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Pulmonary fibrosis: from mechanisms to therapies

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Abstract
Pulmonary fibrosis (PF) is a chronic, progressive interstitial lung disease characterized by excessive deposition of extracellular matrix (ECM) and abnormal fibroblast proliferation, which is mainly caused by air pollution, smoking, aging, occupational exposure, environmental pollutants exposure, and microbial infections. Although antifibrotic agents such as pirfenidone and nintedanib, approved by the United States (US) Food and Drug Administration (FDA), can slow the decline in lung function and disease progression, their side effects and delivery inefficiency limit the overall prognosis of PF. Therefore, there is an urgent need to develop effective therapeutic targets and delivery approaches for PF in clinical settings. This review provides an overview of the pathogenic mechanisms, therapeutic drug targeting signaling pathways, and promising drug delivery strategies for treating PF.

Keywords Pulmonary fibrosis, Pathogenic mechanisms, Therapeutic targets, Drug delivery system

Introduction

Pulmonary fibrosis (PF) is a progressive, destructive, and fatal interstitial lung disease characterized by the substantial presence of abnormally activated fibroblasts, tissue remodeling, and excessive ECM proteins (like collagens) deposition, with limited therapeutic options, resulting in an average life expectancy of only 3 to 5 years [1, 2]. The reported incidence of PF ranges from 0.9 to 9.3 cases per 100,000 individuals in Europe and North America, and from 3.5 to 13.0 cases per 100,000 people in Asia and South America [3]. Currently, only nintedanib and pirfenidone are approved as targeted therapies for PF [4]. In the United Kingdom (UK), the annual cost of pirfenidone is approximately $77227.66, whereas in the US, the combined annual cost for both pirfenidone and nintedanib exceeds $100,000 [5, 6]. For Asian countries, a recent study found the median direct medical cost for PF patients in China was 9,378.3 Chinese yuan (approximately $1,300) per patient per admission [7]. Moreover, PF predominantly affects older individuals, with most cases occurring between 50 and 70 years of age, and it is more common in males than in females [8]. However, female mice showed higher mortality rates and more severe fibrosis than male mice, as female mice exhibit direct fibrogenic effects on lung fibroblasts, mediated by their endogenous sex hormones [9]. The growing burden of PF poses a significant threat to public health worldwide, substantially affecting health-related quality of life [10]. Despite its clinical severity, currently approved treatments have shown limited efficacy and

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considerable side effects, rendering them less than satisfactory [11–13]. The dynamic evolution of PF further complicates diagnostic efforts and limits opportunities for early intervention [14]. Therefore, a deeper understanding of the pathogenic mechanisms underlying PF and the development of effective treatment strategies are urgently needed. Here, we review the underlying mechanisms (including risk factors and cellular as well as molecular mechanisms) of PF and also summarize the therapeutic intervention strategies against PF. Collectively, our review aims to shed new light on the pathogenic mechanisms and intervention strategies for PF.

Pathogenesis and mechanisms of PF

Despite the limited understanding of the mechanisms underlying PF, the current paradigm of disease pathogenesis encompasses specific cellular processes and molecular pathways. The initial injury to the alveolar epithelium triggers a cascade of events, including inflammation and alveolar epithelial injury, which is crucial for the onset of the disease [15, 16]. Following this, lung fibroblasts become activated and differentiate into myofibroblasts in response to the release of cytokines and growth factors from the damaged lung epithelium, accompanied by pro-fibrotic signaling pathways. This process ultimately leads to the deposition of ECM and the development of progressive fibrotic scars within the lung parenchyma, resulting in lung dysfunction [17, 18].

Risk factors

Multiple risk factors, including intrinsic factors (e.g., genetic predisposition and aging) and extrinsic factors (e.g., air pollution, smoking, occupational/environmental exposures, and microbial infections), can initiate the progression of PF. The primary risk factors involved in PF are further illustrated in Fig. 1.

