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REVIEW

Interstitial Lung Disease Associated With Systemic Sclerosis and Idiopathic Pulmonary Fibrosis

How Similar and Distinct?

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Introduction

Fibrosis of the lung, a common complication of systemic sclerosis (SSc) and the hallmark of idiopathic pulmonary fibrosis (IPF), is associated with substantial mortality and has no approved therapy. Despite some degree of overlap in their clinical features and pathogenesis, SSc-associated interstitial lung disease (ILD) and IPF have differences, with significant implications for diagnosis, evaluation, and management. To shed light on these issues, this review compares and contrasts salient features of these 2 entities, focusing on clinical manifestations, lung imaging, and pathology, along with current concepts of pathogenesis, including animal models, translational studies, genetic factors, and predictive biomarkers. We conclude by posing questions that might unveil new areas of investigation and inform novel and targeted approaches to therapy.

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Clinical features

Definitions, epidemiology, and clinical presentation. SSc-associated ILD is diagnosed when radiographic evidence of diffuse parenchymal lung disease is detected in a patient with SSc (1). In contrast, IPF is a clinicopathologic entity defined by the radiographic appearance of usual interstitial pneumonia on high-resolution computed tomography (HRCT) scan and/or the histologic appearance of usual interstitial pneumonia on lung biopsy in the absence of ILD risk factors, such as occupational exposures and connective tissue or autoimmune disease (2). Patients with SSc-associated ILD are predominantly women between the ages of 30 and 55 years (3,4), whereas IPF occurs more commonly in men, with a peak age of 60–75 years (2,3). The prevalence of SSc in the US is 50–300 cases per million, with up to 90% developing some degree of ILD (3,5), while the prevalence of IPF is 140 cases per million and appears to be rising (2). Significantly, the prevalence of IPF—but not SSc—increases with age, reaching 230 per million in those ≥75 years of age (2). Table 1 highlights the clinical and demographic features of SSc-associated ILD and IPF.

Table 1. Comparison of clinical features of SSc-associated ILD and IPF*

	SSc-associated ILD	IPF
Extrapulmonary manifestations	Multisystem involvement characteristic of SSc	Digital clubbing
Autoantibodies	Anti–Scl-70, antifibrillarin, anti-Th/To, anti–PM-Scl, anti–U1 RNP, anti–U11/U12 RNP	None; presence of clinically relevant autoantibodies rules out IPF
Environmental exposure	Canola oil, rapeseed oil, bleomycin, vinyl chloride	None; presence of clinically relevant environmental exposure rules out IPF
Lung histologic features	Fibrotic NSIP, cellular NSIP, infrequent UIP, no role for biopsy	UIP, may require biopsy for diagnosis
Radiographic features	Ground-glass opacities, areas of subpleural sparing, honeycombing in basilar and peripheral predominant distribution, reticular markings, traction bronchiectasis	Ground-glass opacities not seen, honeycombing in basilar and peripheral predominant distribution, reticular markings, traction bronchiectasis
Clinical course	Early decline in lung function, variable progression; may respond to immunosuppression, spontaneous regression observed	Progressive decline in lung function, lack of response to immunosuppression, spontaneous regression not reported, acute exacerbations

* SSc = systemic sclerosis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

Both SSc-associated ILD and IPF present with dyspnea on exertion, which may be accompanied by nonproductive cough, and bilateral basilar inspiratory crackles on auscultation. Digital clubbing affects up to 50% of patients with IPF but is infrequent in SSc-associated ILD (2). Occasionally, ILD might be the initial disease manifestation of SSc (3). In these patients, careful evaluation may reveal mucocutaneous telangiectasia, Raynaud's phenomenon, and abnormal nailfold capillaries (5). While various environmental exposures, including drugs and chemical substances (vinyl chloride and silica), have been associated with SSc (3), cigarette smoking is the major risk factor for IPF (2).

Virtually all patients with SSc-associated ILD are positive for antinuclear antibodies (ANAs), which are frequently accompanied by anti–Scl-70, anti-Th/To, or other SSc-specific autoantibodies (3). In contrast, the presence of clinically relevant autoantibodies rules out a diagnosis of IPF (2). Pulmonary function testing in both conditions reveals restrictive physiology, with reduced forced vital capacity (FVC) and diffusing capacity for carbon monoxide (D_LCO) (2). This is where the clinical similarities end.

Radiographic features. In patients with SSc-associated ILD, chest HRCT typically demonstrates a nonspecific interstitial pneumonia pattern of ground-glass opacities that are bilateral and most prominent in the lower lobes (5,6). When longstanding, SSc-associated ILD may be associated with lower lobe traction bronchiectasis and fibrotic changes (5). The radiographic pattern of usual interstitial pneumonia, characterized by reticular abnormalities and honeycombing in a predominantly subpleural and basal distribution, is infrequently seen (7). Additional radiographic findings include evidence of pulmonary arterial hypertension (PAH) and a dilated esophagus (7).

