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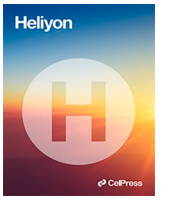

Review article

Dissecting pulmonary fibroblasts heterogeneity in lung development, health and diseases

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ABSTRACT

Lung fibroblasts are the major components in the connective tissue of the pulmonary interstitium and play essential roles in the developing of postnatal lung, synthesizing the extracellular matrix and maintaining the integrity of the lung architecture. Fibroblasts are activated in various disease conditions and exhibit functional heterogeneities according to their origin, spatial location, activated state and microenvironment. In recent years, advances in technology have enabled researchers to identify fibroblast subpopulations in both mouse and human. Here, we discuss pulmonary fibroblast heterogeneity, focusing on the developing, healthy and pathological lung conditions. We firstly review the expression profiles of fibroblasts during lung development, and then consider fibroblast diversity according to different anatomical sites of lung architecture. Subsequently, we discuss fibroblast heterogeneity in genetic lineage. Finally, we focus on how fibroblast heterogeneity may shed light on different pathological lung conditions such as fibrotic diseases, infectious diseases including COVID-19, and lung cancers. We emphasize the importance of comparative studies to illuminate the overlapping characteristics, expression profiles and signaling pathways of the fibroblast subpopulations across disease conditions, a better characterization of the functional complexity rather than the expression of a particular gene may have important therapeutic applications.

1. Introduction

Fibroblasts are defined as "spindle-shaped cells of connective tissue" that are capable of producing extracellular matrix (ECM) and ECM remodeling enzymes in developing organs and upon wound healing to maintain a wide range of important functions [1,2]. They are characterized by the expression of collagen and vimentin and lacking the expression of epithelial, endothelial and immune cell markers [2,3]. Differentiated from mesenchymal cells at the embryonic stage, fibroblasts are the main component of loose connective tissue embedded in the tissue parenchyma [4]. They possess strong proliferative and adaptive capacities, and play an essential role in

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maintaining the homeostasis of organ function.

Fibroblasts exhibit vigorous functional activity. In the physiological state, fibroblasts are in the resting state with a long shuttle-shaped or flattened triangular cell body and primarily participate in shaping and maintaining tissue structure through ECM remodeling [5]. They also provide and maintain essential niches for neighboring cells such as epithelial and hematopoietic stem cells [6,7]. Upon stimulation by factors such as wound, infection, and inflammation, some resting-state fibroblasts are activated in response to cytokines and growth factors such as transforming growth factor beta 1 following the injury of epithelium, accompanied by distinct phenotypic changes such as increased cell size and alpha smooth muscle actin (α-SMA) expression [8–10]. As a result, these cells are transformed to an activated state and participate in fibrosis and inflammation through fibroproliferation, migration, ECM production and remodeling, and immune cell recruitment [11,12]. In addition, activated fibroblasts also play roles in modulating inflammatory responses in injured tissues [13,14].

Researchers have proposed fibroblast subtypes depending on different states, including: 1) spindle-shaped quiescent or resting fibroblasts in normal state, 2) stellate-shaped normal activated fibroblasts with higher contractile or synthetic phenotype when stimulated by stress, wounding or inflammation, 3) cancer-associated fibroblasts or fibrosis-associated fibroblasts which are generated during chronic tissue injury and acquire enhanced secretory, migratory and proliferative properties [2].

Histological observation of diverse tissue types also shows variable connective tissue compartments (e.g. various cellular constituents as well as various matrix morphology, density and composition), and in fact fibroblasts with divergent features are separated in different sites within the same tissue [15–20]. In the past few years, the existence of fibroblast subtypes has been demonstrated by several approaches. Advances in genetic lineage tracing, single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have provided valuable insights into the cell subpopulations based on different gene expression signatures with markedly improved resolution.

This review aims to construct a blueprint of fibroblast heterogeneity in the lung under various circumstances (Fig. 1). Studies that are performed using genetic lineage tracing or scRNA-seq of human/mouse lung were searched in PubMed to identify articles for inclusion (https://pubmed.ncbi.nlm.nih.gov/, last accessed: Dec. 16, 2022). All the articles were reviewed except those only describe classical fibroblasts such as collagen producing fibroblasts and myofibroblasts, as classical fibroblasts are widely reported, and are mentioned in almost all the other scRNA-seq articles.

2. Fibroblast heterogeneity in lung development

The lung is a developmentally distinct organ. Lung epithelium is derived from endoderm while the lung mesenchymal cells, which

