

Fibroblasts as regulators of lung immunity, repair and fibrosis

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Abstract

Fibrosis is a complex disorder characterized by the excessive deposition of extracellular matrix, which disrupts normal tissue architecture and compromises organ function. Fibrosis can affect any organ, with pulmonary fibrosis being one of the most common and life-threatening forms. Despite marked research efforts, effective antifibrotic therapies remain limited, largely due to an incomplete understanding of the underlying disease mechanisms. At the centre of fibrotic processes are fibroblasts, which are tissue-resident mesenchymal cells responsible for extracellular matrix production, tissue remodelling, wound healing and fibrosis. For decades, the biology of fibroblasts remained poorly understood, but advances in single-cell sequencing have recently provided deeper insights into their heterogeneity, plasticity and functional diversity. These insights have prompted renewed efforts to identify the core regulatory programmes that govern fibroblast states in health and disease. In this Review, we examine how immunological, mechanical and metabolic regulators influence fibroblast function in fibrosing interstitial lung diseases. We show how loss of stromal regulation through chronic inflammation, immune dysfunction, altered tissue biomechanics and metabolic stress can tip the balance from successful tissue repair to progressive fibrosis.

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Introduction

Pulmonary fibrosis is a common and often fatal outcome of interstitial lung disease (ILD), resulting from excessive deposition of extracellular matrix (ECM) and destruction of alveolar architecture. It represents a final common pathway following various injurious stimuli, culminating in impaired gas exchange and respiratory failure. ILDs with a progressive fibrosing phenotype have a poor prognosis, often associated with rapid and unpredictable disease progression¹. Although current antifibrotic therapies can slow disease progression, they do not halt or reverse fibrosis. A deeper understanding of the molecular mechanisms that drive pulmonary fibrosis is essential for the development of more effective antifibrotic therapies.

Fibroblasts produce ECM components, such as collagens, glycoproteins, laminins and proteoglycans, which provide structural scaffolding to tissues². The precise composition of these ECM components determines the biophysical properties of the tissue, and dysregulation in ECM production or degradation leads to altered

tissue biomechanics and fibrosis³. Although an understanding of the complex biology of fibroblasts has long remained incomplete, recent advances in single-cell sequencing technologies have offered considerable insights into fibroblast heterogeneity and plasticity. Traditionally, fibroblasts were considered relatively inert structural bystanders, but now they are recognized to have diverse functions at the intersection of innate immunity, mechanobiology and tissue regeneration. Fibroblasts also display an extraordinary capacity to adopt a wide range of states according to changing environmental demands, a phenomenon known as phenotypic plasticity.

In this Review, we examine bidirectional interactions among fibroblasts, epithelial stem cells and the immune system in health and fibrosing ILDs (fILDs). We first highlight the major unmet clinical needs and identify factors that have obscured scientific and clinical inroads. Next, we review insights from single-cell multiomics, outlining emerging principles including fibroblast heterogeneity, organization and phenotypic plasticity (Box 1). We then examine how immunological,

Box 1 | Fibroblast heterogeneity

Single-cell sequencing has transformed our understanding of fibroblast biology by overcoming long-standing challenges associated with the lack of reliable cell surface markers. Owing to concerted efforts by large consortia such as the International Human Cell Atlas initiative²²⁷, fibroblast atlases are now available across multiple organs, developmental stages and diseases, enabling cross-tissue meta-analyses that shed light on universal and tissue-specific properties of fibroblasts^{75,97,228,229}. Pan-tissue transcriptional signatures have been identified across diverse fibroblasts from different tissues, including *PI16*⁺ adventitial fibroblasts surrounding blood vessels²³⁰, *COL15A1*⁺ fibroblasts within tissue basement membranes²³⁰ and *CCL19*⁺*CCL21*⁺ fibroblastic reticular-like cells in secondary and tertiary lymphoid organs²³¹. However, such 'universal' transcriptional states appear to be exceptions rather than the norm. Canonical makers used to identify fibroblast subsets often do not overlap between organs

and integrated cross-tissue single-cell RNA-sequencing analyses reveal striking interorgan heterogeneity^{228,229}. These findings suggest that fibroblasts adopt highly specialized phenotypes shaped by their local niche.

Emerging spatially resolved genomic atlases of human lungs reveal that fibroblast heterogeneity varies according to microanatomical niche²³². Distinct fibroblast subsets occupy specialized anatomical niches: alveolar fibroblasts form the alveolar scaffold; peribronchial fibroblasts line the airway epithelia; perichondrial fibroblasts surround cartilage; adventitial fibroblasts populate the adventitial space; pericytes associate with capillaries and venules; reticular-like fibroblasts organize bronchial immune follicles; and nerve-associated fibroblasts colocalize with nerve bundles²³³. In addition, novel fibroblast states emerge in interstitial lung disease (see the figure).

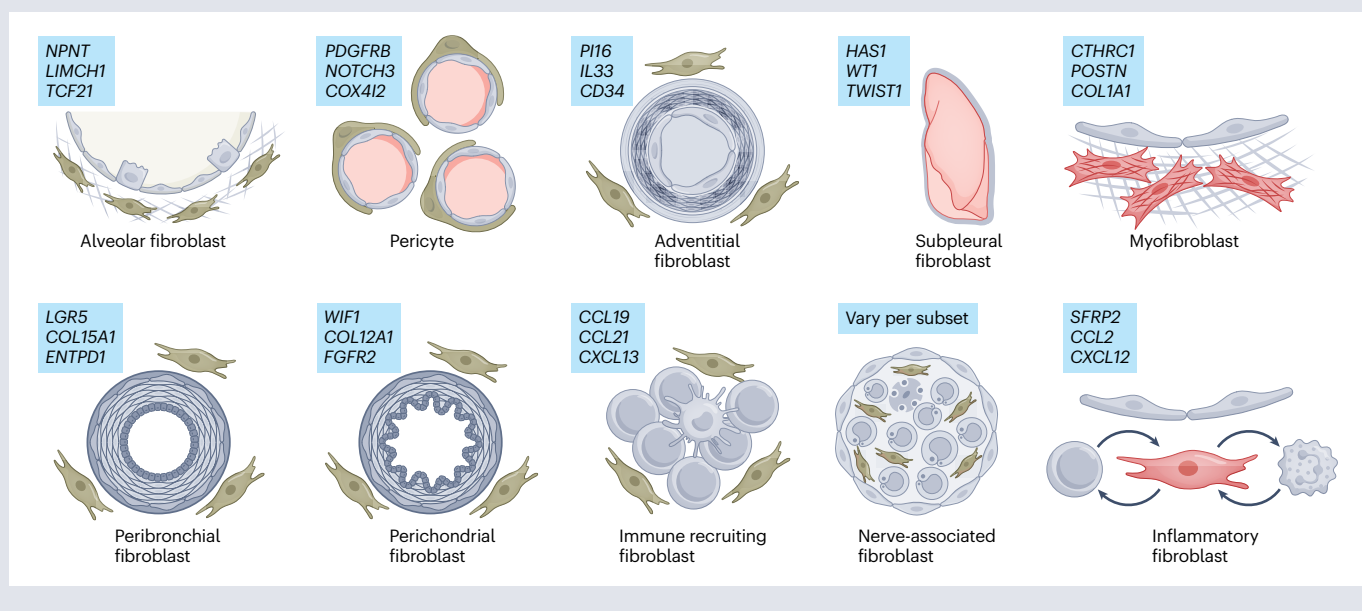


Table 1 | Clinical spectrum of fibrotic interstitial lung diseases

Condition	Epidemiology	Characteristic histopathology	Risk of progressive pulmonary fibrosis (PPF)	Management
Idiopathic pulmonary fibrosis (IPF) ^{1,186}	Highest incidence in males aged >50 years, often associated with a history of smoking or other occupational exposures	Usual interstitial pneumonia (UIP) characterized by fibroblastic foci and cystic honeycombing. Areas of active fibrosis together with other regions of mature scar reflect the spatiotemporal heterogeneity of the disease process	~100%. Risk factors include familial disease, age, UIP and reduced lung function at diagnosis	Nintedanib or pirfenidone. Avoidance of immunosuppression due to potential to cause harm
Systemic sclerosis-associated interstitial lung disease (SSc-ILD) ²²³	ILD is common (up to 80%) with ~30–40% requiring treatment. Systemic sclerosis (SSc) most common in women aged 30–60 years	Nonspecific interstitial pneumonia (NSIP) characterized by a temporally uniform pattern of interstitial inflammation and/or fibrosis. The interstitial infiltrate is typically composed of lymphocytes and plasma cells. Less commonly, other histological patterns including organizing pneumonia and UIP are seen	~40%. Risk factors include age, male sex, African-American ethnicity, diffuse cutaneous SSc subtype, presence of anti-SCL70 antibody and elevated acute phase reactants	Immunosuppression is standard of care. This can include various combinations of mycophenolate, rituximab, tocilizumab and cyclophosphamide. The addition of nintedanib or pirfenidone can also be considered in progressive pulmonary fibrosis
Rheumatoid arthritis interstitial lung disease (RA-ILD) ^{1,224}	Clinically relevant ILD most commonly affects older males with a history of smoking	UIP is the most common histological pattern, followed by NSIP	~30%. Risk factors include age, male sex, UIP and/or extensive disease on imaging and/or impaired lung function	Role of immunosuppression is uncertain; however, some combination of steroids, rituximab, mycophenolate, methotrexate or tumour necrosis factor (TNF) inhibitors is often trialled. Nintedanib can also be considered in patients with progressive pulmonary fibrosis
Pulmonary sarcoidosis ^{1,225}	Most often affects adults aged 20–40 years. Higher risk of fibrotic sarcoid in individuals of African-American descent	Non-necrotizing granulomas surrounded by multinucleated giant cells and lymphocytes. Granulomas are typically found along lymphatic routes, including the bronchovascular bundles, subpleural regions and interlobular septa	~10–15%. Risk factors include African-American ethnicity, female sex, concomitant pulmonary vascular disease and impaired lung function	In pulmonary sarcoidosis with high-risk features, corticosteroids are used with addition of methotrexate or azathioprine as steroid-sparing agents. Second-line therapies include TNF inhibitors and nintedanib
Fibrotic hypersensitivity pneumonitis (fHP) ²²⁶	Usually aged >40 years. Higher risk in individuals exposed to inciting antigens such as farmers or bird handlers	Non-necrotizing granulomas or giant cells with or without chronic bronchiolitis and peribronchiolar lymphocyte-predominant chronic inflammation	~20%. Risk factors include age, male sex, unidentifiable inciting antigen, absence of lymphocytosis on bronchoalveolar lavage, impaired lung function, UIP pattern on imaging or histology	Antigen avoidance, trial of corticosteroids and/or nintedanib. Mycophenolate may be used as a steroid-sparing agent in certain circumstances but benefit of immunosuppression in chronically progressive fHP is uncertain

mechanical and metabolic regulators influence fibroblast function in healthy and fibrotic tissues. Finally, we propose a model to explain how loss of stromal regulation through chronic injury, immune dysfunction, altered tissue biomechanics and metabolic stress results in tissue repair failure and fibrosis.

