The pro-fibrotic effect of TGF beta 1 and basic fibroblast growth factor (FGF) was found to be dependent on a Ca^{2+}-activated K^+ channel ($K_{Ca}3.1$). Inhibiting this channel can block the function of pro-fibrotic human lung myofibroblasts. This makes the $K_{Ca}3.1$ channel an attractive pharmacological target, particularly as it appears to play only a minor role in normal physiology[29]. So far, inhibitors of this channel have been used in humans with sickle cell disease with few side effects.

PLASMA MEMBRANE-CYTOSOL INTERPLAY

Tyrosine kinase (TK) inhibition also attenuates downstream signaling in cells and might be useful if a mutation in the gene coding for tyrosine kinase leads to uncontrolled activation of the cell, manifested as unregulated cell cycle or protein production. Several authors have suggested that similar features and pathogenic pathways might play a key role in idiopathic pulmonary fibrosis and lung cancer[30]. In both diseases, epigenetic and genetic changes result in altered responses to regulatory signals, abnormal expression of microRNAs and activation of specific signaling pathways, which raises suspicion that a similar treatment approach could be useful. Inhibitors of TKs or TK-dependent signal transduction pathways might be very helpful in controlling the growth of cancer cells[31]. Although studies with imatinib mesylate in IPF patients showed a lack of efficacy, this compound is not the only inhibitor of TK signal transduction that has been tested. Nintedanib is a triple inhibitor of TK receptors (platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor receptors) and is just one of the new drugs that may improve the prognosis of IPF patients[32]. Recently published data show that nintedanib reduces lung function decline and slows the progression of IPF[33].

Another member of the protein kinase family is a group of serine-threonine kinases. Rho-kinase (ROCK) is a member of this group and is involved in the regulation of cell movement and shape and plays a role in the function of the tumor suppressor gene PTEN and the mechanism of apoptosis[34]. The rho-kinase inhibitor fasudil has potential as a new treatment in systemic scleroderma patients. Additionally, this molecule was found to inhibit lung fibrosis in the bleomycin mouse model and has been suggested as a possible treatment for IPF patients[35].

As mentioned above, pathological remodeling of the extracellular matrix by fibroblasts plays a role in IPF pathogenesis. Parker *et al*[36] noted that expansion of fibrotic lesions after the initial insult leading to fibrogenesis is likely driven by a positive feedback loop between fibroblasts and the extracellular matrix. An interesting option for blocking this loop could be miR-29, which is a potent negative regulator of extracellular matrix genes. Generally, miRNAs are a type of non-coding, small-sized, evolutionarily preserved RNA and they act as repressors of gene expression at the post-transcriptional level. Other miRNAs that may play a role in IPF and may represent treatment opportunities include miR-21, miR-155 and miR-200[37].

NUCLEUS

Novel treatment targets are not just limited to the cell surface or cytoplasm; some potential treatments also target the nucleus. Transcription factors are proteins necessary for the transcription of DNA into mRNA. There are specific transcription factors involved in development, response to environmental stimuli, cell cycle control and response to intercellular signals. Immediate-early response transcription factor (Egr-1) takes part in mitogenesis and differentiation. It is thought to be a tumor suppressor gene. Egr-1 has been found to play a role in the fibrotic process, in addition to oncogenesis. It can regulate the expression of extracellular matrix components, matrix remodeling enzymes and fibrogenic cytokines, and drive myofibroblast differentiation[38,39]. Although several drugs have been found to have potent inhibitory activity against Egr-1 induction or activity (*e.g.*, mycophenolate mofetil, cyclosporine, imatinib mesylate), clinical studies have only supported their potential use in a subset of patients (ILD associated with CTD)[40]. Although mycophenolate mofetil, cyclosporine or imatinib mesylate may be useful in patients with autoimmune disorders that also affect the lung, they are not routinely recommended for IPF patients. The role of simvastatin and rosiglitazone still needs to be established[41,42].

Gene therapy has been suggested as a potential treatment option in numerous respiratory diseases. Gene preparations can be administered to target organs by intravenous, intramuscular or intra-tumor injections. One possible noninvasive delivery strategy includes intranasal administration[43]. Effective introduction to the lungs is thought to be possible because of the large absorption area of the mucous membrane and high perfusion. Most research in this area is concentrated on monogenic diseases and lung cancer, with few data on IPF thus far. Gene therapy has been combined with conventional treatment in cancer models and seems to offer interesting treatment possibilities in cases with a known genetic cause - especially for familial lung fibrosis due to short telomere syndrome or MUC5B (gene for mucin) gene polymorphisms[44-46].