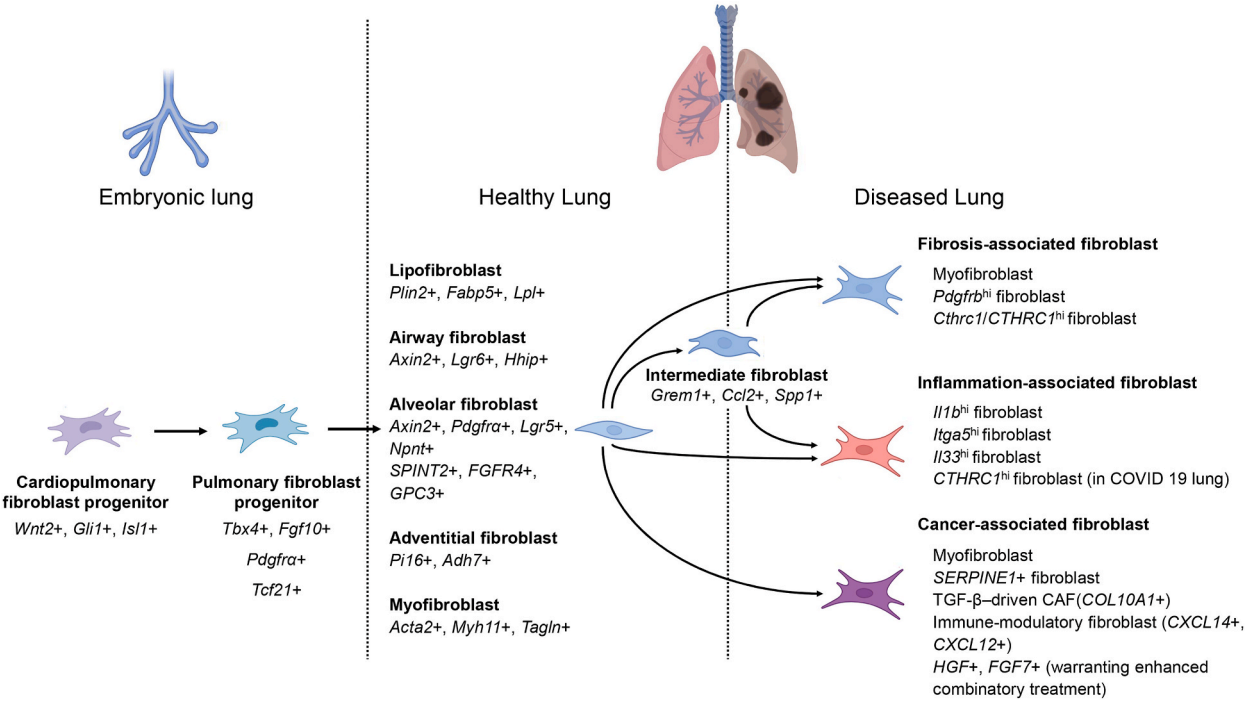

Fig. 1. Scheme of fibroblast heterogeneity across embryonic, healthy and diseased conditions in the lung. Left panel represents fibroblast lineages during lung development. Middle panel shows fibroblasts heterogeneity with their discriminating markers in normal lungs. Right panel represents activated fibroblast spectrum in pathological conditions such as fibrosis, inflammation, and cancer. Arrows represent the directions of differentiation. Different colors/shapes of the fibroblast icons represent different states of fibroblasts. Icons adapted from "Lung, mesenchymal cell, Fibroblasts", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

will differentiate into fibroblasts and produce ECM, originate from mesoderm [4,21]. Lineage analysis demonstrates that pulmonary mesoderm cell lineages are generated by cardiopulmonary mesoderm progenitors characterized by the expression of Wnt family member 2 (*Wnt2*), GLI family zinc finger 1 (*Gli1*) and ISL LIM homeobox1 (*Isl1*) [21,22]. During the later mouse lung morphogenesis, T-box transcription factor 4 (*Tbx4*) and fibroblast growth factor 10 (*Fgf10*), which are expressed in the mesenchyme of the early stage of the developing lung, are responsible for the growth and branching of the adjacent endoderm [23–26]. Intriguingly, in injured adult lungs, myofibroblasts have been shown to be predominantly derived from *Tbx4*+ mesenchymal progenitors [27], indicating the role of early mesodermal lung progenitors for injury response in adult lungs. Therapeutic treatments that target these cells for patients with fibrotic diseases remain an active research area. While platelet derived growth factor receptor alpha (*Pdgfrα*)+ lineage are demonstrated to be responsible for promoting alveolar septal formation and matrix fibroblast differentiation at the embryonic stage of the fetal lung [28–31]. Besides, a recent study shows that the transcription factor 21 (*Tcf21*)+ lineage at embryonic lung functions as fibroblast progenitors and generates lipofibroblasts as well as a subpopulation of interstitial fibroblasts [32].

Thereafter, mesenchymal cell subtypes differentiation depend on their location associated with pulmonary structures, origin, functional phenotypes, disease conditions, etc., and their functions seem to extend beyond the role of synthesizing ECM to that of modulating immune response, promoting angiogenesis and remodeling the microenvironment [33,34].

3. Fibroblasts heterogeneity in lung architecture

The lung is also an architecturally distinct organ, which affects the extent to which the fibroblasts are regionally diverse. The lung parenchyma comprises a highly branched bronchial tree that ends in expandable air sacs called alveoli and is composed of conducting portion (airway) and respiratory portion (distal lung), both surrounded by interstitial connective tissue. Fibroblasts are the most common cells in the pulmonary interstitium and are responsible for the formation and maintenance of interstitial fibers (collagen and elastic fibers) and matrix. The airway fibroblasts are located in two distinct locations - the connective tissue surrounding bronchovascular bundles and just below the epithelium (sub-epithelial) [35]. In the distal lung, fibroblasts are mainly located at the thicker area of the interstitial ECM between the basement membrane of alveolar type 1 (AT1) cells and endothelial cells [36]. Besides, there are also fibroblasts in the adventitia of pulmonary vessels termed adventitial fibroblasts, which are considered to contribute to pulmonary vascular remodeling, and fibroblasts residing in the connective tissue of bronchi, which may be responsible for airway remodeling [37,38]. The airway fibroblasts are considered to be different from fibroblasts in distal lung in morphology, proliferation, α-SMA expression and collagen production [19]. Compared to distal lung fibroblasts, the airway fibroblasts are significantly larger, manifest a weaker proliferative capacity, and express higher amounts of collagen and lower amounts of α-SMA [19,35].