Fibrosing interstitial lung diseases

fILDs are a heterogeneous group of disorders characterized by immune cell infiltration and fibrotic remodelling of the alveolar interstitium. Clinically, these diseases are classified based on identifiable causes, patient comorbidities and characteristic radiological and histopathological features^{1,4} (Table 1). Idiopathic pulmonary fibrosis (IPF) is the archetypal and most common form of fILD, marked by a rapid disease course that typically leads to respiratory failure and death within 3–5 years⁵. Other ILDs also exhibit similar progressive fibrotic behaviour, including systemic autoimmune rheumatic disease-associated ILD, hypersensitivity pneumonitis, sarcoidosis and pneumoconioses¹. Despite varied aetiologies, advanced-stage fILDs tend to converge on overlapping radiological patterns, histological features and clinical behaviours⁹.

Currently, only two drugs are licensed by the FDA for progressive fILD⁷, with no approved antifibrotic treatments for fibroses affecting other organs. Pirfenidone and nintedanib gained approval for IPF in 2014 after demonstrating efficacy in phase III randomized controlled trials^{8–10}. More recently, nerandomilast, an oral phosphodiesterase 4B inhibitor, has shown promise in slowing lung function decline in IPF¹¹ and is awaiting regulatory approval. Notably, these antifibrotic agents have also demonstrated efficacy in non-IPF fILDs, including systemic sclerosis-associated ILD¹², unclassifiable ILD¹³ and other fILDs with a progressive fibrosing phenotype^{14–16}, implying shared molecular pathways across different clinical entities⁶. Although these available therapies reduce the rate of lung function decline by up to 50% (refs. 9,10), they do not halt or reverse fibrosis, highlighting the urgent need for novel therapeutics.

Insights from single-cell genomics

Advances in human single-cell genomic atlases have improved our understanding of end-stage pulmonary fibrosis by mapping diverse and aberrant cellular states. Single-cell RNA sequencing (scRNA-seq) analyses have identified a distinct population of ‘aberrant basaloid’

epithelial cells, characterized by overlapping signatures of airway basal epithelial cell, mesenchymal cell and senescence markers^{17–20}. Fibroblast heterogeneity has also been mapped in fILD^{18,20–26}, uncovering pathological subsets such as CTHRC1⁺ myofibroblasts, which are highly enriched for collagens and ECM products and localize to fibroblastic foci^{19,20,22,23}. In addition, tissue-resident alveolar macrophages are replaced by pathogenic SPPI⁺ monocyte-derived macrophages, which express a suite of profibrotic mediators^{19–21,27}. Furthermore, ectopic systemic endothelial cells, which are usually restricted to the bronchial vasculature, have been identified in the distal lung parenchyma^{17,20,28} and may contribute to lymphocyte recruitment and aggregation in fibrotic lungs²⁰.

Although these findings are informative, several caveats must be acknowledged. By the time that symptoms develop and patients seek medical attention, pulmonary fibrosis is typically advanced (Fig. 1). Moreover, surgical lung biopsies pose considerable mortality risk owing to the potential for acute lung injury (that is, an ‘acute exacerbation’) in patients with fILD²⁹, limiting access to human lung tissue. Consequently, genomic analyses predominantly rely on explanted lung tissue obtained at transplantation or autopsy. At this very end stage of disease, lung tissue is severely distorted, brittle and hypoxic, bearing little resemblance to healthy elastic lung architecture. Thus, although single-cell genomics can map the cellular landscape of advanced pulmonary fibrosis, fundamental questions about upstream mechanisms remain unresolved. Given these challenges, computational approaches such as RNA velocity and pseudotime analyses have been used to reconstruct and infer dynamic cellular transitions, but their application to end-stage tissue can misrepresent actual biological trajectories. These computational predictions therefore require careful validation with earlier stage tissue and *in vivo* fate-mapping experiments in animal models (Box 2).

Owing to these limitations, most mechanistic insights into fibrosis biology derive from animal models. Mouse systems provide powerful genetic tools to interrogate the complexity of the mammalian respiratory system but also fail to fully recapitulate human fibrotic progression (Box 3). This Review draws on such models while recognizing their limitations and the ongoing barriers they pose for clinical translation.

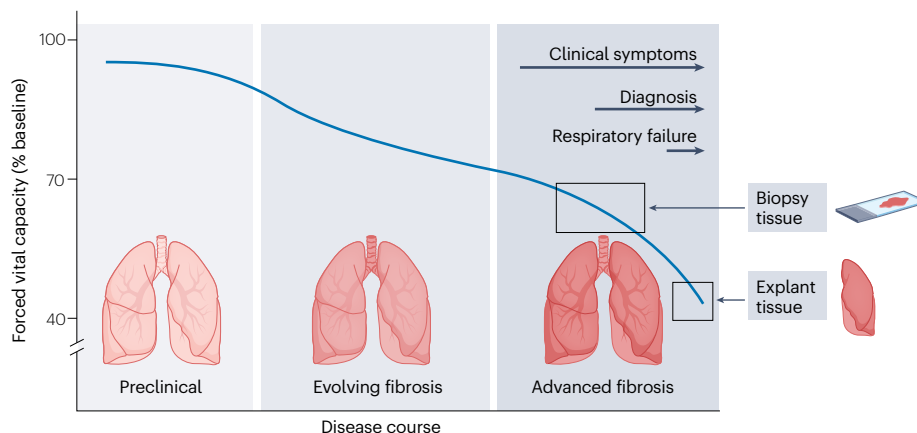


Fig. 1 Barriers to elucidating early pathogenic mechanisms in human pulmonary fibrosis. Patients with fibrosing interstitial lung diseases typically seek medical attention after the onset of respiratory symptoms, which occurs late in the disease course, at which time fibrosis is usually firmly established and often advanced. The risks associated with lung biopsy in patients with pulmonary fibrosis limit tissue sampling at diagnosis, and therefore most single-cell RNA-sequencing studies have relied on explanted tissue obtained at transplantation or

Fibroblast plasticity in tissue repair and regeneration

Tissue repair in vertebrates follows a tightly regulated sequence of overlapping events including inflammation, cell migration, ECM deposition, angiogenesis and wound contraction³⁰. Fibroblasts are central orchestrators of this reparative cascade, organizing immune cells, producing collagenous matrix and driving wound contraction. In a process termed fibroblast-to-myofibroblast transition, fibroblasts adopt specialized repair states, which are characterized by upregulation of cytoskeletal contractile proteins and secretion of copious ECM molecules^{31,32}. Successful wound healing requires not only the activation of these repair programmes but also their timely termination³³. To achieve this, myofibroblasts adopt a range of fates after tissue repair: some become senescent (marked by *p16^{INK4a}* expression) and shift their function towards matrix degradation and scar resolution^{34,35}; others adopt quiescent^{36–38} or alternative phenotypes³⁹, transdifferentiate into other lineages⁴⁰ or undergo programmed cell death by apoptosis^{33,41,42}.

Although all adult wound healing is somewhat imperfect, leaving behind a residual collagenous scar³⁰, fibrotic disorders display a highly dysregulated repair sequence, resulting in excessive scar formation and sustained tissue remodelling driven by the persistence of myofibroblasts³³. In conditions such as pulmonary fibrosis, scarring can become self-perpetuating, resulting in progressive fibrosis and organ failure⁶. Although persistent myofibroblast activity is a final common pathway shared across all fibrotic disorders⁴³, as we discuss, it is currently not clear why the normal regulatory checkpoints fail in patients with fILD.