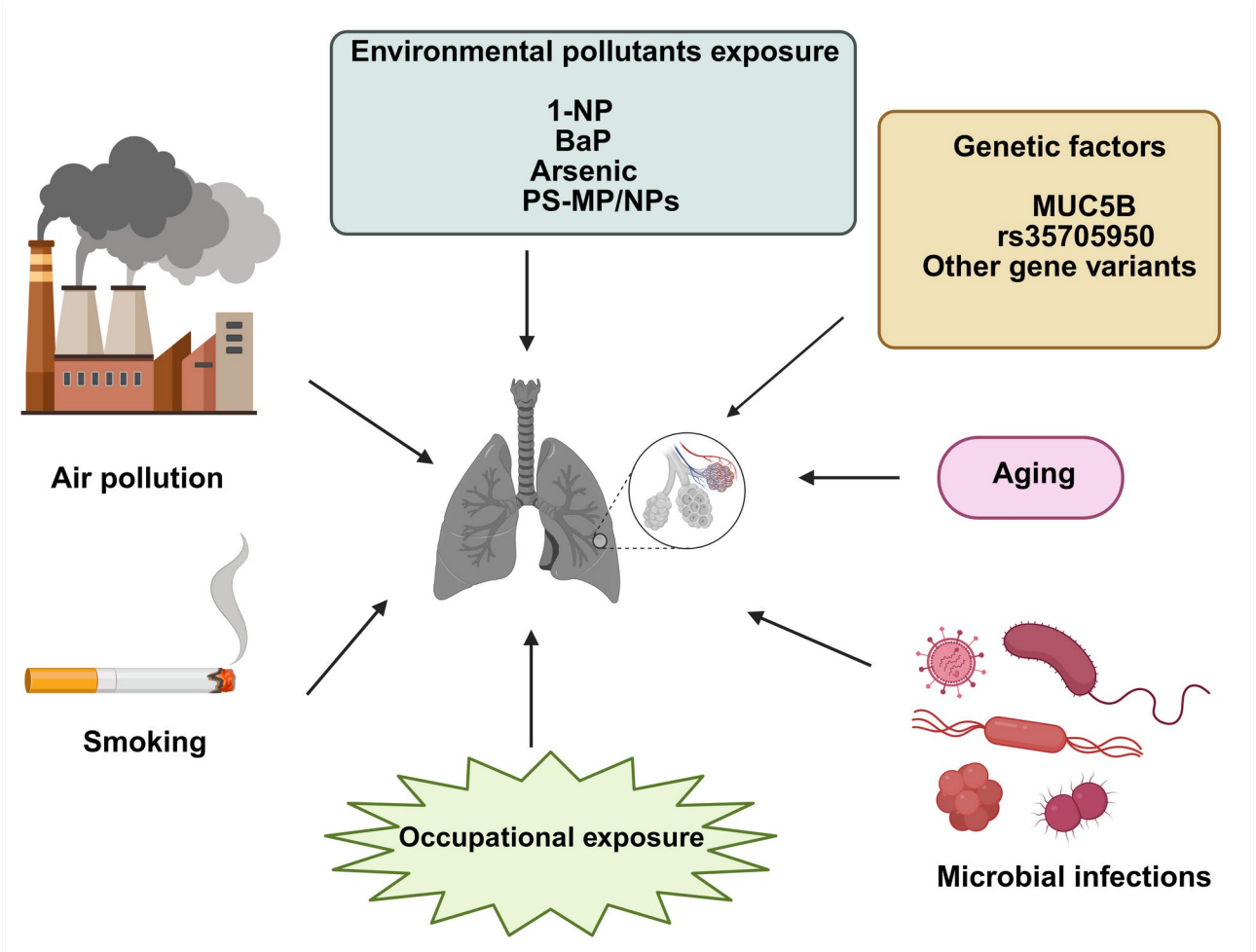

Fig. 1 Schematic representation of PF potential risk factors. Diverse risk factors, including intrinsic factors (including genetic factors and aging), and extrinsic factors (including air pollution, smoking, occupational exposure, environmental pollutants exposure, and microbial infections) contribute to PF. Image Created in https://BioRender.com

Intrinsic factors

Genetic Factors.