Besides the resident connective tissue fibroblasts, circulating fibrocytes, characterized by their expression of Vimentin, CD34 and Collagen I, were raised by Bucala et al., in 1994 [39]. These cells could rapidly enter injured sites and contribute to wound repair and fibrosis. In patients with allergic asthma and idiopathic pulmonary fibrosis (IPF), circulating fibrocytes accumulate in the bronchial mucosa and lung, consequently contribute to fibrosis [40–42]. Intriguingly, human fibrocytes are also demonstrated to accumulate in the lungs of bleomycin-treated mice and lead to pulmonary fibrosis [43]. Given the capacity of scRNA-seq to explore the relationship between cells including their physiological transitions and differentiation trajectories [44,45], further intensive studies such as scRNA-seq are still required to provide more evidence that collagen-expressing fibrocytes are of hematopoietic origin.

4. Fibroblasts heterogeneity in genetic lineage

Pulmonary fibroblasts have been demonstrated to be heterogeneous in both patients and mouse models with pulmonary fibrosis, as the pathogenic myofibroblasts present different stages of proliferation and may be derived from diverse populations, including mesenchymal progenitors, pericytes, fibrocytes and fibroblasts [46–51]. In vitro study shows that myofibroblasts differentiated from diverse cell types display unique differences in gene expression [52]. In addition, in pathological conditions such as fibrosis or inflammation, epithelial or endothelial cells may obtain mesenchymal or quasi-mesenchymal phenotypes, which also contributes to the diversity of mesenchymal characteristics [53,54]. Besides the general fibroblasts markers such as vimentin (*Vim*), fibronectin 1 (*Fn1*), collagen type I alpha 1 (*Col1a1*) and collagen type I alpha 3 (*Col1a3*), the expression of genes such as *Fgf10*, perilipin 2 (*Plin2*), nerve/glial antigen 2 (*NG2*) and actin alpha 2, smooth muscle (*Acta2*), are also reported in various fibroblast subsets [26,27,48,55], which provides more insights into subtypes of fibroblast.

Spatially different fibroblasts show distinct transcriptional profiles. By using genetic lineage tracing and scRNA-seq, researchers have demonstrated that axin 2 (*Axin2*)+/*Pdgfrα*+/leucine rich repeat containing G protein coupled receptor 5 (*Lgr5*)+ mesenchymal cells, including lipofibroblasts that normally locate close to alveolar cells, may promote alveolar type 2 (AT2) cells proliferation and differentiation, while *Axin2*+/*Pdgfrα*-/leucine rich repeat containing G protein-coupled receptor 6 (*Lgr6*)+ cells are found in the connective tissue surrounding the bronchial tree or blood vessels [56–58]. Tsukui and colleagues have made a more specific classification of fibroblast subpopulations with distinct gene expression signatures based on their anatomical localizations, including alveolar fibroblasts expressing nephronectin (*Npnt*) and carboxylesterase 1D (*Ces1d*), peribronchial fibroblasts (airway fibroblasts) expressing hedgehog interacting protein (*Hhip*) and asporin (*Aspn*), and adventitial fibroblasts (surrounding bronchovascular bundles) expressing peptidase inhibitor 16 (*Pi16*) and alcohol dehydrogenase 7 (*Adh7*) [35]. Researchers find alveolar fibroblasts also express *Plin2* and lipoprotein lipase (*Lpl*), which are general lipofibroblast markers; this is in concordance with previous studies that *Pdgfrα*+ *Tcf21*+ alveolar fibroblasts show some phenotypic features of lipofibroblasts [32,56]. The spatially classification is further confirmed by proximity ligation in situ hybridization (ISH). ScRNA-seq of human lung tissues of patients with IPF and scleroderma exhibits similar heterogeneity [35].

By using scRNA-seq, fibroblasts are further divided into five subtypes (myofibroblasts, collagen type XIII alpha 1 (*Col13a1*) matrix fibroblasts, collagen type XIV alpha 1 (*Col14a1*) matrix fibroblasts, lipofibroblasts and mesenchymal progenitors) in the normal lung with their discriminating markers [59]. The authors consider that myofibroblasts and platelet derived growth factor receptor beta (*Pdgfrb*) high subgroup are similar to the *Axin2*+/*Pdgfrα*-/*Lgr6*+ airway fibroblasts described above, while *Col13a1/Col14a1* matrix fibroblasts are similar to the *Axin2*+/*Pdgfrα*+/*Lgr5*+ alveolar fibroblasts. *Plin2*-expressing lipofibroblasts are lipid-containing interstitial fibroblasts considered crucial for alveolar development and regeneration [60], while mesenchymal progenitors are at a proliferation state with the expression of DNA topoisomerase II alpha (*Top2a*) and marker of proliferation Ki-67 (*Mki67*).