In contrast to SSc-associated ILD, the radiographic diagnosis of IPF *requires* the presence of a usual interstitial pneumonia pattern in the absence of ground-glass opacities, micronodules, or a peribronchovascular or upper lobe–predominant distribution (2). A large study comparing chest radiographic findings in patients with SSc-associated ILD and patients with biopsy-proven IPF found that those with IPF more frequently had extensive and coarse fibrosis, while ground-glass changes were less frequent (8), consistent with radiographic criteria for distinguishing nonspecific interstitial pneumonia from usual interstitial pneumonia (8,9). The applicability of the findings from this decade-old study to the currently accepted definition of IPF is uncertain (2). It is important to note that the existence of a usual interstitial pneumonia pattern on HRCT or lung pathology and a diagnosis of IPF are not clinically interchangeable, as not all patients with usual interstitial pneumonia will have IPF, while by definition all patients with IPF will have usual interstitial pneumonia. As with SSc-associated ILD, radiographic evidence of PAH and chronic aspiration are often detected in IPF (7). Characteristic radiographic findings of SSc-associated ILD and IPF are shown in Figure 1 and summarized in Table 1.

Lung pathology. In patients with SSc-associated ILD, histopathologic examination of the lungs typically shows interstitial fibrosis that is temporally homogeneous and is associated with only modest inflammatory

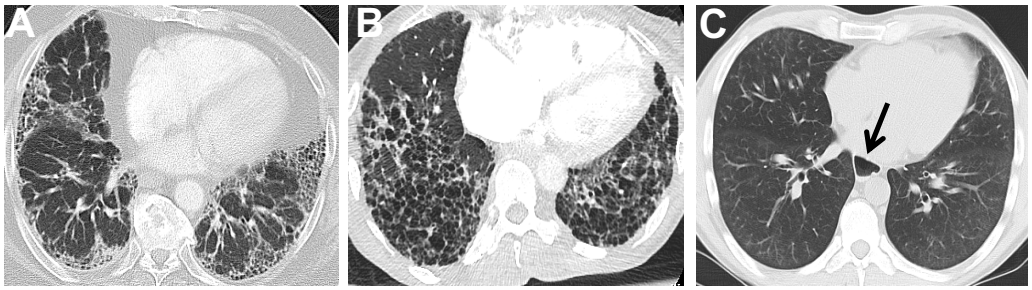

Figure 1. High-resolution computed tomography of systemic sclerosis (SSc)–associated interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF). **A,** IPF. Prone axial image shows subpleural cysts/honeycombing, architectural distortion, and reticular interstitial markings in a basilar distribution with absence of ground-glass opacities and nodules. **B,** Nonspecific interstitial pneumonia in SSc-associated ILD. Note increased reticular markings, traction bronchiectasis, and ground-glass opacities. **C,** Cellular nonspecific interstitial pneumonia in SSc-associated ILD. Note peripheral ground-glass opacities with areas of subpleural sparing. **Arrow** indicates dilated esophagus.

cell infiltrates, a pattern referred to as fibrotic nonspecific interstitial pneumonia (10) (Figure 2A). In <10% of patients with SSc-associated ILD, the lungs exhibit interstitial lymphocytic infiltrates in the absence of fibrosis, a pattern referred to as cellular nonspecific interstitial pneumonia. The usual interstitial pneumonia