Fibroblast–epithelial crosstalk in alveolar repair

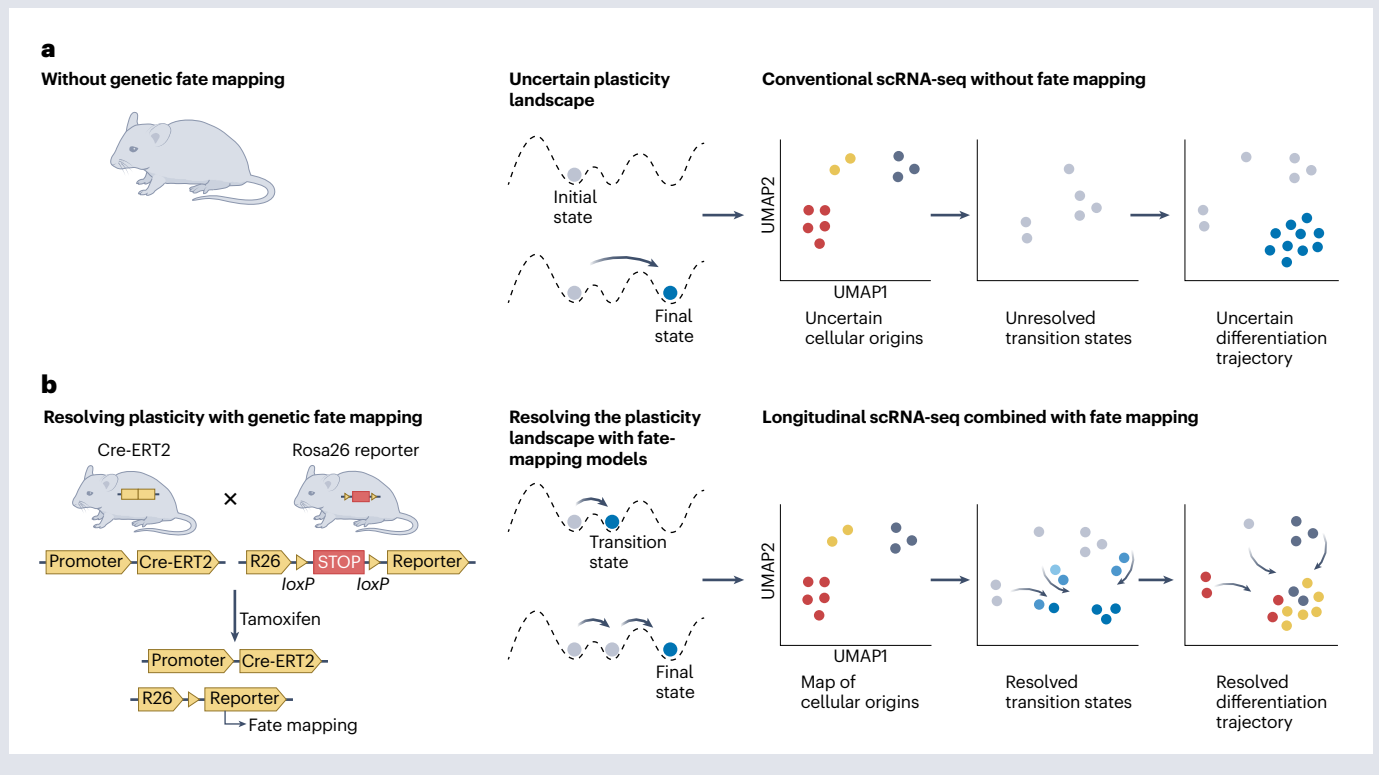
Mesenchymal–epithelial crosstalk is essential for normal development, mediated by mesenchyme-derived growth factors including WNTs, fibroblast growth factors, bone morphogenic proteins and transforming growth factor- β (TGF β)⁴⁴. Evidence increasingly supports that adult mucosal tissues depend on such crosstalk for epithelial repair and maintenance of barrier integrity^{45,46}. For example, in the healthy adult gut, subepithelial pericryptal PDGFR α ⁺ stromal cells form a stem cell

autopsy. Such specimens represent the very end stage of disease. These tissues are grossly distorted, brittle and hypoxic and often contain features of superimposed acute lung injury, making it complicated to define earlier immunopathogenic processes. Although transbronchial cryobiopsy or surgical lung biopsy can provide tissue earlier in disease, these procedures are performed infrequently and usually still only capture relatively advanced disease, limiting opportunities to define the earliest cellular and molecular pathways in human pulmonary fibrosis.

Box 2 | Mapping fibroblast plasticity and fate

A fundamental property of biological systems is the ability of cells to transition between distinct states in response to changing environmental demands. Cellular state transitions underlie key processes such as embryonic development, tissue homeostasis and wound healing. The dynamics of these transitions are regulated by multiple layers of epigenetic, transcriptional and metabolic control²³⁴. Increasingly, it is becoming clear that loss of such regulation can lead to maladaptive transitions that promote inflammation, fibrosis and cancer.

Innovative approaches combining fate-mapping and longitudinal single-cell genomics now provide a framework for mapping state transitions after tissue perturbation. Equipped with these technologies, the field has begun to move beyond conventional approaches that compare static molecular states across disease groups or time points (see the figure, panel a). Instead, combining in vivo fate mapping with time-series single-cell RNA sequencing (scRNA-seq) allows dynamic regulatory landscapes to be mapped throughout development and disease evolution (see the figure, panel b).



niche by supplying WNT proteins and R-spondins, which regulate proliferation and differentiation necessary for crypt maintenance^{47,48}. Similarly, in the adult mouse lung, a subset of WNT-responsive type 2 alveolar epithelial (AT2) cells (marked by expression of direct WNT target gene *Axin2*) functions as stem cells in alveoli^{49,50}. These AT2 stem cells are supported by specialized PDGFR α ⁺ alveolar fibroblasts that provide juxtacrine WNT signals to maintain AT2 cell stemness and guide epithelial fate⁵⁰.

Studies of lung repair highlight the crucial role of alveolar fibroblasts in coordinating epithelial stem cell regeneration^{38,39,51}. After mild injury, the alveolar epithelium undergoes euplastic regeneration via AT2 cell proliferation and differentiation into type 1 alveolar epithelial (AT1) cells to rapidly restore alveolar integrity^{44,52}. However, severe injury induces a dysplastic repair response, with airway progenitors mobilizing, proliferating and invading into the injured alveolar niche. In mouse models, *Trp63*⁺ airway basal epithelial stem cells migrate distally to alveoli, upregulate keratin 5 (*Krt5*) and form ectopic scar-like cystic structures, known as *Krt5*⁺ pods^{49,52,53}. Although airway-derived

stem cells provide emergency barrier protection, preventing death by respiratory failure⁵³, their presence impairs alveolar function by repopulating the niche with fate-restricted dysplastic epithelial progenitors⁵².

A recent fate-mapping and longitudinal scRNA-seq study shows how alveolar fibroblast plasticity can influence stem cell behaviour and repair outcomes after acute influenza virus infection and bleomycin-induced lung injury in mouse models³⁹. In this study, two distinct alveolar fibroblast populations – *Pdgfra*⁺ alveolar fibroblasts and *Pdgfrb*⁺ pericytes – were traced following injury using fate-mapping systems³⁹. *Pdgfra*⁺ alveolar fibroblasts transitioned through proliferative, inflammatory and myofibroblastic states, before adopting a *Pdgfrb*⁺ pericyte-like state³⁹. This *Pdgfra*-to-*Pdgfrb* phenotypic switch altered the signalling networks that orchestrate epithelial stem cell activity³⁹. Injury-induced *Pdgfrb*⁺ fibroblasts expressed high levels of the receptor Notch3 and received Notch ligands from *Krt5*⁺ epithelial cells, forming a feedback loop with invading stem cells³⁹. Genetic inactivation of intracellular Notch signalling in *Pdgfra*⁺ fibroblasts

Box 3 | Bridging species: translational challenges in modelling fibrosis

Given the conserved features across mouse and human lungs, mouse models have provided considerable insights into mammalian lung biology and *in vivo* systems for testing candidate antifibrotic compounds. Indeed, much of our understanding of lung biology is derived from mouse models, which have enabled scientists to dissect molecular pathways involved in lung inflammation, repair and fibrosis. However, many drugs that have shown promise in preclinical mouse models fail to demonstrate efficacy in early-phase human clinical trials. This is, in part, owing to shortcomings of current models, which fail to recapitulate core aspects of human anatomy (reviewed elsewhere²³⁵), physiology and disease. Indeed, mouse models do not fully capture key features of disease chronicity, particularly the spatiotemporal heterogeneity that is characteristic of human fibrosing interstitial lung diseases. Mouse systems also fail to accurately model the complex influences of ageing, environmental exposure, comorbidity and genetic diversity present in human populations. However, perhaps the most important limitation of conventional mouse injury models is their tendency towards fibrosis resolution following fibroproliferative injury, limiting our ability to model the persistent fibrotic progression that characterizes the human fibrosing interstitial lung diseases. The bleomycin lung injury model — the most widely used and influential preclinical model of pulmonary fibrosis — exemplifies this. Intratracheal or systemic delivery of bleomycin results in an acute lung inflammatory injury (days 0–7) followed by established fibrosis (days 14–28) and eventually partial fibrosis resolution²³⁶.

Emerging molecular and genetic tools have renewed efforts to model fibrotic progression in animal models. Genetic knockout systems that impair type 2 alveolar epithelial (AT2) cell differentiation result in a spontaneous subpleural-to-central pattern of fibrosis reminiscent of idiopathic pulmonary fibrosis¹⁸¹. Similarly, deletion of genes involved in telomere maintenance^{237,238} or negative regulators of senescence^{38,239} in AT2 cells induces spontaneous progressive pulmonary fibrosis. Fibroblast-specific ablation of the FAS-induced extrinsic apoptosis pathway impairs the clearance of profibrotic myofibroblasts and attenuates resolution of fibrosis after bleomycin injury²⁴⁰. Finally, genetic systems that dysregulate immune signalling, such as *Ifngr1^{-/-}Rag2^{-/-}* mice with overactive group 2 innate lymphoid cells, induce spontaneous progressive fibrosis¹¹⁸. This next generation of model systems now enables the study of epithelial–stromal–immune interactions in an *in vivo* context that more accurately reflects human fibrotic progression.

Complementary human model systems, such as precision-cut lung slices and lung organoids, also offer promising avenues to bridge the divide between basic discovery science and clinical translation. Additional insights may also emerge from studying human acute lung injuries, such as SARS-CoV-2-associated pneumonitis, which is known to induce profibrotic macrophage and myofibroblastic responses^{25,241}. Molecular analyses of post-mortem tissue from patients with severe acute lung injury such as SARS-CoV-2 may reveal early entry points into fibrotic pathways and identify key regulators of repair failure and fibrotic remodelling.

blocked dysplastic repair and promoted euplastic regeneration, illustrating how fibroblast plasticity can shape repair outcomes³⁹. Dysplastic alveolar repair is further compounded by chronic inflammation, with recent work showing that chronic IL-1 β impairs AT2-to-AT1 cell differentiation by stalling the transition of alveolar differentiation intermediate cells (ADI cells) into mature AT1 cells^{54,55}, contributing to a gradual accumulation of profibrotic ADI cells that further impair regeneration and promote fibrosis⁵⁴ (Fig. 2).