The fibroblast subtypes characterized in mouse lungs by different research groups are verified by Travaglini and colleagues who present an atlas of human lung fibroblasts [61]. Five molecular cell types are identified, including myofibroblasts, fibromyocytes, adventitial fibroblasts, alveolar fibroblasts and lipofibroblasts. Myofibroblasts and fibromyocytes are both characterized by the

Table 1
Fibroblast subtypes, gene markers and their locations, functions or relationship with diseases.

	Gene markers	Locations/Functions/Relationship with diseases	References
Fibroblasts in embryonic stages			
cardiopulmonary fibroblast progenitors	*Wnt2*, *Gli1*, *Isl1*	generate pulmonary fibroblast progenitors	[21,22]
pulmonary fibroblast progenitors	*Tbx4*, *Fgf10*	responsible for the lung morphogenesis and differentiate into myofibroblasts during tissue injury	[23–27]
	Pdgfrα	promoting alveolar septal formation and matrix fibroblast differentiation	[28–31]
	Tcf21	generates lipofibroblasts	[32]
Fibroblasts in mouse lungs			
circulating fibrocytes	*Vim*, *Cd34*, *Cxcr4*	accumulate in lung and contribute to wound repair and fibrosis	[39,40]
lipofibroblasts	*Plin2*, *Fabp5*, *Lpl*, *Fabp1*, *Fabp4*		[59,60]
airway fibroblasts	*Axin2*, *Lgr6*, *Hhip*, *Aspn*	proximal to conducting airways (surrounding the bronchovascular bundles and below the epithelium (sub-epithelial)), myofibrogenic progenitor	[35,57,58]
Alveolar fibroblasts	*Axin2*, *Pdgfrα*, *Lgr5*, *Eln*, *Npnt*, *Ces1d*	occupy alveolar regions of the lung, promote AT2 cell self-renewal and proliferates	[35,56–58]
Adventitial fibroblasts	*Pi16*, *Adh7*	near bronchovascular bundles	[35]
myofibroblasts	*Acta2*, *Myh11*, *Tagln*, *Aspn*, *Mustn1*		[36,59,63]
mesenchymal progenitors	*Top2a*, *Mki67*, *Hist1h2ap*, *Ube2c*, *Hmgb2*, *Ccnb2*	at a proliferation state	[59]
Col13a1 matrix fibroblasts	*Col13a1*, *Itga8*, *Cxcl14*, *Npnt*	increased in fibrotic lung	[59]
Col14a1 matrix fibroblasts	*Col14a1*, *Pi16*, *Mmp3*, *Cygb*	increased in fibrotic lung	[59]
Pdgfrb high fibroblasts	*Pdgfrb*, *Postn*, *Higd1b*, *Cox4i2*, *Notch3*, *Col8a1*	only in fibrotic lung	[59]
Cthrc1+ fibroblasts	*Cthrc1*, *Postn*, *Spp1*, *Fn1*, *Col1a1*, *Col3a1*	only in fibrotic lung, differentiate from alveolar fibroblasts	[35]
inflammatory-proliferative fibroblasts	*Grem1*, *Ccl2*, *Spp1*	intermediate fibroblasts, in the early stage of silica-induced lung damage	[64]
Inflammatory fibroblasts	*Il1b*	emerge in the inflammatory phase of silica-induced mouse lungs	[64]
damage-responsive fibroblasts	*Itga5, Il6, Cxcl1*	increase in infections with influenza A virus	[65]
interferon-responsive fibroblasts	*Il33*, *Irf7*, *Bst2*	emerge in infections with influenza A virus and helminth, localized to perivascular adventitial cuffs	[65,66]
Fibroblasts in human lungs			
circulating fibrocytes	*VIM*, *CD34*, *CXCR4*	accumulate in lung and contribute to wound repair and fibrosis	[39–43]
lipofibroblasts	*PLIN2*, *APOE*		[61]
myofibroblasts	*ACTA2*, *WIF1*, *FGF18*, *ASPN*, *ACTG1*, *DCN*	increased in fibrotic, COVID 19 lungs and lung cancer	[61,62,67,68]
fibromyocytes/airway fibroblasts	*ACTA2*, *MYH11*, *LGR6*, *CNN1*, *TAGLN*	preferentially isolated from samples of proximal lungs	[61,62]
Alveolar fibroblasts	*SPINT2*, *FGFR4*, *GPC3*	localize to alveoli	[61,62]
adventitial fibroblasts	*SFRP2*, *PI16*, *SERPINF1*	localize to vascular adventitia and nearby airways	[61,62]
proliferative fibroblasts	*TOP2A*, *MKI67*	at a proliferation state	[68]
CTHRC1-high fibroblasts	*CTHRC1,POSTN,COL10A1, COL15A1*	in fibrotic lungs, concentrated within fibroblastic foci	[35,62,67]
pathological fibroblasts	*COL1A1*, *LUM*, *CTHRC1*	increase in COVID-19 lungs	[69]
intermediate pathological fibroblasts	*COL1A1*, *LUM*, *CTHRC1*, *ADAM12*, *POSTN*	increase in COVID-19 lungs	[62,69]
TGF-β–driven CAFs	*COL10A1*	strongly enriched in tumors, involved in EMT signaling and ECM production	[70,71]
SERPINE1+ CAFs	*SERPINE1*, *IGF1*, *WT1*, *CLDN1*	promote cell migration and/or wound healing	[71]
Immune-modulatory CAFs	*CFD*, *CXCL14*, *CXCL12*, *CD74*	associate with better clinical response and immune cell migration	[72,73]
HGF + *FGF7*+ CAFs	*HGF*, *FGF7*	protect cancer cells and response poorly to clinical treatment	[73]

