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Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs)

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ABSTRACT

Interstitial lung diseases (ILDs), which can arise from a broad spectrum of distinct aetiologies, can manifest as a pulmonary complication of an underlying autoimmune and connective tissue disease (CTD-ILD), such as rheumatoid arthritis-ILD and systemic sclerosis (SSc-ILD). Patients with clinically distinct ILDs, whether CTD-related or not, can exhibit a pattern of common clinical disease behaviour (declining lung function, worsening respiratory symptoms and higher mortality), attributable to progressive fibrosis in the lungs. In recent years, the tyrosine kinase inhibitor nintedanib has demonstrated efficacy and safety in idiopathic pulmonary fibrosis (IPF), SSc-ILD and a broad range of other fibrosing ILDs with a progressive phenotype, including those associated with CTDs. Data from phase II studies also suggest that pirfenidone, which has a different—yet largely unknown—mechanism of action, may also have activity in other fibrosing ILDs with a progressive phenotype, in addition to its known efficacy in IPF. Collectively, these studies add weight to the hypothesis that, irrespective of the original clinical diagnosis of ILD, a progressive fibrosing phenotype may arise from common, underlying pathophysiological mechanisms of fibrosis involving pathways associated with the targets of nintedanib and, potentially, pirfenidone. However, despite the early proof of concept provided by these clinical studies, very little is known about the mechanistic commonalities and differences between ILDs with a progressive phenotype. In this review, we explore the biological and genetic mechanisms that drive fibrosis, and identify the missing evidence needed to provide the rationale for further studies that use the progressive phenotype as a target population.

INTERSTITIAL LUNG DISEASES AND THE CURRENT TREATMENT LANDSCAPE

Interstitial (or diffuse parenchymal) lung diseases (ILDs) represent a large, heterogeneous group of several hundred generally rare pulmonary pathologies, some of which are associated with significant morbidity and mortality.[1–4] They are characterised by damage to the lung parenchyma and mediated by varying degrees of inflammation and fibrosis.[5] ILDs may arise from a broad spectrum of distinct aetiologies, both known and unknown. They can manifest as a pulmonary complication of an underlying connective tissue disease (CTD-ILD, such as rheumatoid arthritis (RA-ILD)[6–8] and systemic sclerosis (SSc-ILD)[9–11]), as a result of environmental exposure to antigens (eg, chronic hypersensitivity pneumonitis)[12 13] or due to unknown cause/s, as typified by idiopathic pulmonary fibrosis (IPF).[1 14 15] Patients with clinically distinct ILDs have different comorbidities and treatment profiles, and are heterogeneous in both their clinical course and pathophysiology. Nevertheless, a variable proportion of patients within each ILD subgroup can have a similar clinical lung phenotype characterised by declining lung function, worsening respiratory symptoms and health-related quality of life, and higher mortality. In recent literature, these have been termed 'progressive fibrosing ILDs', or 'fibrosing ILDs with a progressive phenotype' (in this review, we use the latter term).[16]

Phase II and III clinical trials have established the efficacy and safety of the antifibrotic drugs pirfenidone[17 18] and nintedanib[19 20] for the management of IPF (the archetypal ILD with a progressive phenotype), and both drugs are now approved for the treatment of IPF.[21 22] In the phase III SENSCIS trial, nintedanib proved efficacious in reducing the annual rate of decline in forced vital capacity (FVC) versus placebo in patients with SSc-ILD.[23] Post hoc analyses showed no heterogeneity in the treatment effect of nintedanib compared with placebo on the rate of FVC decline in subgroups defined by the presence or absence of ground-glass opacities.[24] Nintedanib was subsequently approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of SSc-ILD in September 2019 and April 2020, respectively.[25 26]

Most recently, results from the phase III INBUILD study have shown that nintedanib is also efficacious in treating a pooled group of patients who have fibrosing ILDs with a progressive phenotype (consisting of several clinically distinct disease categories, including CTD-ILDs), by reducing the annual rate of decline in lung function after 52 weeks of treatment.[16] Of particular interest for rheumatologists are the proportions of patients in the nintedanib arm of INBUILD who have ILDs of autoimmune origin (24.7% in total): RA (12.7%), SSc (6.9%), mixed CTD (2.1%) and other autoimmune-related ILDs (3.0%). Subgroup analyses have indicated consistent efficacy across these autoimmune subgroups;[27] however, since INBUILD was not powered to assess efficacy by subgroup, the conclusions that can be drawn regarding the efficacy of nintedanib in individual autoimmune diseases are limited. For patients with unclassifiable ILD with a progressive phenotype, pirfenidone may