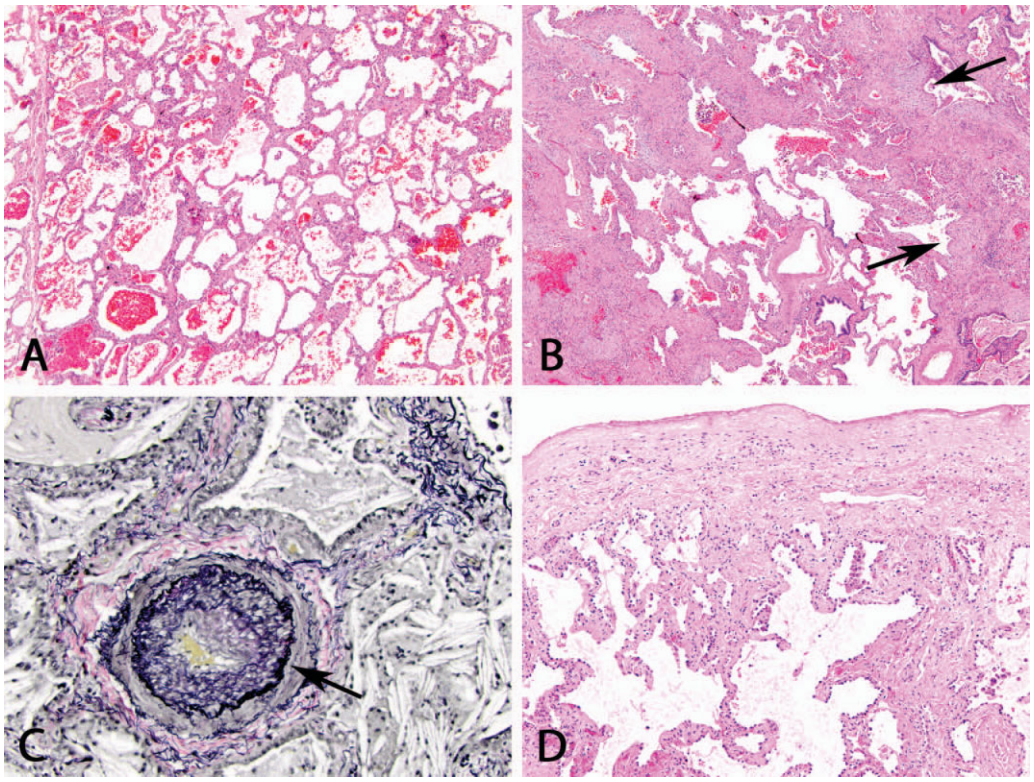

Figure 2. Systemic sclerosis (SSc)–associated interstitial lung disease (ILD). **A,** Nonspecific interstitial pneumonia. Note diffuse alveolar septal thickening throughout the lobule with lack of peripheral accentuation in the area of an interlobular septum on the left. **B,** Usual interstitial pneumonia. Note peripheral involvement of a pulmonary lobule sparing the centrilobular area containing the bronchovascular bundle. **Arrows** indicate fibroblastic foci. **C,** Pulmonary arterial hypertension. Note hypertensive arterial changes with prominent intimal fibrosis. **Arrow** indicates separation of the media and intima by the internal elastic lamina. **D,** Pleural fibrosis. Its presence supports the diagnosis of SSc-associated ILD in the appropriate clinical setting. Hematoxylin and eosin stained in **A, B,** and **D**; Verhoeff–van Gieson stained in **C**. Original magnification × 40 in **A** and **B**; × 200 in **C**; × 100 in **D**.

pattern characterized by juxtaposition of normal lung tissue with areas of dense fibrosis and fibroblast foci is the hallmark of IPF, but it also occurs in <30% of patients with SSc-associated ILD (2,5). Pulmonary vascular changes, such as concentric intimal proliferation and luminal occlusion, are seen in patients with SSc-associated PAH but only rarely in IPF-associated PAH (Figures 2C and D). Organizing pneumonia and pleural involvement may be seen in SSc-associated ILD (5,11). The pathologic findings of SSc-associated ILD and IPF are contrasted in Table 1.

Natural history. The clinical course and natural history of SSc-associated ILD and IPF are distinct. Median survival is 5–8 years in SSc-associated ILD, compared to 2–3 years in IPF (2,12). While some patients with SSc-associated ILD experience a rapid pulmonary decline within the first 3 years of disease, others remain stable over time or may even experience spontaneous clinical improvement (5). In contrast, IPF generally follows a progressive downhill course with gradual loss of ventilatory function leading to respiratory failure and death, although subsets of IPF patients with a rapidly or slowly progressive disease course are recognized (2).

Episodes of acute and potentially fatal worsening occur in 5–10% of IPF patients per year (2). These acute exacerbations are triggered by unknown causes and may punctuate periods of relative stability. Acute deterioration of lung function may also occur in SSc-associated ILD, but it is not well characterized (13). Spontaneous improvement, seen in some patients with clinically significant SSc-associated ILD, has not been described in IPF. Physiologic parameters such as advanced age, CT evidence of extensive lung disease, and reduced lung function are predictive of mortality in SSc (14), whereas in IPF, a combined index called the "GAP" (gender, age, physiology) score demonstrates reduced survival for older male patients with impaired lung function (15). Circulating biomarkers that can accurately predict the clinical course of lung disease (indolent versus aggressive) are still lacking for both SSc-associated ILD and IPF.

Chronic gastroesophageal reflux and associated recurrent microaspiration are important and underappreciated contributors to the progression of lung disease in both SSc-associated ILD and IPF (2,5). In SSc-associated ILD, the severity of gastroesophageal reflux is correlated with loss of diffusing capacity and lung volumes and with the extent of radiographic fibrosis (5). In patients with IPF, use of antireflux medications was found to be an independent predictor of survival and radiographic fibrosis scores (16). PAH occurs in up to 46% of patients with IPF and in up to 20% of patients with SSc-associated ILD; in both diseases, PAH has a significant adverse impact on survival (2,5,11,17). While PAH associated with SSc is thought to reflect inherent vasculopathy, PAH associated with IPF may be more likely a complication of longstanding ILD (11), although emerging evidence questions this notion (18). A comparison of the clinical course of SSc-associated ILD and IPF is presented in Table 1.