CAF, cancer-associated fibroblast
Fibroblast subtypes with light blue backgrounds are activated fibroblasts which increase/emerge in diseased conditions.

expression of *ACTA2*. Classical myofibroblasts (WNT inhibitory factor 1 (*WIF1*)+, fibroblast growth factor 18 (*FGF18*)+, *ASPN*+) are found to localize to alveolar ducts, while fibromyocytes express higher levels of genes with contractile phenotype (myosin heavy chain 11 (*MYH11*), calponin 1 (*CNN1*) and transgelin (*TAGLN*)), and are predominantly located at proximal lung regions. Another study characterizes fibromyocytes with the expression of *LGR6* [62], so we consider fibromyocytes as airway fibroblasts defined in the mouse lungs [35,57,58]. Alveolar fibroblasts (serine peptidase inhibitor, Kunitz type 2 (*SPINT2*)+, fibroblast growth factor receptor 4 (*FGFR4*)+, glypican 3 (*GPC3*)+) localize to alveoli; meanwhile, adventitial fibroblasts (secreted frizzled related protein 2 (*SFRP2*)+, *PI16*+, serpin family F member 1 (*SERPINF1*)+) are located in mesenchymal niches in the vascular adventitia and adjacent airways. Lipofibroblasts express genes with roles in lipid metabolism (*PLIN2* and apolipoprotein E (*APOE*)).

In normal conditions, fibroblasts are characterized by the region and function with specific gene expression profiles, while in disease states, the phenotype of fibroblasts changes due to the activation of fibroblasts and altered gene expression levels.

The discriminative markers for the above-mentioned fibroblast subtypes are listed in Table 1.

5. Fibroblasts heterogeneity in lung disease

Given that the role of different fibroblast subtypes varies among different pathological processes, it is necessary to characterize the heterogeneity of fibroblasts, which will provide essential clues for further understanding of disease progression.

5.1. Fibroblasts heterogeneity in pulmonary fibrosis

Lung fibrosis is a pathological feature of multiple diseases (for example, IPF, silicosis and systemic sclerosis), characterized with progressive collagen deposition. Myofibroblasts have been defined as fibrosis-relevant fibroblasts with the acquisition of a highly contractile phenotype and the expression of collagen and α-SMA [50,74–76].

Zepp and colleagues show that, *Axin2*+ fibroblasts are enriched for *Acta2* and amine oxidase copper containing 3 (*Aoc3*), the expression of which can represent a myofibroblast lineage. During lung fibrosis, *Axin2* lineage contributes to almost half of the myofibroblasts and is responsible for pathogenic myofibrogenesis [57]. Peyser and colleagues find an activated fibroblast population in fibrotic mouse lungs, and the fraction of this myofibroblast-like subcluster is remarkably increased in bleomycin treated lung and decreased after treatment with nintedanib/BIBF1120, indicating the myofibroblast-like subtype is the disease-relevant fibroblast population [63]. This population expresses signature genes associated with ECM, contractile, and focal adhesion. Similar to the result, a significantly increased fraction of contractile myofibroblasts with high expression of *ACTA2* and periostin (*POSTN*) is identified in human lung tissues with systemic sclerosis-associated interstitial lung disease (ILD) compared with healthy lungs [67]. During the development of disease, this activated myofibroblast population is anticipated to experience considerable phenotypic alterations, including increased expression of collagen genes and other pro-fibrotic genes.

In a separate study, researchers find that compared to normal lungs, a previously undescribed fibroblast-subtype with high expression levels of *Pdgfrb* is discovered in fibrotic lungs and can be distinguished from pericytes [59]. Although this subtype is distinguished from the aforementioned myofibroblasts by low expression of *Acta2*, high expression of *Postn* is observed, indicating *Pdgfrb* high-fibroblasts may be a subpopulation of the myofibroblasts. This subtype is suggested to participate in the Notch and Wnt signaling pathways. Besides, the fractions of *Col13a1* and *Col14a1* matrix fibroblasts are also increased in the fibrotic lung. By comparing of the transcriptional patterns, combining pseudotime trajectory analysis, lipofibroblasts appear to be the major source of *Pdgfrb* high-fibroblasts, and this subtype then differentiates into the *Col13a1* and *Col14a1* matrix fibroblasts sequentially [59].

Tsukui and colleagues report another fibroblast subtype characterized by the expression of collagen triple helix repeat containing 1 (*Cthrc1*) as well as ECM-producing genes, emerges in bleomycin-treated mouse lungs [35]. This subcluster can be distinguished from myofibroblasts with a low level of *Acta2* expression. Trajectory analysis and RNA velocity demonstrate that this subcluster of ECM-producing cells may principally differentiate from alveolar fibroblasts. ScRNA-seq of human lungs from patients with IPF, scleroderma and ILD, shows consistent results that *CTHRC1*+ fibroblasts appear only in fibrotic lungs [35,67]. Immunostaining and RNAScope ISH demonstrate that they are gathered in fibroblastic foci.