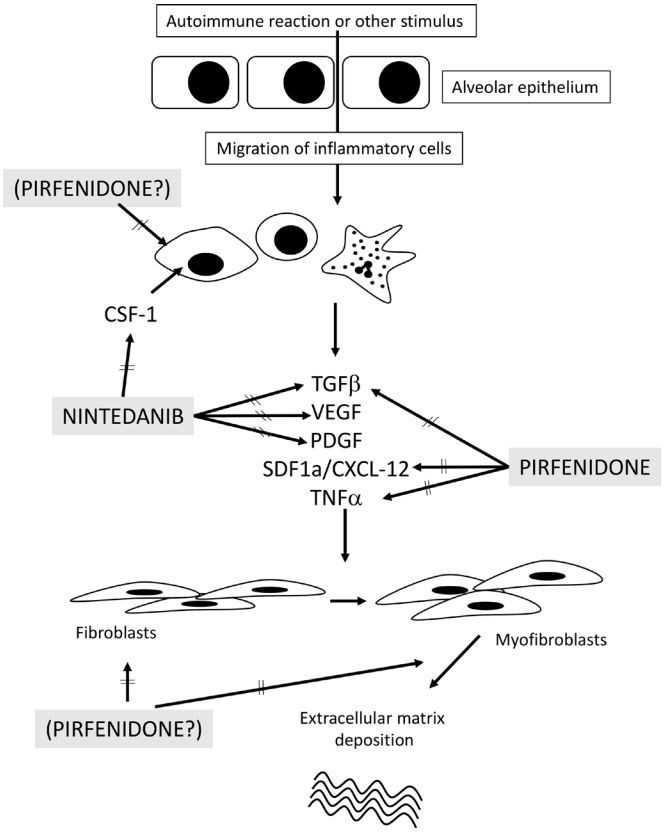

Figure 1 Known and proposed targets for the antifibrotic actions of nintedanib and pirfenidone. CSF, colony-stimulating factor-1; CXCL, C-X-C ligand; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TNF, tumour necrosis factor; SDF, stromal cell-derived factor; VEGF, vascular endothelial growth factor.

have some clinical benefit. In one phase II study, mean change in FVC% predicted in patients with a range of unclassifiable idiopathic interstitial pneumonias, or interstitial pneumonia with autoimmune features (IPAF) showing a progressive fibrosing phenotype, was lower over 24 weeks in those who received pirfenidone compared with placebo (in this study, progression was defined as >10% fibrosis on high-resolution CT (HRCT) within the previous 12 months, and an annual decline in FVC predicted ≥5%); however, the planned statistical model could not be applied to these primary endpoint data.[28] In a separate phase II study, which was terminated early due to futility based on an interim analysis, patients with progressive forms of fibrotic ILD (annual decline in FVC predicted ≥5%) had a lower decline in FVC% predicted over 48 weeks when taking pirfenidone compared with placebo (after imputation of missing data). However, a major limitation of this study was its small sample size (collagen-vascular disease-ILD (n=37), fibrotic non-specific interstitial pneumonia (NSIP) (n=27), chronic hypersensitivity pneumonitis (n=57) and asbestos-related lung fibrosis (n=6)), and the full results have not yet been published.[29]