TISSUE REPAIR- POTENTIAL FOR STEM CELLS

Stem cells represent a more complex treatment approach than specific molecular targeted therapy. Stem cells were expected to be the ultimate strategy for restoring diseased lungs, including structural repair (engraftment of cells) and immunomodulation. Endogenous lung progenitors, endothelial stem cells, induced pluripotent cells, mesenchymal stem cells and epithelial stem cells have all been proposed as prospective treatments, especially for IPF patients[47,48]. Intravenous and intratracheal administration of epithelial type Ⅱ alveolar cells is now being tested in humans. Mesenchymal stem cells (MSCs) were found to be immunosuppressive, they have low immunogenicity and they home to sites of injury after systemic administration. However, MSCs appear to be more efficient in resolving diseases with high inflammatory activity and are less able to preserve organ function or restore cell derangements in patients with chronic disease. It has been suggested that systematically administered bone marrow MSCs can differentiate into type Ⅱ epithelial cells and suppress the expression of proinflammatory and profibrotic genes[49,50]. However, ongoing studies in IPF patients were designed as safety studies and their results are still somewhat controversial. The therapeutic potential of bone marrow MSCs may be further enhanced by using a cell-based gene delivery approach.

CHRONOBIOLOGY

Although circadian rhythms have proved to be strong regulators of many tissue-specific genes, the data concerning lung fibrosis patients are limited. A study by Pekovic-Vaughan suggests that susceptibility to oxidative stress lung injury may vary during the day, because the activity of redox-sensitive transcription factor Nrf2 correlates with the circadian rhythm[51]. Not only does Nrf2 enhance oxidative stress, it also points toward a new site for lung fibrosis research[52]. Chronobiology has demonstrated that timed drug administration can improve treatment outcomes.

NON-IPF DISORDERS

In patients with non-IPF fibrosing interstitial lung disorders that continue to progress despite conventional immunosuppression, the anti-CD20 monoclonal antibody rituximab has been tested and appears to be an effective therapeutic intervention, regardless of the final diagnosis[53]. However, the data on the optimal treatment strategy in CTD-related fibrosing lung disease are still limited. In patients with systemic lupus erythematosus (SLE), belimumab (IgG1 lambda monoclonal antibody binding circulating B-lymphocyte stimulator) may be an attractive alternative to rituximab. The anti-interferon antibody sifalimumab is being studied in SLE patients and may represent a new treatment option for other autoimmune disorders[54]. Whether it could also be beneficial in patients with associated interstitial lung disease is still unknown.

Pulmonary involvement in systemic sclerosis (SSc) patients is common and it is considered to a major cause of death in SSc patients. The pathogenesis of SSc is characterized by significant accumulation of inflammatory cells in the lung parenchyma, even in patients with an otherwise usual interstitial pneumonia (UIP) pattern of interstitial lung fibrosis. There is an ongoing debate regarding the optimal immunosuppressive agents for SSc ILD patients, especially concerning newer agents such as mycophenolate or rituximab. According to some authors, cyclophosphamide should not be routinely replaced by mycophenolate in SSc ILD subjects[55]. Several studies have indicated that rituximab can be useful, but it should be further investigated[56]. Pirfenidone, STX-100 and fasudil represent interesting possible treatment options in SSc ILD patients.

CONCLUSION

Despite recent advances and deeper insight into the pathogenesis of fibrosing lung disorders, we are still unable to successfully treat our patients. Several points need to be addressed, and several intriguing questions need to be answered: (1) How do we define effective treatment? Should effective treatment be defined in terms of disease stabilization and prevention of further decline in lung function? Should we define effective treatment as an improvement in patient quality of life, without necessarily extending it? Should the optimal definition of "effective treatment" include restoration of the lung parenchyma and resolution of both fibrosis and inflammation (if any is present)? It is reasonable to assume that blocking specific pathways will more likely lead to disease stabilization, while stem cell-based treatments could potentially restore lung architecture. Gene therapy could be a candidate for preventive care in families with proven specific gene polymorphisms and documented familial lung fibrosis; (2) Radiological and histopathological patterns of usual interstitial pneumonia (UIP) may be observed in patients with fibrosing lung disease of known cause, such as CTDs, drug-induced lung fibrosis or in patients with a history of exposure to inorganic/organic inhalation antigens. Can any of the above-mentioned therapeutic approaches also be used in non-IPF patients with a radiographic/histopathologic UIP pattern? (3) Should a combination of drugs and therapeutic approaches be used instead of monotherapy? and (4) Similarities between IPF and lung cancer were listed above. What should we learn from the oncological approach? Should we use different treatment strategies according to the stage of the disease and the individual genetic background of patients? If so, what should the staging of lung fibrosis be based on?

We believe that a multifaceted approach to IPF, including cooperation between those doing basic research and clinical doctors as well as tailoring research and treatment strategies toward (until now) unmet medical needs, could improve our understanding of the disease and, above all, provide benefits for our patients.

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