PF arises from the interplay between genetic and environmental factors, with genetic susceptibility playing a crucial role in determining the risk of developing the disease. Previous genome-wide association studies (GWAS) have identified common genetic variants associated with PF, particularly in genes linked to immune function, epithelial barrier function, telomeres, and cell cycle regulation [19, 20]. Ongoing GWAS are expected to uncover additional gene polymorphisms related to PF risk, and these specific variants may influence the disease's natural history and predict clinical outcomes [21]. In patients with familial pulmonary fibrosis (FPF), telomere maintenance-related causal genes are implicated in about 30% of cases [22]. The variant rs35705950, a common gain-of-function promoter variant located in the promoter region of the MUC5B gene, has been identified as the strongest risk factor for PF, correlating with a five-fold increase in disease risk [23, 24]. The association between rs35705950 and PF has been validated across multiple independent cohorts, including studies conducted in France [25] and Mexico [26]. Besides the MUC5B promoter variant, other rare variants (MAF < 1%) related to telomere and surfactant genes may also contribute to FPF and sporadic PF cases [27]. Furthermore, pro-fibrotic signaling variants, such as those in the toll-interacting protein (TOLLIP) gene variants (including rs111521887, rs5743894, and rs574389), have been suggested to associate with PF [28]. Although our understanding of the genetic risk factors for PF is still evolving, these findings provide valuable biological insights into the susceptibility to the disease.

Aging

Aging is a normal biological process that ultimately leads to death, characterized by the gradual weakening and loss of an organism's structure and function [29, 30]. Age-related diseases, including cardiovascular diseases, cancers, and interstitial lung diseases, identify aging as a significant risk factor for various chronic conditions in adults [31]. Natural lung aging is a complex process that involves molecular and physiological changes resulting in a decline in lung function, reduced regenerative capacity, and eventual chronic alterations in lung interstitial structure [32]. In contrast to normal cells, senescent cells exhibit distinct genetic and morphologic characteristics, including genomic instability, telomere shortening, epigenetic dysregulation, and mitochondrial dysfunction [33]. Recent studies have investigated mechanisms underlying accelerated cellular aging, particularly the loss of epithelial progenitor cell function during PF progression [34]. Primary lung fibroblasts isolated from PF patients demonstrate a more pronounced senescent phenotype, characterized by the overexpression of α smooth muscle actin (α-SMA) and excessive ECM deposition [35, 36]. Overall, the current understanding of cellular senescence indicates that it is a significant risk factor for the development and progression of PF.

Extrinsic factors

Air Pollution

Recent studies have increasingly highlighted the significant role of air pollution, particularly particulate matter (PM, including PM10 and PM2.5), nitrogen oxides (NO), and other pollutants, in the development and exacerbation of PF. Long-term exposure to PM10 and NO, which are prevalent in urban environments due to traffic and industrial emissions, has been strongly linked to heightened risk and increased mortality in PF patients. This is largely attributed to the triggering of inflammatory responses and oxidative stress [37]. Specifically, PM10 exposure has been associated with lung tissue damage and the progression of fibrosis, likely through mechanisms involving epithelial cell death, oxidative damage, and the activation of inflammatory signaling pathways [38]. Nitrogen oxides, particularly NO_2, further exacerbate the inflammatory cascade within the lungs, leading to epithelial injury, fibroblast activation, and the deposition of extracellular matrix components, all of which are critical drivers of fibrosis [39]. Furthermore, exposure to both PM2.5 and NO_2 has been found to amplify the risk of acute exacerbations in PF patients, likely through mechanisms involving inflammatory mediators such as interleukins [40, 41]. Studies have also demonstrated that exposure to PM2.5 has been shown to trigger PF through mechanisms such as epithelial-mesenchymal transition (EMT) [42, 43]. Additionally, short-term exposure to PM2.5 is associated with significant lung inflammation and injury [44, 45].