The immunosuppressive agents cyclophosphamide (CYC) and mycophenolate mofetil (MMF) have also been evaluated in SSc-ILD. In one study, CYC showed beneficial effects on lung function compared with placebo after 1 year of treatment, although these mostly dissipated after 2 years.[30] In a subsequent trial, 2 years of treatment with MMF did not significantly change the primary FVC endpoint compared with 1 year of CYC, though FVC improved in both groups, and MMF was better tolerated.[31] The anti-interleukin (IL)-6 receptor antibody tocilizumab has been evaluated in patients with SSc and demonstrated preservation of lung function in a phase II study,[32] although a phase III trial did not meet its primary modified Rodnan Skin Score endpoint.[33] The tyrosine kinase inhibitor imatinib is approved for the treatment of chronic myeloid leukaemia and targets the Bcr-Abl/c-Abl, a kinase downstream of transforming growth factor-β (TGF-β) signalling.[34] Imatinib also inhibits the platelet-derived growth factor (PDGF) receptor tyrosine kinase and has been evaluated in small open-label studies in SSc-ILD,[35 36] although no large randomised trials have been conducted and its efficacy is unclear.

Collectively, these trial results suggest that common fibrotic pathways in patients progressing to end-stage lung disease (involving the targets of nintedanib and, potentially, pirfenidone) may exist. The mechanisms of action of nintedanib and pirfenidone may therefore shed some light on the pathways involved in disease pathogenesis. Nintedanib is a small molecule tyrosine kinase inhibitor that targets receptor tyrosine kinases involved in fibrosis, including those for PDGF, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and TGF-β, as well as non-receptor kinases involved in inflammation and proliferation (Src family kinases), and activation and polarisation of macrophages (colony-stimulating factor-1).[37 38] Nintedanib also inhibits the proliferation of vascular cells[39] and modulates fibroblast activity.[40] The molecular mechanism of pirfenidone is not fully understood, but in preclinical models it reduces bleomycin-induced lung fibrosis in mice.[41] Pirfenidone inhibits stress-activated kinases[42] and modulates expression of several growth factors, as well as cytokines that are thought to be relevant to fibrosis, including TGF-β, PDGF, stromal cell-derived factor/C-X-C ligand 12 (SDF-1a/CXCL12) and tumour necrosis factor-α. It may also reduce fibroblast proliferation and alveolar macrophage activation, and modulate extracellular matrix (ECM) deposition.[43 44] Known and possible targets for the antifibrotic action of nintedanib and pirfenidone are shown in figure 1, although the relative weight or importance of specific pathways in different ILDs cannot reliably be made based on the current level of evidence. This review appraises current pathobiological concepts of fibrosis in ILDs exhibiting a progressive fibrosing phenotype, with a particular focus on some of the ILDs most commonly encountered by the rheumatologist, including ILDs associated with SSc, RA, inflammatory myopathy and Sjögren's syndrome.

Fibrosing CTD-ILDs with a progressive phenotype

Although IPF is the archetypal ILD with a progressive phenotype, a proportion of patients with non-IPF ILDs experience a disease course similar to that seen in IPF.[45] ILDs in which patients are at risk of developing a progressive fibrosing phenotype include chronic hypersensitivity pneumonitis, idiopathic NSIP (iNSIP), CTD-associated ILDs (including RA, SSc, mixed CTD, Sjögren's syndrome (though rarely) and inflammatory myopathies), pneumoconiosis (eg, asbestosis), drug-induced ILDs, unclassifiable ILDs, pulmonary sarcoidosis, and rare ILDs, such as pleuroparenchymal fibroelastosis (PPFE).[13 16 28 46 47] However, the proportion of patients who develop a progressive fibrosing phenotype varies by disease, and for many ILDs, the incidence is not known.

The term 'progressive' has been used for a long time in clinical and research settings; however, definitions of progression in the context of the fibrotic phenotype have varied and there are no definitive criteria. Most recently, the INBUILD study used a definition of progression based on fulfilment of ≥1 of the following

Table 1 Studies including patients that would meet the INBUILD criteria for progression

ILD subtype	Study size	Proportion of patients with a progressive phenotype
SSc-ILD	n=695	~33% of patients with DLco pred <50% within 3 years of the onset of Raynaud's phenomenon[121]
Limited cutaneous SSc	n=326	Worsening of ILD (>10% decline in FVC from baseline to second visit) observed in 19.9% of patients at 24 months follow-up[122]
RA-ILD	n=167*	14% of patients with FVC <50% pred at diagnosis, increasing to 22% after 5 years; 29% of patients with DLco <40% pred at diagnosis, increasing to 40% after 5 years[8]
Inflammatory myopathy-associated ILD	n=107	Worsening of pulmonary symptoms, deterioration on HRCT, and decline in lung function (≥10% in FVC or ≥15% in DLco) observed in 15.9% of patients (despite therapy), after a median 34 months of follow-up (range 4–372 months)[89]
Sjögren's syndrome-associated ILD	n=18†	5 patients (28%) had a decline in FVC pred of ≥10% or a decline in DLco pred of ≥15%, despite immunosuppression (median follow-up: 38 months)[123]