To determine the shared cell types across lung fibrosis caused by different diseases, scRNA-seq is performed in lung tissues from IPF, chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, sarcoidosis, unclassifiable ILD patients and normal controls, a newly emerging hyaluronan synthase 1 (*HAS1*)+ fibroblast subtype is identified and emerges only in IPF lungs [77]. By using RNA ISH and immunofluorescence, *HAS1*+ cells are identified almost only in subpleural regions and located deeper in IPF lungs compared to control lungs, indicating a potential invasive phenotype. While an isolated study cannot provide sufficient evidence of *HAS1*+ fibroblasts in the pathological process, the importance and generalizability of this subtype should be further examined.

Although different studies identify different new fibrogenic fibroblast subtypes (*Pdgfrb* high, *Cthrc1/CTHRC1* high and *HAS1* high fibroblasts), they are all co-expressed with collagen producing genes (Table 1), indicating they may participate in similar signaling pathway.

In silico-exposed mouse models, researchers find a novel inflammation-related fibroblast-subtype. Shi and colleagues perform scRNA-seq in lung tissues of mice treated with silica for 7 and 56 days and reveal a novel subtype (inflammatory-proliferative fibroblasts) with the high expression of gremlin 1 (*Grem1*), mainly at the early pathological stage [64]. This subtype is considered to transdifferentiate from resting fibroblasts and is shown to be concentrated in the lesion area by spatial transcriptomics. Functional study indicates *Grem1* may be the driving factor and initiates the inflammatory response, and *Grem1*-fibroblasts are considered intermediate fibroblasts between resting fibroblasts and inflammatory/ECM-fibroblasts in pulmonary fibrosis. Thus, blocking the transition of resting fibroblasts into inflammatory-proliferative fibroblasts at an early stage may slow or even reverse the progressive

development of the pathological process.

Myofibroblasts are generally considered as fibrotic fibroblasts during the progression of disease, while recent studies demonstrate that α-SMA is no longer an unique marker of pathologic fibroblasts during lung fibrosis. Intensive studies are expected to elucidate the lineage correlations, overlapping features and pathologic functions of these fibroblast subtypes.

5.2. Fibroblast heterogeneity in infectious lung disease

While there is extensive literature on how fibroblasts regulate the process of fibrosis, there is less information on the heterogeneity and role of fibroblasts in infectious diseases. Boyd and colleagues profile the heterogeneity of fibroblasts in CD45-negative lung cells from mice 0, 1, 3 and 6 days after infection with influenza A virus [65]. Three primary functional fibroblast subtypes are identified: ECM-synthesizing fibroblasts enriched for genes encoding ECM structural proteins, inflammatory fibroblasts with inflammatory signatures, and resting fibroblasts lacking either ECM-producing or inflammatory phenotype. Among inflammatory fibroblasts, two activated states, including integrin subunit alpha 5 (*Itga5*)-expressing damage-responsive fibroblasts and interleukin 33 (*Il33*)-expressing interferon-responsive fibroblasts, are identified. Damage-responsive fibroblasts increase in frequency and number during infection and specifically localize in regions of interstitial inflammation, indicating their importance in the pathological process. Similar temporal dynamics is observed for damage-responsive fibroblasts and interferon-responsive fibroblasts in human lung biopsies. In a separate study investigating the role of pulmonary fibroblasts in lung type 2 immune response, a population of *Il33*+ stromal cells similar to the interferon-responsive fibroblasts is identified to be localized to perivascular adventitial cuffs. This subtype of fibroblast functions as regulators of type 2 immune response, and expands along with type 2 lymphocytes after helminth infection [66].

Inflammatory fibroblasts are the most critical fibroblasts responsible for infectious disease and exhibit high expression of genes involved in type I interferon, interleukin-6 or NF-κB signaling. In silica-induced mouse lungs, inflammatory fibroblasts are also identified, mainly in the lungs obtained seven days after treatment with silica [64]. This result is consistent with the notion that the initial event in silica-exposed lung is an inflammatory response [78,79].

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 infection, manifests as acute lung injury and acute respiratory distress syndrome (ARDS) in severe cases [80–84]. Histological examinations in the lung tissues of patients who have died of COVID-19 show bilateral diffuse alveolar damage as well as fibrosis [85,86]. Delorey and colleagues perform a scRNA-seq study in normal and COVID-19 lungs, three stromal subsets are identified, including fibroblasts (collagen type VI alpha 6 (*COL6A6*)+, collagen type V alpha 2 (*COL5A2*)+, integrin subunit beta like 1 (*ITGBL1*)+, fibroblast growth factor 14 (*FGF14*)+), proliferative fibroblasts (*TOP2A*+, *MKI67*+) and myofibroblasts (actin gamma 1 (*ACTG1*)+, decorin (*DCN*)+). Compared to normal lungs, fibroblasts are increased in COVID-19 patients and fibroblast expansions are observed [68]. In a separate research, Wang and colleagues perform scRNA-seq in lung tissue samples from COVID-19 patients and controls with no known history of any infectious diseases and depict a comprehensive cellular atlas including fibroblasts in the lungs of COVID-19 patients [87]. Alveolar fibroblasts, adventitial fibroblasts and myofibroblasts are identified in both control and patient lungs. Among all cell types, differentially expressed genes in COVID-19 compared to control groups are most prevalent in myofibroblasts and alveolar fibroblasts, indicating a fibrogenic phenotype in the lungs of COVID-19 cases. In addition, increased pro-fibrotic pathways and cell-cell interactions are also revealed. In COVID-19 lungs, myofibroblasts are found to increase by about threefold and are more proliferative. Most of the increased myofibroblasts originate from fibroblasts, while pseudotime analysis shows that epithelial cells could also convert into myofibroblasts, indicating the heterogeneity of myofibroblasts. Notably, Melms and colleagues profile subsets of *CTHRC1*-expressing pathological fibroblasts (including pathological and intermediate pathological fibroblasts) similar to the above-mentioned myofibroblasts that are increased in the COVID-19 lungs [69]. *Cthrc1/CTHRC1*+ fibroblasts have been reported as key drivers of lung fibrosis in mouse models and in patients with IPF or scleroderma (Fig. 1, Table 1) [35], indicating that the increased pathological fibroblasts are responsible for rapidly evolving pulmonary fibrosis in individuals with COVID-19. A comparative study also demonstrates similar gene expression profiles for fibroblasts between patients with severe COVID-19 and patients with pulmonary fibrosis [88]. Pulmonary fibrosis has been reported to be one of the persistent symptoms of the long-term consequences of the COVID-19 and ARDS-induced fibrosis may act as a major contributor to morbidity in the following years [89–91]. Moreover, a recent study has demonstrated that the number of fibroblasts and the deposition of collagen dramatically increases in fatal COVID-19 cases [92], indicating the crucial role of fibroblasts in the prognosis of long-term sequelae of COVID-19. Targeting the fibrotic fibroblasts may be a promising anti-fibrotic medication in preventing the initiating fibroproliferative cascade in ARDS or treating the potential for fibrosis.