Overall, mouse models demonstrate that severe acute lung injury results in proximal-to-distal airway-derived stem cell migration, long-term persistence of dysplastic epithelial progenitors and a shift from regenerative to aberrant mesenchymal–epithelial signalling^{39,52,56}. These observations parallel clinical findings in human fILD, in which histological features include neo-bronchiolization (a dysplastic remodelling process by which ‘proximalized’ alveolar epithelia acquire bronchiolar-like epithelial characteristics)^{26,52,56–58} and formation of honeycomb cystic structures which are lined by epithelial cells that express airway epithelial markers⁵⁹ and display hyperactive Notch signalling⁵⁶. This supports the hypothesis that migrating airway-derived epithelial progenitors contribute to neo-bronchiolization, hyperactive Notch signalling and dysplastic repair of distal lung parenchyma in human fILD, as they attempt to fill the regenerative void left by failing AT2 cells⁴⁶.

Fibroblast immune regulatory programmes

Fibroblasts are increasingly recognized as ‘non-classical’ members of the innate immune system⁶⁰. They directly sense and respond to

damage-associated molecular patterns and pathogen-associated molecular patterns, activating inflammatory pathways to recruit and regulate immune cells^{60,61}. Fibroblasts produce chemokines, growth factors and other inflammatory cues, and can rapidly switch between tolerogenic and pro-inflammatory states, exerting powerful control over local tissue immunity.

In secondary lymphoid organs such as the spleen, lymph nodes and Peyer’s patches, specialized fibroblasts, termed fibroblastic reticular cells (FRCs), form distinct immune niches. FRC subsets maintain immune homeostasis by secreting homeostatic cytokines such as CCL19, CCL21 and CXCL13 to organize lymphocytes into segregated T and B cell zones and promote immune tolerance^{62–65}. During an immune response, FRCs adopt a pro-inflammatory state, increasing the production of acute-phase proteins, activating antigen processing and presentation machinery⁶⁶, and remodelling their local collagen network to facilitate lymphocyte interactions^{67–69}. As inflammation resolves, FRCs restore tissue architecture and promote lymphocyte extravasation to complete the immune response^{70,71}.

Similar dynamic inflammatory programmes occur in fibroblasts of non-lymphoid tissues to organize immune responses and promote immune resolution after acute injury⁶⁰. Conversely, in chronically inflamed tissue, fibroblasts can be reprogrammed to perpetuate inflammation and induce the formation of *de novo* ectopic tertiary lymphoid structures (TLSs)⁶⁰. In the following sections, we examine how fibroblasts influence lung immunity in inflammation, fibrosis and cancer and examine factors that regulate their plasticity during acute and chronic immune responses.

Fibroblast plasticity in disease

Fibrotic disorders and solid tumours share several features including aberrant repair, fibroblast polarization and ECM remodelling. Cancer-associated fibroblasts (CAFs), major components of the tumour microenvironment, share properties with fibroblast states in fibroinflammatory disorders and thus offer an opportunity to study general principles of fibroblast regulation. CAFs broadly polarize into myofibroblastic and inflammatory CAF states, each with unique epigenetic, transcriptional, spatial and functional profiles^{23,72–74}. These states are differentially regulated: myofibroblastic CAFs are activated by TGF β family ligands and mechanical stimulation⁷², whereas inflammatory CAFs respond to IL-1 and tumour necrosis factor (TNF), which promote downstream expression of pro-inflammatory genes via nuclear factor-kappa B and JAK–STAT pathways^{72,75}. These phenotypes demonstrate considerable plasticity in vitro and can interconvert depending on their extracellular cytokine milieu⁷⁶.

Similarly, in non-malignant fibroinflammatory disorders, fibroblasts adopt distinct inflammatory and myofibroblastic states^{17–19,60,77–86}. Inflammatory fibroblasts are induced by IL-1 β , TNF, IL-17 and oncostatin M via signalling pathways such as JAK–STAT, which promote the secretion of IL-6 and other inflammatory mediators⁶⁰. By contrast, myofibroblasts are activated by TGF β and mechanical cues, resulting in the expression of profibrotic mediators and ECM contraction³². These distinct polarization states are controlled by multiple layers of epigenetic and transcriptional regulation. For example, the transcription factor PU.1 has been proposed as a core transcriptional regulator of fibroblast plasticity in multiple fibrotic conditions⁸⁷. However, its role in pulmonary fibrosis has become less clear based on recent scRNA-seq data suggesting minimal PU.1 mRNA expression in pathogenic stromal subsets in fibrosis models⁸⁸. Collectively, these studies indicate that the local cytokine milieu shapes fibroblast polarization and phenotype through coordinated transcriptional and post-transcriptional regulation.

Fibroblast plasticity in pulmonary fibrosis

Pulmonary fibroblast phenotypes have been tracked using mouse in vivo fate-mapping studies after lung injury^{23,39,88,89}. Indeed, after bleomycin-induced lung injury, fibroblast behaviour can be mapped over time, revealing a complex spectrum of inflammatory, fibrotic and reparative states^{23,38,90}. During the early inflammatory phase (0–14 days post-injury), alveolar fibroblasts upregulate pro-inflammatory cytokines (such as CCL2, CXCL12 and CXCL13), interferon-response genes and acute-phase proteins (SAA3 and LCN2) involved in innate immunity and chemotaxis^{23,39}. This pro-inflammatory cytokine signature suggests that inflammatory fibroblasts may be involved in the recruitment of: CCR2⁺ monocytes via CCL2, CXCR5⁺ B cells and T follicular helper cells via CXCL13 (ref. 91) and other lymphocyte lineages via the CXCR4–CXCL12 axis⁹¹. Emerging data demonstrate a crucial role for fibroblast-derived cytokines such as CXCL12 (ref. 92) and CCL2 (ref. 93) in wound healing in other organs; however, direct functional evidence for their contributions to lung repair is still awaited. In contrast to inflammatory states, profibrotic myofibroblasts dominate at later timepoints (days 21–28 post-injury). Profibrotic myofibroblasts are characterized by high expression of *Cthrc1*, abundant production of ECM proteins^{23,39,88,94} and transcriptional similarity with CTHRC1⁺ myofibroblasts identified within fibroblastic foci of patients with fILD^{21–23}. Pseudotime trajectory analyses suggest that inflammatory fibroblasts may transition into profibrotic myofibroblasts²³, but this remains to be experimentally confirmed.

Interestingly, similar fibroblast plasticity has been observed in other lung injury mouse models including influenza virus infection^{39,78}, butylated hydroxyanisole³⁸, selective AT1 cell ablation³⁸ and silicosis²³, suggesting that alveolar fibroblasts have a common injury–response programme.

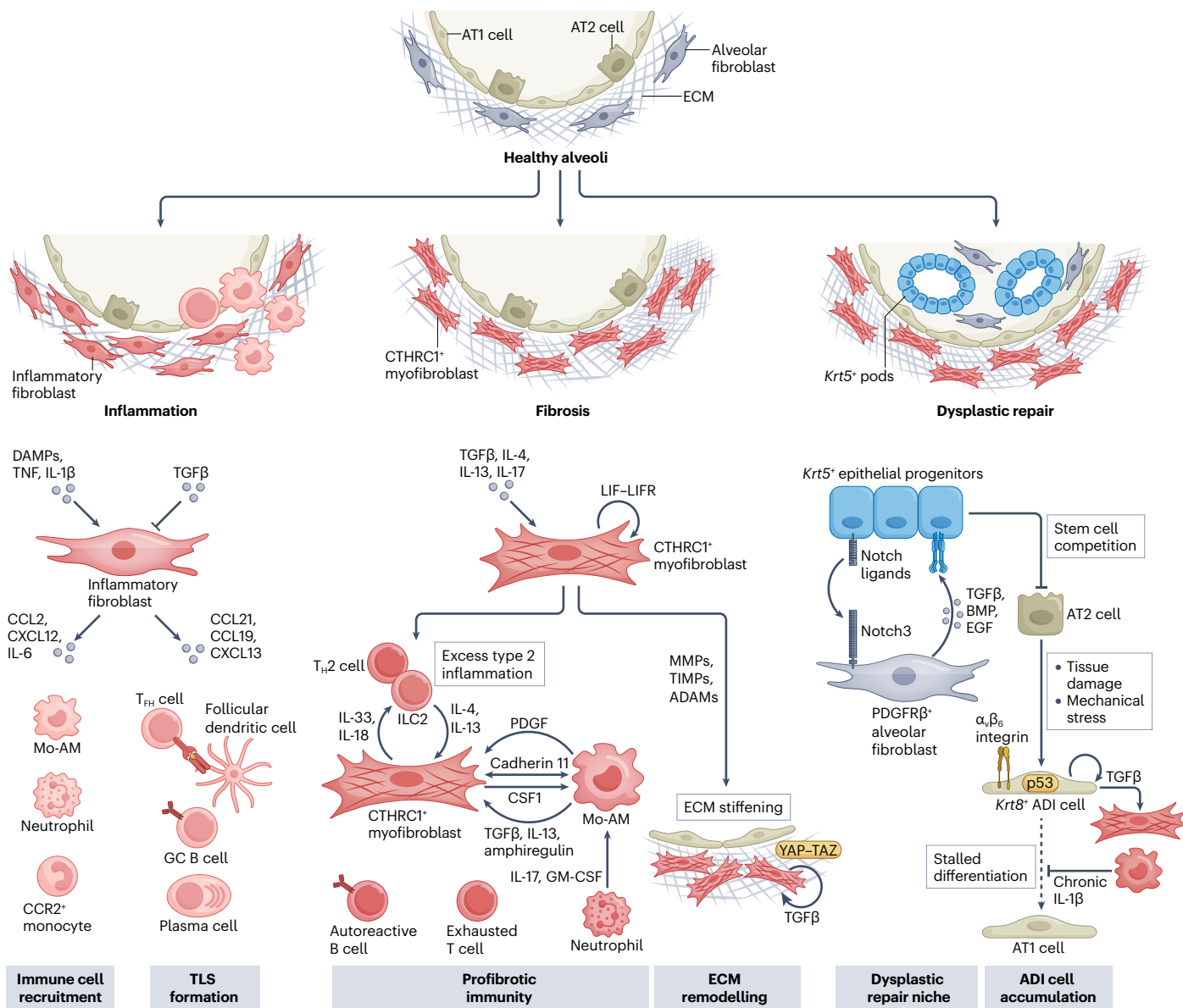
Recent attention has turned to the role of fibroblasts in resolution of pulmonary fibrosis. A study by Guo et al.⁹⁴ mapped the kinetics of bleomycin-induced aberration of ECM architecture during fibrosis and resolution using high-dimensional collagen fibre mapping and multi-omic profiling. They identified a unique population of *Cd248⁺Pdgfra⁺* ‘pro-resolving’ fibroblasts enriched for genes involved in ECM remodelling, angiogenesis and repair⁹⁴. Intratracheal delivery of *Cd248⁺Pdgfra⁺* fibroblasts during active fibrogenesis enhanced fibrosis resolution after bleomycin-induced lung injury⁹⁴, suggesting that fibroblast transition states directly influence lung repair in mice.