Pathogenesis and genetic risk factors

A summary synthesis of current concepts of the pathogenesis of lung fibrosis in SSc-associated ILD and IPF is illustrated in Figure 3. While by no means comprehensive, it depicts a paradigm that is useful when considering the specific initiating and amplifying events that culminate in fibroblast activation and myofibroblast accumulation that represent the final common pathways of lung fibrosis in both SSc-associated ILD and IPF. Tissue damage and lung fibrosis are thought to be initiated by injury to structural cells. In SSc-associated ILD, interest has centered on the endothelium, whereas IPF studies have focused on the contribution of the alveolar epithelium (2,5). Another key difference between the 2 forms of lung disease involves the role of inflammation, which is well supported in the case of SSc-associated ILD (3) but remains less clear for IPF. In IPF, accumulating data indicate that detection of adaptive immune responses in the lungs and circulation may reflect a particularly poor prognosis, indicating that the inflammatory response may perpetuate and amplify IPF but may not be the driving force behind its development (14,19). In both diseases, the final common pathway is believed to involve the recruitment and stimulation of activated myofibroblasts (7).

Animal experiments have been used extensively to model IPF and SSc-associated ILD. Lung fibrosis is induced in rodents by bleomycin, silica, fluorescein isothiocyanate, and angiotensin II, by immunization with recombinant topoisomerase I, by irradiation, or by treatment with ectopic transforming growth factor β (TGFβ1) (14). Many of these agents are administered by intratracheal installation, while others induce lung fibrosis along with scleroderma-like cutaneous changes and widespread organ fibrosis when injected subcutaneously. Recent studies have further demonstrated the development of lung fibrosis in transgenic mice overexpressing Fra-2 or platelet-derived growth factor (PDGF) receptor α or in mice with deletion of urokinase-type plas-

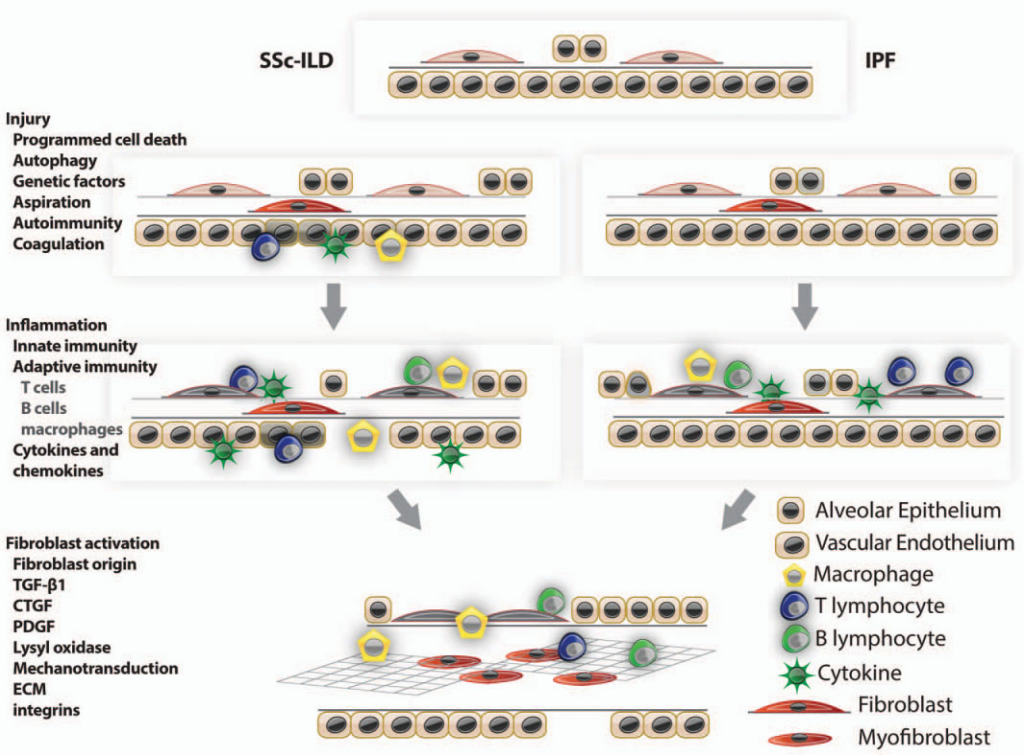

Figure 3. Schematic representation of key pathways implicated in systemic sclerosis (SSc)–associated interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF). Recurrent epithelial and/or endothelial injury promotes recruitment of macrophages and lymphocytes with resulting production of profibrotic mediators, including transforming growth factor β1 (TGFβ1), connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF). Together, this enhances fibroblast activation, proliferation, survival, and differentiation to a contractile myofibroblast phenotype with resulting overproduction and accumulation of extracellular matrix (ECM).

minogen activator receptor (20). While these animal models of disease recapitulate important features of pulmonary fibrosis, their usefulness for understanding pathogenesis or developing targeted therapy for IPF and SSc-associated ILD is restricted by important differences that distinguish them from the human diseases. These include relatively rapid onset of lung fibrosis in animals, failure to recapitulate pulmonary histopathologic changes, reversibility of fibrosis upon cessation of profibrotic stimulus, and efficacy of multiple antifibrotic agents in animals that have subsequently failed in human clinical trials.