*167 patients encountered in clinical practice and referred for multi-specialty evaluation in a tertiary care centre (potential centre bias: severe cases are more often encountered at a specialised centre).
†18 patients selected over a 13-year period.
DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; pred, predicted; RA, rheumatoid arthritis; SSc, systemic sclerosis.

criteria for progression of ILD within a 24-month period (despite management with standard treatments, excluding nintedanib or pirfenidone): relative decline in FVC predicted ≥10%; relative decline in FVC predicted ≥5–<10% with either worsened respiratory symptoms or increased extent of fibrosis on chest HRCT; or a combination of worsened respiratory symptoms and an increased extent of fibrosis on HRCT. This definition did appear to enrich for patients with progressive disease in the overall population, as demonstrated by the decline in patients in the placebo arm.[16] However, small patient numbers and the lack of a comparator group without enrichment criteria mean it is not possible to draw definite conclusions regarding enrichment in certain subgroups, including the CTD-ILDs.

In our review of the literature, we found only a small number of studies that included patients that would meet the INBUILD inclusion criteria of a progressive phenotype. These studies, which include SSc-ILD, RA-ILD, ILD associated with inflammatory myopathy (polymyositis and dermatomyositis), and Sjögren's syndrome-ILD, are summarised in table 1 and reviewed in further detail elsewhere.[48] Although these studies give an approximate indication of the proportion of patients who may develop a progressive fibrosing phenotype in certain ILDs, further longitudinal studies are needed to expand the evidence base.

In patients with certain ILDs, a specific radiographic pattern of fibrosis (usual interstitial pneumonia, UIP) identified by HRCT is often associated with more rapid disease progression compared with other fibrotic patterns. This association has been observed in patients with a range of ILDs, including IPF, chronic hypersensitivity pneumonitis, RA-ILD[45 49–53] and, though rarely, sarcoidosis.[54] In patients with SSc-ILD, the most common pattern of fibrosis on HRCT is NSIP.[55] However, radiographic patterns appear not to be related to a progressive fibrosing phenotype in SSc-ILD,[56] indicating that while fibrosing ILDs with a progressive phenotype share some similarities, differences also exist. In CTD-ILDs, NSIP is generally the most frequently observed pattern (with the exception of RA).

Biological mechanisms driving progressive pulmonary fibrosis

Broadly, fibrosis is characterised by the overgrowth, stiffening and/or scarring of tissues due to excess deposition of ECM components, notably collagen.[57] In fibrotic lung diseases, repetitive cycles of alveolar epithelial injury and attempted repair are thought to lead to the gradual destruction of functional lung parenchyma and its replacement by increasing deposits of non-functional connective tissue (fibrosis). This loss of functional alveoli due to sustained fibrosis leads to respiratory insufficiency and early mortality.[58 59]

In addition to epithelial lung injury, other forms of initial lung injuries (depending on the disease) might contribute to progression of the fibrotic phenotype. These include cellular and/or humoral autoimmunity (as in all CTD-ILDs, but to a varying degree),[55] endothelial cell dysfunction (as in SSc or asbestosis),[60–62] granuloma formation (as in sarcoidosis)[63] or alveolar macrophage activation (as in asbestosis).[64] For some ILDs, the initiating event may be hard to identify, such as in RA, where infections, cigarette-smoking, mucosal dysbiosis, immune response (including autoantibodies against citrullinated proteins), host genetics and premature senescence have all been proposed to play a role.[55 65–67] Chronic microaspiration secondary to gastro-oesophageal reflux, a common complication of SSc due to oesophageal motor dysfunction, can lead to persistent alveolar epithelial injury, potentially accelerating the progression of lung fibrosis.[68] Moreover, the increased negative intrathoracic pressure during inspiration caused by lung fibrosis may aggravate gastro-oesophageal reflux in a vicious circle.[68]