Insights into the origin and plasticity of *Cthrc1⁺* myofibroblasts have raised questions about their regulation. Using a genetic *Tgfb2* conditional knockout system, Tsukui et al.²³ demonstrated that TGF β 1 signalling is essential for the transition to *Cthrc1⁺* profibrotic states after bleomycin-induced injury. The transcription factors RUNX1 and RUNX2 have also been shown to be necessary for the transition of quiescent alveolar fibroblasts into *Cthrc1⁺* myofibroblasts^{38,88}. However, caution is warranted: as ablation of profibrotic myofibroblasts at certain phases of repair can lead to lethal complications such as ventricular wall rupture after myocardial infarction⁹⁵ and exaggerated neuroinflammation following brain injury⁹². Similarly, in the lungs, profibrotic myofibroblasts contribute to healthy wound healing, but their dysregulation has adverse consequences²³. Although deletion of *Tgfb2* in alveolar fibroblasts prevents the emergence of *Cthrc1⁺* myofibroblasts and abrogates fibrosis, this comes at the cost of more severe inflammation, greater alveolar permeability, more intense monocyte recruitment, and increased mortality²³. Likewise, conditional genetic deletion of *Runx1* in *Pdgfra⁺* alveolar fibroblasts reduces pulmonary fibrosis but results in ECM disorganization and loss of alveolar structural complexity after lung injury³⁸. Thus, tightly controlled fibroblast transitions are essential for proper tissue repair.

Immunological regulators of fibroblast plasticity Macrophages

Inflammatory monocytes and tissue-resident macrophages are key regulators of wound healing at different stages of the regenerative process^{96–98}. The timing, phenotype and ontogeny of macrophages are crucial factors in determining wound healing outcomes⁹⁹. Indeed, experimental depletion of macrophages during active fibrogenesis ameliorates fibrosis, whereas depletion during the scar resolution phase impairs matrix degradation¹⁰⁰. In injury models of pulmonary fibrosis, monocyte-derived alveolar macrophages are recruited to the injured lung and replace homeostatic yolk sac-derived tissue-resident populations¹⁰¹. Initially pro-repair, their prolonged presence promotes fibrosis⁹⁹ through the production of matricellular proteins and profibrotic mediators including IL-1 β , TGF β , amphiregulin and IL-13 (refs. 96,99,102,103).

At homeostasis, macrophages and fibroblasts maintain each other via reciprocal exchange of growth factors and cytokines¹⁰⁴. In fibrosis, this circuit becomes dysregulated, resulting in feedback loops that amplify inflammation and fibrosis^{97,105}. Monocyte-derived alveolar macrophages secrete mediators such as platelet-derived growth factors that promote fibroblast activation and survival^{97,101}. In turn, fibroblasts



secrete trophic factors including CSF1 that promote macrophage persistence and expansion⁹⁷. This feedback loop perpetuates a chronic fibroblast activation state and macrophage accumulation in fibrosing tissue^{97,99}.

Multicellular myeloid circuits

Macrophage–fibroblast crosstalk seen in fibrosis operates within complex multicellular immune networks. Profibrotic macrophages and myofibroblasts colocalize with IL-17⁺GM-CSF⁺MMP9⁺ neutrophils near fibrotic scars in lung and liver fibrosis²⁷. Here, neutrophils promote profibrotic macrophage polarization through the production of TGFβ1 and type 3 cytokines (IL-17A and GM-CSF)²⁷ that directly induce fibroblast-to-myofibroblast transition via IL-17 and neutrophil extracellular traps^{106–109}, representing key pathways in IPF pathogenesis^{106,108–110}. Tissue-resident CD103⁺ dendritic cells also contribute to myofibroblast activation by increasing local production of IL-6, IL-17 and other

profibrotic mediators¹¹¹, illustrating how diverse myeloid–stromal circuits support fibrogenesis.

Neuroimmune networks

Mammalian lungs are richly innervated by a dense neural network, comprising sensory and autonomic neurons, that can influence immune dynamics. Sensory TRPV1⁺ nociceptors release neuropeptide calcitonin gene-related peptide that regulates wound healing by both limiting pro-inflammatory myeloid cell recruitment and promoting macrophage polarization towards a pro-repair phenotype¹¹². Selective ablation of TRPV1⁺ nociceptors results in dysregulated recruitment and activation of pro-inflammatory monocytes and neutrophils, worsening outcomes in influenza A virus infection¹¹³ and pulmonary fibrosis after bleomycin injury¹¹⁴. Conversely, sympathetic GABAergic neurons have been shown to amplify a macrophage-induced cytokine storm in severe bacterial pneumonia¹¹⁵. Collectively, these data show how

Fig. 2 | Alveolar fibroblasts orchestrate lung immunity and repair.

The alveolar unit is supported by a delicate stromal compartment composed primarily of resident alveolar fibroblasts, which synthesize and remodel the extracellular matrix (ECM), maintain tissue tensile strength and provide paracrine signals that promote epithelial cell homeostasis. During lung inflammation (left panel), alveolar fibroblasts adopt a pro-inflammatory state in response to danger signals and cytokines such as tumour necrosis factor (TNF) and IL-1 β . Inflammatory fibroblasts secrete chemokines and mediators that recruit and activate myeloid cells, such as monocyte-derived alveolar macrophages (Mo-AMs) and neutrophils. In chronic inflammatory settings, fibroblasts can adopt phenotypic properties of fibroblastic reticular cells, including expression of CCL21, CCL19 and CXCL13 and upregulation of adhesion molecules to attract and retain lymphocytes for the formation of tertiary lymphoid structures (TLSs). As TLSs mature, they gain additional features of secondary lymphoid organs, including formation of high endothelial venules for specialized lymphocyte trafficking and de novo germinal centres (GCs), which produce antigen-experienced memory B cells and plasma cells. In pulmonary fibrosis (middle panel), alveolar fibroblasts transition into CTHRC1⁺ myofibroblasts in response to profibrotic cytokines that include transforming growth factor- β (TGF β), IL-4, IL-13 and IL-17. CTHRC1⁺ myofibroblasts secrete abundant collagen and ECM-modifying proteases including matrix metalloproteinases (MMPs) and tissue inhibitors

of metalloproteases (TIMPs) and a disintegrin and metalloproteases (ADAMs), resulting in remodelling and stiffening of the ECM. Increased tissue stiffness is sensed by myofibroblasts leading to activation mechanotransduction pathways, including YAP–TAZ, which drive feedforward myofibroblast activation and promote survival. Myofibroblasts also make bidirectional interactions with immune cells that reinforce profibrotic polarization states. Severe lung injury activates dysplastic repair pathways (right panel), resulting in the emergency egress and migration of keratin 5 (*Krt5*)⁺ airway basal epithelial cells to the distal lung parenchyma. Long-term persistence of invading *Krt5*⁺ dysplastic airway-derived stem cells is supported by mesenchymal Notch signalling in an injury-induced mesenchymal–epithelial cell niche, leading to stem cell competition with type 2 alveolar epithelial (AT2) cells in the alveoli. In response to damage signals and mechanical stress, AT2 cells differentiate into *Krt5*⁺ alveolar differentiation intermediate (ADI) cells, which express features of senescence and have a profibrotic secretome. A chronic inflammatory milieu stalls the transition of ADI cells into mature type 1 alveolar epithelial (AT1) cells, resulting in an accumulation of long-term dysplastic ADI cells that impair normal alveolar regeneration and promote fibrosis. BMP, bone morphogenetic protein; CSF1, colony-stimulating factor 1; DAMP, damage-associated molecular pattern; EGF, epidermal growth factor; ILC, innate lymphoid cell; LIF, leukaemia inhibitory factor; LIFR, leukaemia inhibitory factor receptor; PDGF, platelet-derived growth factor; T_{FH} cell, T follicular helper cell.

neuroimmune regulation of myeloid dynamics shapes the landscape of lung inflammation and repair.