Injury. Epithelial and/or endothelial cell injury and death are thought to be required for initiating the fibrotic cascade in both SSc-associated ILD and IPF (7). The importance of injury is supported by observations showing that its inhibition ameliorates experimentally induced lung fibrosis (21). Injury leads to various forms of cell death, including necrosis, apoptosis, and pyroptosis, as well as to autophagy, activation of the coagulation cascade, and induction of epithelial αvβ6 integrin expression, the last of which in turn activates latent TGFβ and activation of immune responses (22). Epithelial cell injury leads to release of surfactant protein D (SP-D), KL-6, and YKL-40, levels of which are elevated in the circulation in both SSc-associated ILD and IPF (7). These markers reflect disease progression (in IPF) and severity (in SSc-associated ILD) (7). No specific initiating pathways have been identified for either disease, although evidence exists for involvement of early growth response 1 (23), lysophosphatidic acid receptor 1 (LPA_1), the Wnt/β-catenin pathway (7), oxidative stress, and the unfolded protein response/endoplasmic reticulum stress (24) in both presentations. The extent to which these injury pathways contribute to either disease has not been elucidated and remains an important area of investigation.

Immune dysregulation. Autoimmunity is an essential feature of SSc-associated ILD, whereas its role in IPF is less well established. Altered T cell numbers and function in the circulation and bronchoalveolar lavage fluid are prominent both in IPF patients and in patients

with SSc-associated ILD. For instance, alterations in the number and function of CD4+CD25+FoxP3+ Treg cells have been reported both in patients with SSc-associated ILD (25) and in IPF patients (26). Animal models of lung fibrosis suggest that abnormal Treg cells might perpetuate lung injury and fibrosis (27). Increased numbers of circulating Th17 and Th22 cells have been described in patients with SSc-associated ILD (28), but similar results have not been reported in IPF to date (28). However, levels of interleukin-17 (IL-17) in the lungs are elevated in IPF, and IL-17 appears to be sufficient to induce pulmonary fibrosis in animal models (7). A role of B cells in pulmonary fibrosis is also emerging. Elevated circulating levels of BAFF were associated with reduced survival in patients with SSc-associated ILD (7), while in IPF patients, elevated levels of B lymphocyte stimulator predicted reduced event-free survival (29).

Cyclophosphamide, a lymphocyte-modulating agent, has been shown to have modest therapeutic efficacy in SSc-associated ILD but not in IPF, suggesting a key role of adaptive immune responses in the former but not the latter (30,31). Enhanced accumulation of alternatively activated monocytes and macrophages in the blood and lungs has been demonstrated in both SSc-associated ILD and IPF (7). Circulating levels of scavenger receptors as well as profibrotic cytokines and chemokines, such as IL-8, monocyte chemotactic protein 1, and CCL18 secreted by alternatively activated macrophages, were shown to predict reduced survival in IPF but not in SSc-associated ILD (32). As discussed below, microarray-based genome-wide expression profiling of lung biopsy samples from SSc-associated ILD and IPF patients revealed increased expression of genes associated with TGFβ and interferon (IFN) signaling, as well as macrophage activation and evidence of M2 polarization (33,34). Modulation of macrophage phenotypes attenuates lung fibrosis in rodent models, suggesting that these cells play complex roles in pathogenesis (35). Delineation of specific immunopathogenic alterations associated with the 2 forms of ILD might yield important novel insights.

Fibroblasts and the extracellular matrix. Activated myofibroblasts play vital roles in the development of lung fibrosis (7). The source(s) of these cells has been the focus of much investigation and debate. While many myofibroblasts appear to be derived from postembryonic lung fibroblasts, alternative sources such as bone marrow–derived fibrocytes, epithelial cells, endothelial cells, adipocytes, and/or pericytes may also contribute through various forms of transdifferentiation (22,36).

Aberrant TGFβ signaling is a key mechanism underlying myofibroblast activation and differentiation in both SSc-associated ILD and IPF. Additional profibrotic mediators important in lung fibrosis include PDGF, connective tissue growth factor (CTGF), Wnt ligands, and endothelin 1 (7). Fibroblasts explanted from the lungs of IPF patients resist apoptosis ex vivo (22), and their activation can be induced upon exposure to certain collagens and alternatively spliced fibronectin, by glycosaminoglycans such as hyaluronic acid, and by proteoglycans such as periostin (36). This apoptosis-resistant phenotype has recently been reported to be related to age-related alterations in NADPH oxidase 4 (NOX-4) and NF-κB–repressing factor leading to the accumulation of reactive oxygen species and myofibroblast senescence (37). Similar responses have not yet been reported in fibroblasts obtained from the lungs of patients with SSc-associated ILD. Decellularized lung matrices prepared from IPF patient lung explants promote myofibroblast differentiation, and similar studies are ongoing in SSc-associated ILD (38). Current studies suggest that the altered lung fibroblast phenotypes in both forms of pulmonary fibrosis may result from abnormalities both in the composition of the extracellular matrix, including increased accumulation of collagens and tenascin-C in both SSc-associated ILD and IPF (39), and in its mechanical properties, notably including increases in matrix stiffness. However, the unique and overlapping features of these responses in each entity have yet to be defined.