Following the injury, wound-healing responses are induced. If sustained and dysregulated, pathological fibrogenesis then occurs, whereby the rate of new collagen synthesis exceeds the rate of collagen degradation, culminating in the accumulation of collagen over time.[57] The principal cellular mediators of fibrosis, regardless of the initial injury, are collagen-secreting myofibroblasts.[57]

Both the innate and adaptive immune system contribute towards the development of fibrosis. This is mediated by cellular and humoral components, underpinning the rationale for immunomodulatory therapies.[69] Preclinical studies have identified profibrotic (Th2, Th17), antifibrotic (Th1, Th22 and γδ-T) and pleiotropic (T_{regs} and Th9) T cells as mediators of fibrosis,[69] and the profibrotic action of PD-1+ CD4+ T cells (targetable by currently available immunomodulatory therapies) has been specifically demonstrated in models of pulmonary fibrosis associated with IPF and sarcoidosis.[70] B cells also play a role, having been detected at higher levels in the lungs of patients with IPF, RA-ILD and Sjögren's syndrome, among others.[71 72] Other innate immune cells implicated in the process of fibrosis include neutrophils and macrophages, the profibrotic effects of which are mediated via secretion of TGF-β, PDGF and IL-6.[69 73] Blood monocytes are recruited to the lung during the fibrotic process, where they have been shown in both IPF and SSc to differentiate into fibrocytes[74 75] and into myofibroblasts in SSc.[76] Macrophages can undergo polarisation to become either 'proinflammatory'

classical M1 macrophages, which secrete proinflammatory and/or profibrotic cytokines (IL-1β, IL-8, IL-10 and CXCL13), or 'profibrotic' alternative M2a macrophages, which secrete profibrotic cytokines (CCL22, PDGF-BB and IL-6).[69 73] Neutrophils have pleiotropic effects within the fibrotic milieu, including the secretion of elastase and matrix metalloproteinases, which degrade ECM and activate accumulation of ECM driven by TGF-β.[69] Neutrophil extracellular traps play a key role in the development of fibrosis, having been detected in close proximity to alpha-smooth muscle actin-expressing fibroblasts in biopsies from patients with fibrotic ILD.[77] Finally, mast cells are increased in fibrotic areas of alveolar parenchyma in patients with a range of fibrotic lung diseases, with strong evidence for important bidirectional interactions between mast cells and myofibroblasts in fibrotic tissues.[78]

Our current understanding is that immune cells are profibrotic, though there is mounting preclinical and clinical evidence that the composition of the inflammatory infiltrate determines its fibrotic activity, and that some immune/inflammatory cells may even exert direct antifibrotic effects depending on the local environment.[79 80] T cells, for example, have been shown to inhibit fibroblast-to-myofibroblast differentiation in vitro through the secretion of inhibitory prostaglandins.[81] Adoptive transfer of splenic T_{reg} cells has been shown to attenuate bleomycin-induced lung fibrosis in vivo,[82] and global impairment of CD4+CD25+-FOXP3+ T_{reg} cells has been found to correlate strongly with disease severity in IPF, suggesting a role for T_{regs} in the fibrotic process.[83] B cells may also contribute to the formation of an antifibrotic 'shield', acting as regulators of polymorphonuclear cells and restraining the ability of these cells to cause ILD.[84] Gene knockout studies have identified a gene in B cells that appears to regulate lung fibrosis.[85] Interestingly, in an experimental model of cardiac fibrosis, engineered T cells targeting the Fibroblast activation protein protected against cardiac fibrosis,[86] providing proof of principle for the development of immunotherapeutic drugs for the treatment of fibrotic disorders.