These studies suggest that pathogenic fibroblasts arise in response to severe respiratory infections and highlight the important role of fibroblasts in the pathogenesis of inflammation and post-COVID-19 ARDS fibrosis. Comparative study of the fibroblast subpopulations will help illuminate common features and signaling pathways shared by different infectious diseases as well as fibrotic lung diseases, and will help develop better therapeutic strategies.

5.3. Fibroblast heterogeneity in lung cancer

Cancer-associated fibroblasts (CAFs) are the most abundant stromal cells in the cancer microenvironment and form a major constitution of the tumor stroma, playing a pivotal role in tumor development [3]. CAF is a unique subpopulation of heterogeneous fibroblasts and is commonly identified with the expression of α-SMA and fibroblast activation protein (FAP) [3]. CAFs have roles in remodeling ECM structure, recruiting immune cells, regulating tumor immunity, remodeling cancer metabolism, stimulating tumor angiogenesis and modulating chemoresistance [2,93]. Interactions between cancer cells and CAFs have been demonstrated to either suppress or promote tumor progression [94,95]. Thus, stroma-targeting strategies are proposed, and the combination of anti-cancer

and anti-stromal drugs can be more effective in treating cancer patients and improving their outcomes.

CAFs are also highly heterogeneous. In pancreatic cancer, CAFs adjacent to the tumor cells display a matrix-producing contractile feature, while distal CAFs exhibit an immunomodulating secretome [96]. In breast cancer, compared with FAP-low fibroblasts, FAP-high fibroblasts are more relevant to immunosuppression and a poor outcome [97].

By using scRNA-seq, heterogeneous CAF subtypes in lung cancer are further evaluated. Lambrechts and colleagues identify five distinct types of fibroblast in patients with non-small cell lung cancer (NSCLC), including a subtype of non-malignant fibroblast with high expression levels of elastin. While other tumor-related fibroblast subtypes are enriched with unique genes involved in different functions, including epithelial-mesenchymal transition (EMT) signal, myogenesis, angiogenesis and mTOR (mammalian target of rapamycin) signaling [70]. Among these, TGF-β–driven fibrosis-associated fibroblasts (collagen type X alpha 1 (*COL10A1*)+), which show strong EMT signaling and high expression of extracellular matrix proteins, are strongly enriched in tumors, suggesting the potential dynamics of fibroblast evolution from fibrosis to cancer. Qian and colleagues perform scRNA-seq on tumors from three different cancer types: lung, colorectal, and ovary cancer, and construct a pan-cancer blueprint of stromal cell heterogeneity, and identify 11 fibroblast clusters, including three colon-specific clusters, three ovary-specific clusters, and five clusters shared across cancer types. Among the five pan-cancer fibroblasts, three clusters express similar gene signatures with the subtypes reported in NSCLC patients, including myofibroblasts expressing contractile genes, pericytes involved in angiogenesis and fibroblasts expressing ECM genes involved in EMT. Besides, two novel fibroblast subtypes are defined, including serpin family E member 1 (*SERPINE1*)-fibroblasts with highly expressed genes that involved in wound healing and cell migration and adipogenic-fibroblasts with the expression of adipsin (*CFD*) and apolipoprotein D (*APOD*), which are adipocyte markers [71]. Besides the above subtypes, Xing and colleagues profile antigen-presenting CAFs with high expression of C-X-C motif chemokine ligand 12/14 (*CXCL12/14*), CD74 molecule (*CD74*) and MHC II, which are enriched in pulmonary subsolid nodule samples of patients with lung adenocarcinoma [72].