Type 2 immunity

Type 2 immunity is essential for a range of tissue-protective responses including wound healing; however, persistent activation of these pathways can induce paradoxical tissue fibrosis¹¹⁶. Type 2 lymphocytes, and in particular, group 2 innate lymphoid cells (ILC2s), orchestrate type 2 immune responses at mucosal barriers^{116,117} (Fig. 2). Despite central roles in barrier repair, excessive or persistent activation of ILC2s results in fulminant type 2 responses, with recruitment of CD4⁺ T helper 2 cells, type 2 conventional dendritic cells and eosinophils, which together drive fibrotic responses^{118–120}. In the lungs, ILC2s are enriched within perivascular adventitial cuffs where they colocalize with adventitial fibroblasts¹²¹. Adventitial fibroblasts provide trophic factors such as IL-33 and TSLP to regulate ILC2 activity in exchange for IL-13 (ref. 121). During type 2 immune responses¹²² and after fibrotic lung injuries^{118,123}, ILC2s egress from the adventitial niche and migrate to distal lung parenchyma where they directly stimulate fibroblast collagen production and drive fibrogenesis^{118,123}. As the fibrotic tissue stiffens, mechanically activated fibroblasts begin to secrete IL-18, which induces ILC2-to-ILC1 conversion¹²³ resulting in the production of additional TGF β 1 and matrix metalloproteases^{123,124}. Conversely, selective ablation of ILC2 cell surface activating receptors such as neuropilin 1 attenuates pulmonary fibrosis after bleomycin injury¹¹⁷. Thus, pulmonary fibrosis is defined by an interplay between type 2 immunity, dysregulated matrix mechanics, ILC2-niche extrusion and aberrant ILC–fibroblast signalling.

Fibroblasts as regulators of adaptive immunity in fibrosis

T cells

Fibrotic microenvironments, such as tumours, may be immunosuppressive. In end-stage IPF, profibrotic myofibroblasts upregulate PDL1 (an immune checkpoint molecule)^{125,126} and CD47 (a 'don't eat me' signal)^{126,127}, which inhibit T cell and macrophage responses, respectively. In addition, T cells in fibrotic lungs upregulate exhaustion markers (PDI

(refs. 126,128), TIM3 (ref. 126) and CTLA4 (ref. 129)) and show impaired proliferative capacity and upregulation of IL-17A and TGF β 1, enhancing collagen production when cocultured with lung fibroblasts¹²⁸. Exhaustion signatures have also been identified in PDI⁺CD8⁺ T cells in liver fibrosis, lending support to the concept of T cell exhaustion in fibrotic tissues^{130,131}. Blocking PDI signalling using *Pd1* knockout mice or by treating mice with anti-PDL1 mAbs ameliorates pulmonary fibrosis after bleomycin injury¹²⁸. Similarly, treatment with anti-CTLA4 mAb results in reactivation of dysregulated CD8⁺ T cells, which regain cytotoxic responses against *p16*^{Ink4a}-expressing senescent cells and attenuate pulmonary fibrosis in a humanized bleomycin-induced fibrosis mouse model¹²⁹. Furthermore, treatment with anti-CD47 mAb increases macrophage phagocytic activity in vitro and ameliorates pulmonary fibrosis in a JUN overexpression model¹²⁷. However, the aforementioned findings should be interpreted with the understanding that mAbs and in vivo global knockouts have off-target effects on other immune cell populations. In cancer models, TGF β signalling in tumoural stroma drives T cell exclusion¹³², and LRRCL15⁺ myofibroblastic CAFs suppress CD8⁺ T cell effector function¹³³. Together, these data suggest that fibroblasts can alter local inflammatory set points by directly modulating T cell cytolytic activity across diverse fibrotic microenvironments.

Tertiary lymphoid structures and B cells

Chronic inflammatory conditions such as autoimmunity, fibrosis, infection and cancer can lead to the formation of ectopic lymphoid follicles, termed TLSs, which drive antigen-specific adaptive immune responses and modulate local immunity^{62,134}. In chronic inflammation, fibroblasts can adopt phenotypic properties of FRCs^{135–137}, including expression of CCL21, CCL19 and CXCL13 (refs. 135–137) and upregulation of adhesion molecules such as ICAM1, VCAM1 and MADCAM1 to attract and retain lymphocytes^{138,139}. As TLSs mature, they gain additional features of secondary lymphoid organs, including formation of high endothelial venules for specialized lymphocyte trafficking¹⁴⁰, and de novo germinal centres which support B cell affinity maturation, class switching and somatic hypermutation to produce antigen-experienced memory B cell and plasma cells¹³⁴.

The presence of TLSs is a major determinant of disease outcome across diverse fibroinflammatory settings. TLS presence in chronic inflammatory disease signals a breakdown in immune tolerance, autoantibody production and generally poorer clinical outcomes¹³⁴. In IPF, recent advances in spatial transcriptomics reveal widespread TLS formation in lung tissue⁹¹ and infiltration of tissue-resident B cells and plasma cells into fibrotic regions⁹¹. These findings are intriguing given converging lines of evidence suggesting a role for autoantibodies and B cells in IPF¹⁴¹. Indeed, autoreactive IgG and IgA antibodies are both common¹⁴² and associated with disease progression in IPF¹⁴³. A deeper understanding of how TLSs shape and sustain local B cell responses and autoantibody production in fibrotic tissue may reveal novel treatment targets.

Metabolic regulation of fibroblasts and immune cells in fibrosis

The metabolic pathways of oxidative phosphorylation, glycolysis and glutaminolysis are crucial in determining the identity, fate and effector function of immune cells¹⁴⁴. Emerging evidence reveals how fibroblasts are similarly influenced by nutrient availability, metabolic intermediates and regulators of cellular metabolism¹⁴⁵. As a result, fibroblast metabolism is gaining attention as a potential therapeutic target in inflammation, fibrosis and cancer¹⁴⁵.

The transition of fibroblasts into contractile myofibroblasts is energetically demanding, requiring a metabolic shift to support proliferation and protein synthesis¹⁴⁶. TGF β -stimulated human lung fibroblasts and fibroblasts derived from patients with IPF exhibit increased glycolytic activity, characterized by enhanced glucose uptake and upregulation of glycolytic enzymes^{147–149}. These metabolic alterations lead to several downstream effects including: lactic acid build-up, which acidifies the local extracellular environment and enhances activation of TGF β ¹⁵⁰; accumulation of metabolic intermediates required for glycine production and collagen synthesis¹⁵¹; and increased pyruvate flux into the tricarboxylic acid cycle, which raises succinate levels, promotes expression of α -smooth muscle actin and stabilizes HIF α , a key transcriptional regulator of glycolytic enzymes¹⁴⁷. IPF-derived fibroblasts also demonstrate enhanced glutaminolysis, a process that breaks down glutamine to generate α -ketoglutarate, which activates mTOR signalling and promotes collagen protein translation and proline hydroxylation¹⁵². Glutaminolysis directly alters the epigenetic landscape by modifying histone methylation and promoting anti-apoptotic gene expression¹⁵³, illustrating how metabolism and gene regulation intersect to regulate myofibroblast survival. In addition, mitochondrial dysfunction in fibroblasts contributes to fibrosis by impairing mitophagy and increasing reactive oxygen species production, which further activates profibrotic programmes^{145,154,155}.

Fibrotic lungs experience pathological hypoxia at cellular and tissue levels because of impaired gas exchange and aberrant angiogenesis. In vitro, low oxygen availability promotes pulmonary fibroblast proliferation, DNA hypermethylation and a shift towards a profibrotic phenotype by altering cellular metabolism^{156,157}. Hypoxia also has profound effects on innate immune cell behaviour¹⁵⁸, modifying migratory capacity, tissue invasiveness, phagocytic activity and sensitivity to apoptosis¹⁵⁹. Tissue hypoxia also shapes T and B cell maturation, effector function and promotes exhaustion¹⁵⁹. After endotoxin-mediated acute lung injury, systemic hypoxia (fraction inspired oxygen, FiO₂ 10%) was shown to suppress type I interferon signalling, impair monopoiesis and reduce the accumulation of monocyte-derived alveolar macrophages, delaying the resolution of neutrophilic inflammation

and worsening injury¹⁶⁰. These findings highlight a complex interplay among hypoxia, metabolism and inflammation in shaping clinical outcomes after lung injury. How these processes interact in conditions of chronic and progressive respiratory failure remain unclear.

Mechanical regulation of lung immunity and repair

The lungs experience cyclic mechanical forces during breathing, including stretching and relaxation of the alveoli and airways with each ventilatory cycle. These dynamic forces are sensed by resident stromal cells through adhesion molecules, mechanosensitive ion channels and cytoskeletal proteins, triggering intracellular signal transduction pathways including YAP–TAZ and MRTF–SRF, that drive gene expression³¹. In fibrotic tissues, ECM stiffening contributes to the progression of fibrosis by establishing a self-reinforcing loop: stiffer environments promote myofibroblast activation and survival^{161–164}. Additionally, sustained mechanical stress can lead to epigenetic remodelling that makes fibroblasts resistant to returning to quiescent non-contractile states^{33,165–167}. Mechanical tension also stimulates inflammatory cytokine production in fibroblasts¹⁶⁸, linking mechanotransduction to inflammation and wound healing. For example, dermal fibroblasts secrete the monocyte chemoattractant CCL2 in response to mechanical strain¹⁶⁸ and global deletion of *Ccl2* reduces macrophage infiltration and scar formation in a high tension hypertrophic scar model¹⁶⁸. These findings suggest that mechanical tension modulates scarring through fibroblast–immune inflammatory crosstalk.

Immune cell behaviour is also modulated by biomechanical forces such as tissue stiffness, tension, shear stress and cyclical hydrostatic pressure^{169,170}. Stiff substrates enhance the production of pro-inflammatory cytokines by innate immune cells in response to soluble danger signals^{171–173}. Similarly, cyclical hydrostatic pressure promotes pro-inflammatory programmes in lung myeloid cells, exacerbating pulmonary inflammation and fibrosis¹⁷⁴. Furthermore, increased tissue rigidity lowers the threshold for T cell and B cell proliferation, activation and effector function^{175–177}. Together, these findings suggest that tissue biomechanics directly regulate tissue immunity by fine-tuning thresholds for immune cell activation¹⁶⁹. According to this model¹⁶⁹, the threshold for immune cell activation is lowered in mechanically stiffened tissue. When transient, this mechanism serves to protect the host by providing mechanical ‘danger signals’ to alert the immune system to the possibility of barrier injury¹⁶⁹. However, permanent rigidification of tissue – as is seen in ageing and fibrosis – creates a mechanical microenvironment that is conducive of chronic inflammation and autoimmunity¹⁶⁹. In addition to being directly modulated by matrix mechanics, immune cells themselves modify the elastic and tensile properties of the ECM. Macrophages and neutrophils fine-tune the ECM composition through expression of matrix metalloproteinases, tissue inhibitors of metalloproteinases and cytokines that modulate fibroblast-mediated collagen deposition and crosslinking¹⁷⁸. Together, these observations highlight bidirectional coupling between matrix mechanics and immune cell activity, with implications for conditions characterized by altered ECM biomechanics such as fibrosis and ageing.