Several humoral mediators also play a role in fibrogenesis. IL-13 is known to stimulate differentiation of lung fibroblasts to myofibroblasts via c-Jun N-terminal kinase-signalling, whereas IL-17 acts in concert with TGF-β-mediated pathways to promote pulmonary fibrosis. TGF-β itself promotes epithelial-to-mesenchymal transition, induces fibrosis through canonical and non-canonical pathways such as mitogen-activated protein kinase, extracellular signal-regulated kinases and PI3K/Akt signalling, and modulates fibroblast differentiation into myofibroblasts that drive ECM accumulation. PDGF is known to activate and promote ECM gene expression in fibroblasts, and CCL2 may increase fibrocyte recruitment and differentiation into fibroblasts (in addition to its role in monocyte chemotaxis). In some ILDs, antibodies may play a key role. In SSc, for example, anti-topoisomerase I antibodies are associated with the presence and severity of ILD at baseline.[11 87] In RA-ILD, IgA anti-citrullinated protein antibodies (ACPAs) (commonly found in synovial and articular sites) have been identified in sputum from individuals at risk of RA, suggesting that the lung may be the primary site of ACPA generation.[55] The presence of anti-Sjögren's-syndrome-related antigen A antibodies is a predisposing factor for ILD in patients with Sjögren's syndrome.[88] In myositis-associated ILD, however, one study found no correlation between the deterioration of ILD and the presence of antinuclear antibodies, anti-Jo-1 antibodies or anti-PM-Scl antibodies.[89] While an association between antibodies and certain forms of ILDs has been identified, a causal pathogenetic relationship has not.

Little is known about how the mechanisms of fibrosis differ across distinct ILDs, and even less is known about whether progressive fibrosis is driven by a different set of mediators than non-progressive fibrosis. The most studied ILDs from a mechanistic perspective are IPF and SSc-ILD. Common to both diseases are activation of macrophages with a similar chemokine expression profile (M2 profibrotic phenotype), and similar T-cell profiles (Th2-increased T_{regs}, Th22, Th17, increased ratio of CD4 to CD8 T cells).[90] However, the B-cell profiles of patients with IPF and SSc-ILD differ, as do their T-cell chemokine profiles (IL-4, IL-5, IL-10 and IL-17 for IPF, and IL-4, IL-5, IL-6, IL-10, IL-13 and IL-22 for SSc-ILD).[90] In particular, IL-6 is known to play a key role in SSc by increasing collagen production through fibroblast stimulation, myofibroblast differentiation and inhibiting the secretion of metalloproteinase.[91] In one study, serum IL-6 levels appeared to be predictive of early disease progression in patients with mild (FVC >70%) SSc-ILD,[92] yet were not in another study of SSc-ILD,[93] and CXCL4 has also been correlated with the presence and progression of lung fibrosis in SSc.[94] In RA-ILD, as in IPF and SSc-ILD, Th-17-cell-mediated immunity is involved in pathogenesis (the IL-17 receptor is upregulated in both RA-ILD and IPF).[55 66] In addition, lung tissue from individuals with RA-ILD has substantially greater numbers of B cells and CD4+ T cells than lung tissue from individuals with idiopathic UIP, implying that immune dysregulation might be more prevalent in RA-ILD than in idiopathic UIP.[95] Biomarkers of fibrosis could provide an important clue, but to date no serum biomarker has been identified as a sufficiently robust prognostic marker to justify its use in clinical practice. In studies in lung transplantation, it has also been shown that the concentrations of PDGF, FGF-2, VEGF and colony-stimulating factor-1 were significantly increased in lungs with progressive ILDs, including IPF, SSc-ILD and other ILDs, compared with donor lungs.[96]

Genetic mechanisms driving progressive pulmonary fibrosis

Certain genetic mutations are implicated in the aetiology of ILDs. Mutations in telomere-related genes (*TERT*, *TERC*, *RTEL1*, *PARN*, *TINF2*, *NAF1* and *DKC1*) have been associated with a broad range of ILDs, including IPF, iNSIP, RA-ILD, acute interstitial pneumonia, cryptogenic organising pneumonia, chronic hypersensitivity pneumonitis and PPFE.[97–99] Telomeres are distal regions of chromosomes associated with specific protein complexes, which protect the chromosome against degradation and aberration. It is believed that loss of function in the telomerase complex may influence the turnover and healing of alveolar epithelial cells after an initial damaging stimulus, thereby triggering fibrosis.[100] In support of this, mice with defective telomere homeostasis develop spontaneous pulmonary fibrosis or are more susceptible to injury.[100 101] Telomere dysfunction in type II alveolar epithelial cells (mediated by deletion of the telomere shelterin protein TRF1) is also sufficient to cause lung fibrosis in mice.[102] Conversely, vector-induced telomerase expression has shown therapeutic effects in a mouse model of pulmonary fibrosis, indicating that telomerase activation may represent an effective treatment for pulmonary fibrosis provoked by or associated with short telomeres.[103] Telomerase activators have also shown activity in preclinical models of fibrosis.[104] In patients with ILDs, significantly shortened telomeres have been found, and these have been linked to defective immunity[105–107] (the shortest telomeres are found in patients with