The diversity of CAFs leads to an increasing interest in utilizing the therapeutic profiling of CAFs for designing better strategies for personalized cancer therapies. Hu and colleagues explore the CAFs subtypes derived from tumor tissue specimens in patients with NSCLC and demonstrate that the functional subtypes correlate with patients' clinical response to targeted cancer treatments [73]. Researchers co-culture the EGFR/ALK-mutant cancer cell lines with various patient-derived fibroblasts (PDFs) and find that different PDFs provide various degrees of rescues when treated with EGFR/ALK tyrosine kinase inhibitors (EGFRi). Three CAF subtypes with distinctive functions are identified through therapeutic profiling of the PDFs. Subtype I and II CAFs express high levels of hepatocyte growth factor (*HGF*) and fibroblast growth factor 7 (*FGF7*), they demonstrate different capacities to protect cancer cells against EGFRi treatment and warrant enhanced combinatory treatment. While subtype III CAFs, which express *CXCL12*, may bear resemblance to the above-mentioned antigen-presenting CAFs (Table 1). Compared with subtype I and II PDFs, they demonstrate superior chemotactic capacity to recruit immune cells and correlate with a better clinical response. This functional classification of CAFs may have considerable value in personalized cancer treatment.

6. Conclusions and perspectives

As the development of the technologies especially scRNA-seq over the past several years, significant progress has been made in our understanding of fibroblast heterogeneity across different embryonic stages, organs, anatomical regions and conditions. These advances have revealed unique as well as similar characteristics of fibroblasts across different pulmonary diseases. As some unique fibroblast subtypes also have similar pathogenic potentials, whether they have the same embryonic origin in genetic lineage or overlapping signaling pathways remains unclear. Combined studies of the activated fibroblasts in tissues upon both acute and sustained stimulations will provide a better characterization of the functional complexity rather than the expression of a particular gene, and the former will be more beneficial for designing of targeted therapies. Advanced studies warrant to be expected for unravelling more hidden secrets of fibroblasts.

Ethics statement

Review or approval by an ethics committee was not needed for this study because no data of patients or experimental animals was used in the review article.

Informed consent was not required for this study because no clinical data was used in the review article.

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Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

The abbreviations used are

ECM	extracellular matrix
α-SMA	α-smooth muscle actin
scRNA-seq	single-cell RNA sequencing
Wnt2	Wnt family member 2
Gli1	GLI family zinc finger 1
Isl1	ISL LIM homeobox1
Tbx4	T-box transcription factor 4
Fgf10	fibroblast growth factor 10
Pdgfrα	platelet derived growth factor receptor alpha
Tcf21	transcription factor 21
AT1	alveolar type 1
IPF	idiopathic pulmonary fibrosis
Vim	vimentin
Fn1	fibronectin 1
Col1a1	collagen type I alpha 1
Col1a3	collagen type I alpha 3
Fgf10	fibroblast growth factor 10
Plin2	perilipin 2
NG2	nerve/glial antigen 2
Acta2	actin alpha 2 smooth muscle
Axin2	axin 2
Lgr5	leucine rich repeat containing G protein coupled receptor 5
AT2	alveolar type 2
Lgr6	leucine rich repeat containing G protein-coupled receptor 6
Npnt	nephronectin
Ces1d	carboxylesterase 1D
Hhip	hedgehog interacting protein
Aspn	aspirin
Pi16	peptidase inhibitor 16
Adh7	alcohol dehydrogenase 7
Lpl	lipoprotein lipase
ISH	in situ hybridization
Col13a1	collagen type XIII alpha 1
Col14a1	collagen type XIV alpha 1
Pdgfrb	platelet derived growth factor receptor beta
Top2a	DNA topoisomerase II alpha
Mki67	marker of proliferation Ki-67
WIF1	WNT inhibitory factor 1
FGF18	fibroblast growth factor 18
MYH11	myosin heavy chain 11
CNN1	calponin 1
TAGLN	transgelin
SPINT2	serine peptidase inhibitor Kunitz type 2
FGFR4	fibroblast growth factor receptor 4
GPC3	glypican 3
SFRP2	secreted frizzled related protein 2
SERPINF1	serpin family F member 1
APOE	apolipoprotein E
Aoc3	amine oxidase copper containing 3

POSTN periostin
ILD interstitial lung disease
Cthrc1 collagen triple helix repeat containing 1
Grem1 gremlin 1
Itga5 integrin subunit alpha 5
Il33 interleukin 33
COVID-19 coronavirus disease 2019
ARDS acute respiratory distress syndrome
COL6A6 collagen type VI alpha 6
COL5A2 collagen type V alpha 2
ITGBL1 integrin subunit beta like 1
FGF14 fibroblast growth factor 14
ACTG1 actin gamma 1
DCN decorin
CAF cancer-associated fibroblast
FAP fibroblast activation protein
NSCLC non-small cell lung cancer
EMT epithelial-mesenchymal transition
mTOR mammalian target of rapamycin
COL10A1 collagen type X alpha 1
SERPINE1 serpin family E member 1
CFD adipocyte markers adipsin
APOD apolipoprotein D
CXCL12/14 C-X-C motif chemokine ligand 12/14
CD74 CD74 molecule
PDF patient-derived fibroblasts
EGFRi EGFR/ALK tyrosine kinase inhibitors
HGF hepatocyte growth factor
FGF7 fibroblast growth factor 7.

Table 1. **Fibroblast subtypes, gene markers and their locations, functions or relationship with diseases.** The table shows heterogeneous fibroblasts in embryonic stages, mouse lungs and human lungs, respectively. Fibroblast subtypes with light blue backgrounds are activated fibroblasts that increase/emerge in diseased conditions. CAF, cancer-associated fibroblast.

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