Genome-wide expression profiling in lung fibrosis. Recent studies increasingly take advantage of powerful microarray-based "omics" approaches to investigate differential gene expression at the genome-wide level in lungs from patients with SSc-associated ILD and those with IPF. Studies using primary lung fibroblasts have shown that in response to TGFβ, fibroblasts from patients with SSc-associated ILD and those with IPF show marked up-regulation of genes for angiotensin II receptor type 1 (AGTR1), smooth muscle actin (ACTA2), CTGF, plasminogen activator inhibitor 1, and NOX-4 (40,41). Microarray studies performed on lung tissues obtained at surgical biopsy from patients with SSc-associated ILD reveal elevated expression of IFN-regulated genes and genes related to macrophage activation (33). Similar studies of IPF patient lung biopsy samples reveal that expression of genes associated with morphogenesis, oxidative stress, migration/proliferation, and fibroblasts/smooth muscle cells was associated with an accelerated disease course (42), suggesting that path-

Table 2. Distinct genetic architecture of SSc-associated ILD and IPF*

Proposed biologic function	Associations with SSc-associated ILD	Associations with IPF
Epithelial homeostasis	SP-B, HGF	SP-A, SP-C, Muc5b, telomerase
Immune regulation	IRAK-1, IRF-5, NLRP1	SPPL2C, TOLLIP, TLR-3
Fibroblast activation/matrix remodeling	CTGF, MMP-12	None

* SSc = systemic sclerosis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; SP-B = surfactant protein B; HGF = hepatocyte growth factor; IRAK-1 = interleukin-1 receptor–associated kinase 1; IRF-5 = interferon regulatory factor 5; SPPL2C = signal peptide peptidase–like 2C; TOLLIP = Toll-interacting protein; TLR-3 = Toll-like receptor 3; CTGF = connective tissue growth factor; MMP-12 = matrix metalloproteinase 12.

ways related to structural cell integrity might in fact be mediating disease.

In contrast to these studies, which were performed in treatment-naive patients with early-stage disease, cluster analysis of gene expression profiling performed on unstimulated primary lung fibroblasts from explants obtained from patients with end-stage SSc-associated ILD and IPF identified insulin-like growth factor binding protein 3 (IGFBP-3) and IGFBP-7, lysyl oxidase, and sulfatase genes as highly up-regulated in both diseases (42). Findings specific to SSc-associated ILD included genes related to antigen presentation, IL-17 signaling, and chemokine pathways (43). These studies indicate that unlike profiling studies performed in early disease, in the setting of end-stage lung disease substantial overlap exists between SSc-associated ILD and IPF. However, even in this setting, tissues from patients with SSc-associated ILD maintain a strong inflammatory profile, further reflecting its immunopathogenetic origin.

Genetic factors and epigenetic changes

Heritability contributes to the risk of both IPF and SSc-associated ILD (2,3,44). For instance, disease clustering in families is noted with both SSc and IPF (2,3). However, twin studies showed a low concordance rate for disease, in contrast to concordance for ANAs (45). In patients with SSc, polymorphisms at loci for genes involved in epithelial function such as SP-B and hepatocyte growth factor, genes involved in immune responses such as IL-1 receptor–associated kinase 1 and IFN regulatory factor 5, and genes involved in fibroblast activation such as CTGF and matrix metalloproteinase 12 are associated with the presence and/or the severity of pulmonary fibrosis (46). In IPF, familial cases are associated with mutations in the genes encoding surfactant proteins A or C, and telomerase (2,22) abnormalities in these proteins are thought to contribute to epithelial stress responses, although this has not been definitively shown. A genome-wide association study revealed novel associations of IPF with variants at the loci for the membrane-bound protease signal peptide peptidase–like 2C and the innate immune adaptor protein Toll-interacting protein (47). Another IPF study revealed an association with Toll-like receptor 3 (48). A variant of Muc5b, a gene involved in airway epithelial mucus production, is strongly associated with the risk of IPF, where it appears to confer a more indolent disease course (49). It is noteworthy that neither the Muc5b variant nor any of the other known genetic variants linked to IPF has been shown to be associated with SSc-associated ILD (41,50).

This divergence between SSc-associated ILD and IPF suggests that the host genetic background may set the stage for responses to as-yet-undefined environmental factors leading to the variable features of these 2 forms of lung fibrosis. Table 2 shows genetic loci associated with SSc-associated ILD and with IPF, and their potential roles in pathogenesis.

Epigenetic mechanisms elicit stable changes in gene expression that are independent of alterations in the DNA code, and they link transient environmental exposures to persistent phenotypic changes. Emerging studies reveal cell type–specific alterations in DNA methylation, histone modifications, and microRNA expression in patients with SSc-associated ILD (51) and IPF (22). The majority of epigenetic studies in SSc focus on blood cells or explanted skin fibroblasts, while in IPF such studies have concentrated on primary lung fibroblasts (40). While the potential contribution of epigenetic alterations to epithelial and endothelial injury and immune responses in both forms of ILD still remains open to speculation, a thorough characterization of these changes is an important research challenge.