IPF).[108] However, it is important to note that not all individuals with mutations in telomere-related genes will necessarily have short telomeres or develop ILD.[97] In RA-ILD, coding region mutations in the genes *RTEL1* and *TERT* lead to telomere shortening and onset of RA-ILD at a younger age.[99] In hypersensitivity pneumonitis, short telomere length has been associated with extent of fibrosis, histopathological features of UIP, and reduced survival, suggesting shared pathobiology with IPF.[109] Beyond these associations, however, no studies to our knowledge have exposed a direct link between specific telomere-related genotypes and progressive (or non-progressive) fibrosis.

Another gene implicated in some forms of ILD is the mucin 5B gene (MUC5B). A common variant in the promoter region of this gene (rs35705950) has been associated with an increase in IPF susceptibility and overall mortality.[110–113] Similar associations have also been observed in patients with RA-ILD,[65 110] as well as in hypersensitivity pneumonitis[109] and IPAF,[114] but not in SSc-ILD,[115] myositis-associated ILD[116] or sarcoidosis,[117] again highlighting not only the similarities but also the differences between ILDs.

Most of the available genetic data come from studies in IPF, but risk alleles in other genes have also been identified for a range of non-IPF ILDs, primarily in RA-ILD, and chronic hypersensitivity pneumonitis.[118] Currently, it is not clear whether specific genetic risk factors predispose certain individuals to develop a progressive fibrosing phenotype. If confirmed through longitudinal studies, genetic markers might help to identify those most at risk of progression.

Furthermore, epigenetic mechanisms play a key role in biological processes at the level of chromatin structure and organisation, including DNA methylation, post-translational modifications of histone tails and non-coding RNA. Under physiological conditions, the epigenome ultimately determines the silencing or activation of gene expression in a temporally coordinated way, and its dysregulation contributes to a variety of human diseases, including IPF.[119] Epigenetics may explain the profibrotic effect of ageing as a condition, or environmental factors such as tobacco smoke or inhaled air pollution in IPF, and other fibrotic conditions such as RA-ILD.[120]

SUMMARY

In recent years, phase III clinical trials have demonstrated the efficacy and safety of new classes of drugs in slowing disease progression in patients with IPF (nintedanib and pirfenidone), and SSc-ILD (nintedanib). Results from recent phase III clinical trials have now shown that nintedanib can slow the progression of ILD (as measured by FVC decline) in patients with a broad range of fibrosing ILDs with a progressive phenotype, including those associated with CTDs. Available data for pirfenidone in the treatment of clinically distinct ILDs with a progressive phenotype come from phase II trials in which, despite some positive endpoints, the primary endpoints were not met. Though not powered to detect efficacy by disease subgroup, these trials add weight to the hypothesis that in a number of clinically distinct ILDs, a progressive fibrosing phenotype may arise from common, underlying mechanisms of fibrosis, irrespective of the original clinical trigger or association. However, to date, this hypothesis has only been proven for the targets of nintedanib and partially for the targets of pirfenidone. This review found little evidence for other common pathways in progressive fibrosing ILDs, mostly because of the lack of appropriate studies. Thus, there is currently insufficient preclinical support for other treatment studies using the progressive phenotype as a target population. To identify common and distinct pathways, high-throughput genomics, proteomics and metabolomics studies using adequate lung tissue from patients with the progressive phenotype of different aetiologies are urgently needed. These analyses may then provide the preclinical rationale for additional, specific targeted therapies to support the novel and important concept of using the progressive fibrosing phenotype as a common target population in clinical studies.

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