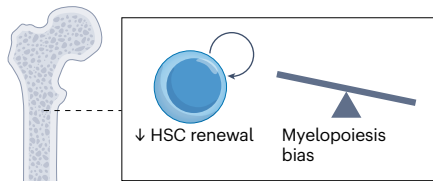
Dysregulation of normal matrix mechanics also interferes with alveolar stem cell function^{179,180}. Recent work has shown that sustained exposure of AT2 cells to elevated mechanical tension promotes spontaneous progressive pulmonary fibrosis in a mouse model¹⁸¹. In this model, AT2 cell-specific deletion of *Cdc42* – a gene encoding a RhoGTPase that is essential for polymerization of actin filaments – results in impaired AT2-to-AT1 cell differentiation¹⁸², loss of functional alveoli

Review article

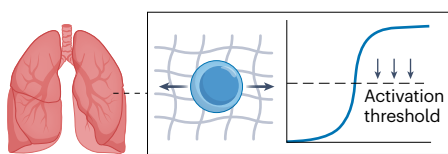
and greater alveolar stretch¹⁸¹. Sustained mechanical tension activates TGF β signalling in stretched AT2 cells¹⁸¹, driving spontaneous fibrosis in a subpleural-to-central pattern that is reminiscent of IPF¹⁸¹.

Complementary work has shown that stressed AT2 cells transition into ADI cells, which secrete profibrotic mediators including abundant TGF β and senescence-associated secretory phenotype (SASP)-related

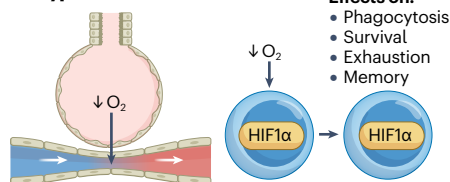
a Immune ageing



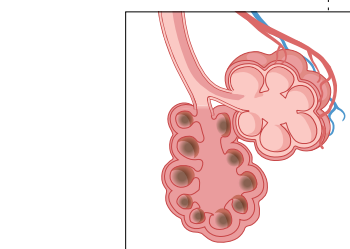
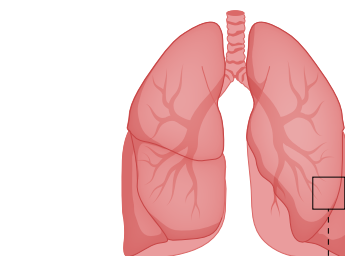
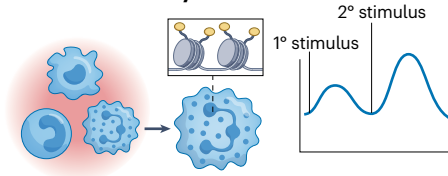
b Mechanical tuning of immune thresholds



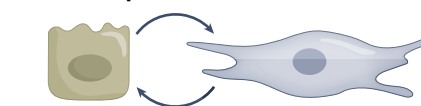
c Hypoxic immunomodulation



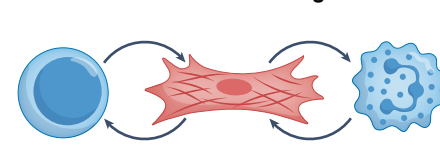
d Trained immunity



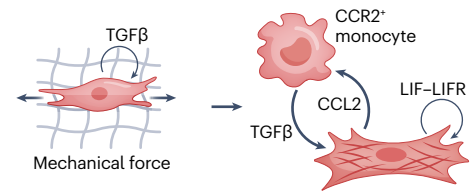
e Stromal-epithelial stem cell circuit



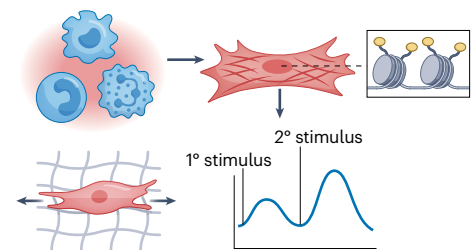
f Stromal-immune circuit rewiring



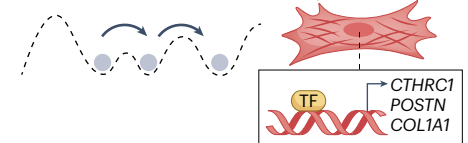
g Mechano-inflammatory circuits



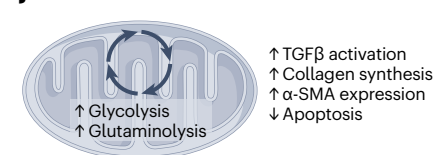
h Inflammatory and mechanical training



i Fibroblast state transitions



j Fibroblast metabolism



Immune adaptations

Stromal-epithelial-immune rewiring

Fibroblast adaptations

Fig. 3 | Stromal-immune regulatory networks in lung repair and fibrosis.

Fibroblast plasticity is subject to several layers of regulation that govern cellular phenotype, immune collaboration and function. Although these regulatory layers are essential for normal wound healing and restoration of homeostasis, if left unchecked, they can perpetuate chronic inflammation and fibrosis. **a**, Ageing is associated with a state of low-grade, systemic inflammation and a bias towards myelopoiesis, which can aggravate fibrotic responses in the lungs. **b**, In conditions of fibrosis and ageing, increased stiffness of the extracellular matrix lowers thresholds for immune cell activation. **c**, Hypoxia has potent effects on immune cell behaviour through crosstalk between oxygen availability and cellular metabolism. Hypoxia alters innate immune cell migratory capacity, tissue invasiveness, phagocytic activity and sensitivity to programmed cell death. In addition, hypoxia also shapes T cell and B cell maturation, effector function and propensity to become exhausted. **d**, Memory of prior inflammatory experience is encoded through epigenetic modifications in innate immune cells, resulting in more rapid and prolonged immune responses upon secondary barrier assault. **e**, Injury-induced fibroblast plasticity promotes an aberrant fibroblast-epithelial stem cell niche that drives dysplastic repair. **f**, Immune-stromal networks are rewired by chronic and/or dysregulated inflammation, resulting in the formation of profibrotic

stromal-immune circuits. **g**, Mechanical activation of fibroblasts results in secretion of CCL2, a potent chemoattractant for monocyte-derived alveolar macrophages. Activated fibroblasts also amplify their own activation via autocrine, paracrine and mechanical feedback loops. **h**, Fibroblasts display memory-like responses following mechanical and inflammatory events. These events result in increased chromatin accessibility at transcription start sites involved in inflammation and tissue remodelling, resulting in states primed for enhanced responses. **i**, Alveolar fibroblasts undergo a series of inflammatory and fibrotic state transitions. Under certain conditions, alveolar fibroblasts adopt a profibrotic state that expresses a suite of extracellular matrix proteins involved in tissue fibrosis. **j**, Myofibroblasts exhibit increased glycolytic activity characterized by enhanced glucose uptake and upregulation of glycolytic enzymes. These metabolic shifts result in multiple downstream effects including excess lactic acid secretion that leads to enhanced transforming growth factor- β (TGF β) activation, accumulation of metabolic intermediates such as glycine which are required for collagen synthesis and increased pyruvate flux into the tricarboxylic acid cycle which raises succinate levels and promotes expression of α -smooth muscle actin (α SMA). HIF1 α , hypoxia-inducible factor 1 α ; HSC, haematopoietic stem cell; LIF, leukaemia inhibitory factor; LIFR, leukaemia inhibitory factor receptor; TF, transcription factor.

Box 4 | Research priorities in fibrosis immunology

1. Construct a spatially resolved multimodal atlas of immune cell organization across early and late stages of fibrosis evolution; integrating spatial, temporal and functional data from human tissues and complementary model systems.
2. Pinpoint early entry points into fibrosis progression with the goal of developing therapeutics that can halt or reverse disease.
3. Identify precision biomarkers to tailor clinical decision-making regarding antifibrotic and immunomodulatory therapies.
4. Broaden the focus of fibrosis immunology beyond myeloid cells to better understand the contributions of other innate and adaptive immune cell populations.
5. Understand how myofibroblasts evade immune surveillance and cell death in fibrosis, with the goal of developing immunotherapies that can augment their elimination.
6. Understand how interactions among tissue mechanics, hypoxia, metabolic stress and inflammation modulate immune cell behaviour in fibrotic tissues.

factors^{54,183–185}, driving positive feedback loops in AT2 cells¹⁸⁴ and promoting *Cthrc1*⁺ myofibroblast activation via epithelial–mesenchymal crosstalk¹⁸⁵. These data highlight a complex relationship among mechanical stress, cellular senescence, ageing and impaired stem cell regeneration in pulmonary fibrosis.

Other factors regulating fibroblast–immune interactions in fibrosis

Immune ageing

Age is a major risk factor for the development of IPF and several other forms of fILD¹⁸⁶. Although senescence of AT2 cells has been implicated¹⁸⁷, recent work also suggests a role for immune ageing in fibrosis pathogenesis^{188,189}. Ageing alters haematopoiesis, leading to reduced haematopoietic stem cell regenerative capacity and a bias towards myelopoiesis at the expense of lymphopoiesis^{190,191}. Recent bone marrow transplant experiments show that young adult mice that received bone marrow from aged donors developed more severe fibrosis following bleomycin-induced lung injury¹⁸⁸. This was associated with a greater influx of profibrotic alveolar macrophages and a delayed transition to a tissue-resident ‘homeostatic’ macrophage phenotype owing to reduced expansion of IL-10-producing CD4⁺CD25⁺FOXP3⁺ regulatory T cells¹⁸⁸. These findings expand the focus beyond ageing-related AT2 cell dysfunction in fibrosis to include haematopoietic and immune compartments.