Table 3. Studies of potential therapies for SSc-associated ILD and IPF*

Therapy	Trial (author, year [ref.])	Study design and outcome
SSc-associated ILD		
MMF	Zamora et al, 2008 (62)	Retrospective chart review of 17 patients; 16 of 17 patients had stable or improved lung function after 12 months of treatment
	Gerbino et al, 2008 (63)	Retrospective chart review; 4% improvement in FVC after at least 6 months of treatment
	Fischer et al, 2013 (64)	Case series of 44 patients with SSc-associated ILD (part of a larger series of 127 patients treated with MMF) demonstrated trend toward improved FVC % predicted at 52, 104, and 156 weeks
CYC (IV) + prednisolone followed by AZA vs. placebo	Hoyles et al, 2006 (65)	Prospective, randomized, placebo-controlled trial; 4.19% difference between active treatment and placebo groups ($P = 0.08$)
CYC (oral) vs. placebo	Tashkin et al, 2006 (66)	Prospective, randomized, placebo-controlled trial; 2.5% difference between active treatment and placebo groups ($P = 0.03$)
AZA + prednisone vs. CYC + prednisone	Nadashkevich et al, 2006 (67)	Prospective randomized trial; FVC and DLCO remained stable in CYC group and worsened in AZA group
Imatinib mesylate	Khanna et al, 2011 (68)	Open-label trial (600 mg/day); trend toward improvement in FVC (1.7%) but large number of adverse events
	Spiera et al, 2011 (61)	One-year open-label trial (400 mg/day); 6.4% improvement in FVC ($P = 0.008$) but large number of mild-to-moderate adverse events
Rituximab vs. standard therapy	Daoussis et al, 2012 (69)	One-year proof-of-principle study; 10.3% improvement in FVC in rituximab group and 5.0% deterioration in standard therapy group ($P = 0.002$)
HSCT vs. CYC (IV)	Burt et al, 2012 (70)	Three-and-one-half year open-label trial; 15% improvement in FVC in the HSCT group compared to worsening (−9%) in the standard therapy (CYC) group at 12 months ($P = 0.006$)
IPF		
AZA + NAC + prednisone vs. NAC vs. placebo	Raghu et al, 2012 (54)	Randomized, placebo-controlled trial; AZA + NAC + prednisone arm stopped after 50% of data collected due to increased rate of death and hospitalization with no statistically significant improvement in lung function; results from 2 remaining arms (NAC alone vs. placebo) not yet available
Pirfenidone vs. placebo	Noble et al, 2011 (71)	Two randomized, placebo-controlled trials: 4.4% difference in FVC between treatment (highest dose) and placebo groups ($P = 0.001$); 0.6% difference in FVC between treatment and placebo groups (P not significant)
Pirfenidone vs. placebo	King et al, 2014 (59)	Randomized, placebo-controlled phase II trial; 48% reduction in significant lung progression (FVC decline >10%) at 52 weeks
Sildenafil vs. placebo	IPFCRN, 2010 (72)	Randomized, placebo-controlled trial; no significant difference in decline in 6-minute walk distance when all subjects evaluated together ($P = 0.39$), less decrement in 6-minute walk distance in subgroup of subjects with right ventricular systolic dysfunction ($P = 0.01$)
Etanercept vs. placebo	Raghu et al, 2008 (73)	Randomized, placebo-controlled trial; no significant difference in FVC, DLCO, or 6-minute walk distance between treatment and placebo groups
NAC + AZA + prednisone vs. placebo + AZA + prednisone	Demedts et al, 2005 (74)	Randomized, placebo-controlled trial; 9% difference in FVC between groups at 12 months
Bosentan vs. placebo	King et al, 2011 (75)	Randomized, placebo-controlled trial; no significant difference in FVC, death, or worsening of IPF between groups
Interferon gamma-1b vs. placebo	King et al, 2009 (76)	Randomized, placebo-controlled trial; no difference in mortality after 64 weeks of treatment
Warfarin vs. placebo	Noth and Olman, 2013 (77)	Trial terminated by Drug Safety Monitoring Board due to increased mortality in the treatment arm
Nintedanib	Richeldi et al, 2011 (78)	Randomized, placebo-controlled trial; reduction in FVC decline at highest dose tested
Nintedanib vs. placebo	Richeldi et al, 2014 (60)	Randomized, placebo-controlled trial; 50% difference in FVC between 2 groups at 52 weeks

* SSc = systemic sclerosis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MMF = mycophenolate mofetil; FVC = forced vital capacity; CYC = cyclophosphamide; IV = intravenous; AZA = azathioprine; DLCO = diffusing capacity for carbon monoxide; HSCT = hematopoietic stem cell transplantation; NAC = *N*-acetylcysteine; IPFCRN = Idiopathic Pulmonary Fibrosis Clinical Research Network.