Smoking

Cigarette smoke contributes to the senescence and/or injury of various cell types, including type-2 alveolar epithelial (AEC2) cells, thus playing a role in the progression of PF [46]. A meta-analysis indicated that tobacco smoking correlates with an increased risk of developing PF [47]. A prospective cohort study from the UK Biobank demonstrated that smoking intensity exhibits a dose-response relationship with the risk of PF [48]. Furthermore, electronic cigarettes have gained popularity as a smoking alternative for adults in recent years. Nicotine is one of the only chemicals consistently found in traditional cigarettes and electronic cigarettes [49]. Several reports indicate that electronic cigarettes emit toxic substances, including volatile organic compounds, heavy metals, and known carcinogens, and these are becoming more harmful to pulmonary and cardiac systems [50, 51]. For example, Dai et al. found that long-term chronic exposure to electronic cigarettes induced irreversible

damage to cardiovascular and respiratory systems in mice, characterized by cardiac fibrosis and PF [52].

Occupational Exposure

Significant associations have been found between occupational exposure and PF. Occupational exposure to airborne hazardous particles, particularly asbestos, silica, and coal dust, represents the primary etiological factor in the development of PF [53, 54]. Experimental evidence demonstrates that intratracheal asbestos exposure induces marked PF, as evidenced by elevated fibrosis in mouse lung tissue [55]. Similarly, silicosis is a progressive and irreversible occupational lung disease resulting from prolonged inhalation of crystalline silica dust, and with millions of new cases reported annually, it continues to pose a significant global public health challenge [56–58]. Coal worker's pneumoconiosis, another common occupational disease in miners, arises from chronic coal dust exposure, resulting in PF and immune dysfunction [59]. Collectively, these findings underscore occupational hazards as critical contributors to PF, necessitating stringent workplace safety measures and early surveillance to mitigate disease progression.

Environmental Pollutants Exposure

Numerous studies indicate that exposure to environmental pollutants may induce the development of PF. For instance, as a common chemical contaminant, arsenic widely exists in air, drinking water, and soil and has been reported to induce PF via mediating H3K18 lactylation [60]. Other environmental pollutants like 1-nitropyrene, which is formed during gas, oil, and coal combustion, could cause various respiratory system diseases, including PF [61]. Benzo[a]pyrene (BaP) is a well-known environmental pollutant, and Li et al. have found that exposure to BaP might induce PF through EMT [62]. In addition, polystyrene nano- and microplastics (PS-NPs/PS-MPs) have emerged as significant contributors to PF, acting through complex and multifaceted pathological mechanisms [63]. Zhang et al. found that PS-MPs triggered PF by promoting cell ferroptosis [64]. Inhalation exposure to PS-NPs can promote EMT in human alveolar epithelial cells, primarily by enhancing reactive oxygen species (ROS) generation and activating NADPH oxidase 4 (NOX4). This process subsequently triggers mitochondrial dysfunction and endoplasmic reticulum stress, critical events implicated in the fibrotic cascade. Notably, the adverse effects of PS-NPs appear highly dependent on particle characteristics, with smaller size and positive surface charges correlating with heightened cytotoxicity [65]. Moreover, exposure to PS-NPs promotes mitochondrial double-stranded DNA release, further activating the cGAS-STING pathway and amplifying pulmonary inflammation and fibrosis [66]. Our study demonstrates that polystyrene nanoplastics induce PF via two parallel mechanisms: (1) direct stimulation of fibroblast proliferation and activation, and (2) GPX4-dependent ferroptosis in alveolar epithelial cells (unpublished data). Together, these findings underscore the potential pathogenic mechanisms in environmental pollutant-induced lung fibrosis, offering new insights into disease mechanisms and promising avenues for intervention.