Fibroblast inflammatory training

Inflammation etches lasting memories on tissues, altering the sensitivity, quality and magnitude of future responses¹⁹². The concept, known as trained immunity¹⁹³, was initially defined as a functional state of the innate immune system, in which long-term epigenetic and metabolic reprogramming of cells enables more rapid and potent responses to subsequent stimuli¹⁹⁴. This concept has since been expanded to non-immune lineages including epithelial stem cells¹⁹⁵ and more recently, stromal cells^{196,197}. In skin epithelial stem cells, trained ‘inflammatory memory’ is maintained through modifications

in chromatin accessibility at specific loci, allowing greater access of stress-response transcription factors and downstream expression of proliferative, inflammatory and stress-associated transcripts. Although many inflammation-associated genomic loci return to their baseline epigenetic state, certain ‘memory domains’ retain chromatin accessibility through active H3K4me1 and H3K4me3 histone modifications^{195,198}. Such epithelial stem cell memory aids wound healing; however, it comes at the cost of lowering the threshold for neoplastic transformation^{199–201}, reflecting an intrinsic trade-off between regeneration and oncogenic potential.

Emerging data suggest that fibroblasts may also encode cell-intrinsic memories of prior inflammatory events²⁰². In vitro studies show that repeated exposure to inflammatory cytokines primes fibroblasts to respond more strongly to subsequent inflammatory stimuli by increasing chromatin accessibility of pro-inflammatory *cis*-regulatory elements^{203,204}. For example, primary embryonic fibroblast cells exposed to interferon- β (IFN β) showed higher and more rapid gene expression following restimulation with IFN β , resulting in more potent antiviral activity in vitro²⁰⁵. In an in vivo experimental arthritis mouse model, re-exposure to inflammatory stimuli caused aggravated and prolonged arthritis, which was mediated by local synovial fibroblasts independently of adaptive immune responses¹⁹⁶. When synovial fibroblasts from joints that had previously experienced repetitive injury were adoptively transferred into naive recipient joints, more intense and prolonged arthritis was observed on inflammatory challenge¹⁹⁶, supporting the notion of cell-intrinsic inflammatory training. Synovial fibroblast training was associated with inflammasome activation, metabolic reprogramming and epigenetic remodelling at loci responsible for inflammation and osteoclastogenesis¹⁹⁶. Fibroblast inflammatory training was recently observed in human disease after external beam radiotherapy was shown to induce durable epigenetic alterations in dermal fibroblasts¹⁹⁷, resulting in long-term functional impairments in fibroblast motility and contractility¹⁹⁷. Taken together, these data suggest that inflammatory events imprint fibroblasts with long-lasting epigenetic and metabolic adaptations that contribute to maladaptive repair programmes upon re-injury.

Myofibroblast persistence

A key barrier to fibrosis resolution is the failure to terminate myofibroblast activities once their wound healing functions are complete³³. Myofibroblast persistence partly reflects the acquisition of apoptosis-resistant and senescent phenotypes that evade programmed cell death and immune-mediated clearance in scar tissue^{33,41,206–208}. This is achieved through upregulation of anti-apoptotic BCL2 family members^{209–211} and decoy receptors^{212,213} that prevent immune effector cells from triggering apoptosis via the extrinsic apoptotic pathway in pulmonary fibrosis. Myofibroblasts also upregulate senescence programmes that result in cell cycle arrest, upregulation of intrinsic pro-survival pathways and expression of a profibrotic secretome (SASP)^{33,206,207}. These senescent myofibroblasts avoid immune-mediated clearance by expressing immune inhibitory ligands^{214,215} that enable evasion by cytotoxic CD8⁺ T cells or natural killer cells^{214,216}. Importantly, much of this current understanding comes from in vitro experiments, thus determinants of myofibroblast fate within native fibrotic tissue environments remain largely unexplored.

Towards an integrated model of pulmonary fibrosis

Emerging concepts such as fibroblast heterogeneity and phenotypic plasticity offer new perspectives for understanding fibrotic disorders.

Fibroblast plasticity is governed by complex regulatory layers that determine cellular phenotype, immune collaboration and effector function (Fig. 3). Although these regulatory layers are essential for normal wound healing and restoration of homeostasis, if left unchecked, they can perpetuate chronic inflammation and fibrosis. For example, immune–fibroblast circuits are vital for orchestrating tissue repair after acute injury, but when these circuits become dysregulated, they perpetuate chronic inflammation and promote dysplastic repair¹¹⁶. Similarly, transient distortions in the ECM provide mechanical danger signals to alert the immune system to the possibility of acute barrier injury¹⁶⁹. However, in conditions of fibrosis and ageing, the permanent rigidification of ECM lowers thresholds for immune cell activation and inflammation. Likewise, inflammatory training prepares tissues to respond more rapidly to future insults, but when damage is repetitive or chronic, a heightened state of preparedness may promote over-exuberant inflammatory and fibrotic responses²¹⁷. Stem cell niche extrusions, such as *Krt5*⁺ airway-stem cell invasion, offer short-term protection by sealing barrier breaches⁵³, but may contribute to long-term dysplastic remodelling and fibrosis³⁹. Finally, transient

myofibroblast senescence may be beneficial for epithelial regeneration and tissue repair^{35,218,219}, but the progressive accumulation of senescent myofibroblasts with age exacerbates pulmonary fibrosis. These examples highlight how loss of normal stromal regulation through chronic injury, immune dysfunction, dysregulated tissue biomechanics, ageing and metabolic stress can tip the balance from successful repair to progressive fibrosis.

Conclusion

Despite recent progress in our understanding of fibrosis biology, translation to effective antifibrotic therapies remains limited, highlighting the need for further fundamental research (Box 4). As has been demonstrated in oncology, the complex, variable and multifaceted nature of fibrosis likely demands a combinatorial therapeutic approach³. Understanding the diverse roles and behaviours of fibroblasts offers new opportunities for intervention. For example, engineered chimeric antigen receptor T cells and immunotherapeutic vaccination approaches targeting pathological fibroblast subsets have shown promise in preclinical fibrosis models^{220,221}. Likewise, strategies that boost

Glossary

Airway basal epithelial cell

A multipotent progenitor cell found in the basal layer of the airway epithelium that serves as a source of regeneration after lung injury.

Alveolar differentiation intermediate cells

(ADI). After mouse lung injury, type 2 alveolar epithelial (AT2) cells adopt a *Krt8*⁺ intermediate transitional state, which has been variably termed damage-associated transient progenitors, pre-alveolar type 1 transient state or ADI cells. This state emerges in response to damage signals and is characterized by loss of AT2 cell marker identity, upregulation of p53 signalling, cell cycle arrest and a shift towards squamous morphology.

Dysplastic repair

After severe lung injury, airway basal epithelial cells expressing keratin 5 (*Krt5*) migrate to alveoli, where they form abnormal cystic structures that cannot participate in gas exchange.

Euplastic regeneration

In response to mild-to-moderate lung injury, AT2 cells re-enter the cell cycle and differentiate into AT1 cells, repopulating the alveolus and restoring normal barrier morphology, integrity and function.

Fibroblastic foci

Discrete aggregates of proliferating fibroblasts and myofibroblasts located beneath the alveolar epithelium, representing sites of active extracellular matrix deposition at the leading edge of active fibrosis.

Fibroblast-to-myofibroblast transition

The process by which fibroblasts acquire specialized repair states characterized by upregulation of contractile features, enhanced extracellular matrix production and increased migratory properties.

Group 2 innate lymphoid cells

(ILC2s). A class of tissue-resident sentinel cell at barrier sites such as the lungs, gut and skin. ILC2s bridge innate and adaptive type 2 immunity by orchestrating allergic inflammation, protective antiparasitic responses and tissue repair. They are major sources of type 2 cytokines such as IL-5, IL-13 and amphiregulin, which they secrete in response to the alarmins IL-33, IL-25 and thymic stromal lymphopoietin.

Interstitial lung disease

(ILD). An umbrella term for a heterogeneous group of disorders resulting in inflammation and/or fibrosis of the alveolar interstitium. ILDs have a broad spectrum of outcomes, from fully reversible inflammation to severe and irreversible scarring.

Progressive fibrosing phenotype

A phenotype of ILD that displays progressive clinical behaviour defined by irreversible and progressive scarring, despite treatment of known or identifiable triggers.

Senescence-associated secretory phenotype

(SASP). A secretory programme comprising the release of cytokines, growth factors and proteases by senescent cells. The SASP secretome has diverse effects on neighbouring cells and tissue microenvironments, including inflammation, fibrosis and tumour promotion or suppression.

Tertiary lymphoid structures

(TLSs). Organized aggregates of immune cells that form in non-lymphoid tissues in pathological conditions such as chronic inflammation, infection or cancer. Mature TLSs drive antigen-specific adaptive immune responses and modulate local immunity. They differ from secondary lymphoid organs in that they are inducible, ectopic and non-encapsulated immune follicles lack an external capsule enabling direct sampling of antigens and danger signals.

Trained immunity

A form of immune memory in which innate immune cells develop enhanced responses to later infections or stimuli after an initial exposure. This memory is encoded through epigenetic changes, such as histone modifications and DNA methylation, that alter chromatin accessibility and transcription factor binding.

regenerative stromal signalling while suppressing profibrotic pathways can be leveraged for therapeutic regeneration²²². Ultimately, by targeting the immune, metabolic, mechanical and epigenetic networks of stromal regulation, future therapeutics may be able to reprogramme pathogenic fibroblasts towards pro-resolving, apoptotic or quiescent fates, offering new hope for treating fibrotic disease.

Published online: 12 February 2026

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Acknowledgements

The authors gratefully acknowledge J. Hudson, M. Z. Chaudhry and C. Armitage for insightful discussions and valuable contributions to the conceptual development of this Review.

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Immunology* thanks Shruti Naik, Tatsuya Tsukui and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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