Management and prognosis

Perhaps the most compelling evidence supporting the notion of disparate pathogenesis of SSc-associated ILD and IPF comes from results from clinical trials. Pulmonary fibrosis in the setting of both IPF and SSc-associated ILD carries a poor prognosis (2,12). The only therapy known to influence survival in either form of lung disease, orthotopic lung transplantation, has comparable survival benefit for both (41,52). A dominant pathogenetic role of immunity in the development or progression of SSc-associated ILD is supported by reports indicating modest benefit of immunomodulatory therapy on stabilizing lung function. To date, there are no reported data demonstrating consistent effects for any agent, immunosuppressive or otherwise, on lung function or survival in IPF. However, promising antifibrotic agents are currently completing evaluation.

Multiple studies have indicated modest benefit of cyclophosphamide in patients with SSc-associated ILD (6,30); subgroup analysis indicated a more pronounced effect in patients with severe respiratory symptoms, radiographic lung involvement, or higher skin scores at baseline (53). In contrast, cyclophosphamide showed no efficacy in patients with IPF (31). Combination therapy with azathioprine and steroids is not effective in either disease and was associated with worse outcomes in IPF in 1 recent study (7,54). Mycophenolate mofetil (MMF) treatment in SSc-associated ILD resulted in improved or stable pulmonary function (55) and is being evaluated in a randomized controlled trial (Scleroderma Lung Study II). In contrast, MMF has not shown benefit in IPF (56). Targeting B cells with rituximab in patients with SSc-associated ILD resulted in significant improvements in FVC and DLCO in a small study (57), while to date there are no reported studies of B cell targeting in IPF. A clinical trial in SSc comparing autologous hematopoietic stem cell transplantation (HSCT) and cyclophosphamide demonstrated significant improvement in FVC at 1 year in patients who received HSCT (58). To date, HSCT has not been investigated for the treatment of IPF. Despite the small sample size and uncontrolled nature of these trials, the results suggest that immunomodulation may be of greater benefit in SSc-associated ILD than in IPF, although substantial patient-to-patient heterogeneity in the clinical response and lack of appropriate biomarkers of response preclude definite conclusions.

Nonimmunomodulating therapies targeting fibrotic pathways in pulmonary fibrosis are of great interest (7). The most advanced agents, pirfenidone and BIBF 1120 (nintedanib), have shown benefit in IPF and have recently completed phase III clinical trials (59,60). Pirfenidone has shown efficacy in preclinical models of fibrosis that are due in part to its pleiotropic effects on fibrogenesis and disruption of cellular TGFβ signaling. In contrast, BIBF 1120 is a triple kinase inhibitor that blocks signaling from PDGF, vascular endothelial growth factor, and fibroblast growth factor receptors. Both of these agents attenuated the decline in lung function in some patients with IPF; their efficacy in SSc-associated ILD remains to be demonstrated. The tyrosine kinase inhibitor imatinib mesylate, evaluated in IPF in a randomized controlled trial, had no effect on survival or lung function, whereas in patients with SSc-associated ILD studied in an open-label single-arm trial, imatinib mesylate treatment was associated with a modest improvement of FVC (61). Ongoing clinical trials in SSc-associated ILD or IPF are examining antioxidant agents and drugs targeting TGFβ or its activation by $\alpha v\beta 6$ integrin, CTGF, alternative macrophage activation, and LPA_1. There is great enthusiasm for the development of personalized therapies in IPF and SSc-associated ILD targeting specific components of the fibrotic response based on individual gene expression profiles and peripheral blood biomarkers (22). A synopsis of recent clinical trials is presented in Table 3.

Conclusions

SSc-associated ILD and IPF encompass distinct forms of pulmonary fibrosis that are associated with characteristic pathologic and radiographic features, natural history, and response to treatment. Despite similarities between these 2 entities, their divergent features reflect differences in the pathways regulating tissue injury and repair, immune dysregulation, and aberrant fibroblast responses. These are determined in part by distinct genetic risk factors and epigenetic modulators.

The following is a list of unanswered questions with significant clinical implications for lung fibrosis:

1. What is the role of injured epithelium and endothelium in pathogenesis?
2. Does the immune response differ between SSc-associated ILD and IPF?
3. To what extent do fibroblasts and extracellular matrix contribute to disease?
4. Are therapies that target epithelial–endothelial cell injury or fibroblast activation likely to be equally efficacious in IPF and SSc-associated ILD?
5. Are SSc-associated ILD and IPF truly differ-

ent entities or are they simply different ends of the same clinical spectrum?

6. What are robust and predictive biomarkers for SSc-associated ILD and IPF?

7. Can personalized medicine approaches guide targeted therapy in SSc-associated ILD and IPF?

Intense effort is needed to address these questions and use the insights to accelerate the development of robust predictive biomarkers and safe and effective targeted therapies. Research directions should include translational studies utilizing well-annotated biologic samples, adequately powered comparative genetic and genomic studies, improved ex vivo models, and animal models that more faithfully recapitulate disease-specific pathology and course. Further studies in these areas will provide better insight into the unique and overlapping factors contributing to these diseases.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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