Microbial Infections

Increasing evidence suggests that microbial infections (especially viral infections) may play a role in the initiation and exacerbation of PF [67, 68]. Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for COVID-19, can lead to a cytokine storm and trigger profibrotic responses, then result in significant fibrotic changes in the lungs [69, 70]. Additionally, previous studies have shown that infection with γ-Herpes virus-68 can exacerbate bleomycin (BLM)-induced PF in mouse models [71]. Moreover, Huang et al. reviewed various viruses, including Human T-cell leukemia virus (HTLV), Cytomegalovirus (CMV), Human immunodeficiency virus (HIV), and Epstein–Barr virus (EBV), highlighting their potential roles as risk factors for the development of PF following infection [72]. Besides, Chlamydia, Mycoplasma, and Aspergillus fumigatus have also been indicated as potential inducers of PF [73, 74]. Spatial transcriptomics also revealed distinct profibrotic and antifibrotic markers expressed by epithelial and non-epithelial cell populations in influenza virus-infected aged murine lungs. This study uncovered spatially resolved molecular networks that drive fibrotic progression in aged tissues, highlighting how viral infection exacerbates dysregulated fibrogenic pathways [75]. Pseudomonas aeruginosa, an opportunistic Gram-negative pathogen, is a major etiological agent of nosocomial infections and a significant contributor to hospital-acquired pneumonia [76]. Furthermore, chronic pseudomonas aeruginosa infection is strongly associated with progressive structural lung damage in chronic respiratory diseases, including cystic fibrosis and PF [77]. These findings may provide new insights into strategies for managing PF by targeting microbial infections as a therapeutic approach.

The risk factors for PF underscore the multifactorial nature of the disease, driven by the interplay between environmental factors and genetic susceptibility. Collectively, these findings emphasize the importance of PF prevention and management, integrating genetic screening, environmental mitigation, and targeted therapies to address the interplay of aging, genetic susceptibility, and cumulative environmental exposures. Future research should aim to elucidate gene-environment interactions, identify biomarkers for early detection, and develop interventions that disrupt shared pathogenic pathways to mitigate the global burden of PF.

The main effector cells and molecular pathways in PF

Cells involved in PF

PF is a complex and dynamic process that involves cell types throughout the progression of pathological fibrogenesis, including epithelial cells, macrophages, fibroblasts, and endothelial cells [78, 79]. In this section, we will illustrate the roles of these cells in the development of PF (Fig. 2).

Alveolar Epithelial Cell

Epithelial cell dysfunction is believed to be susceptible to abnormal injury responses and serves as a critical driver of diffuse parenchymal disease, including PF [80, 81]. In the lung, AEC2 cells play a key role in maintaining alveolar epithelium homeostasis, regenerating surfactant-producing cells, and facilitating the differentiation of type-1 alveolar epithelial (AEC1) cells [82, 83]. When AEC1 cells are injured, the integrity of the epithelial barrier is compromised, leading to aberrant proliferation and differentiation of AEC2. If AEC1 injury persists or the ability to restore the epithelial barrier is impaired, this can result in abnormal activation of fibroblast, increased ECM deposition, and destruction of lung architecture [84, 85].

It has been reported that senescence-associated markers, including the tumor suppressor genes p53 and p21, were upregulated in the distal epithelium of lungs affected by PF [86]. Furthermore, single-cell RNA sequencing of AEC2 derived from both PF and healthy control lungs has highlighted the role of p53 in fibrotic AEC2 [87]. Specifically, oxidative stress and ER stress-induced injury in AECs can promote the release of injury-associated molecules, such as damage-associated molecular patterns (DAMPs), which are linked to the initiation of tissue repair and fibrotic response [88]. EMT is a cellular process in which epithelial cells lose their characteristic features, acquire mesenchymal properties, and adopt fibroblast-like phenotypes [89]. EMT is implicated in several pathological conditions, including cancer and fibrosis [90, 91]. Collectively, these studies suggest that dysfunction in alveolar epithelial cells, including senescence, oxidative and ER stress-induced injury, and dysregulated EMT, significantly contribute to the pathogenesis of PF.

Macrophages

Macrophages play a crucial role in host defense, which includes the phagocytic clearance of microorganisms and apoptotic cells [92]. As the most abundant immune

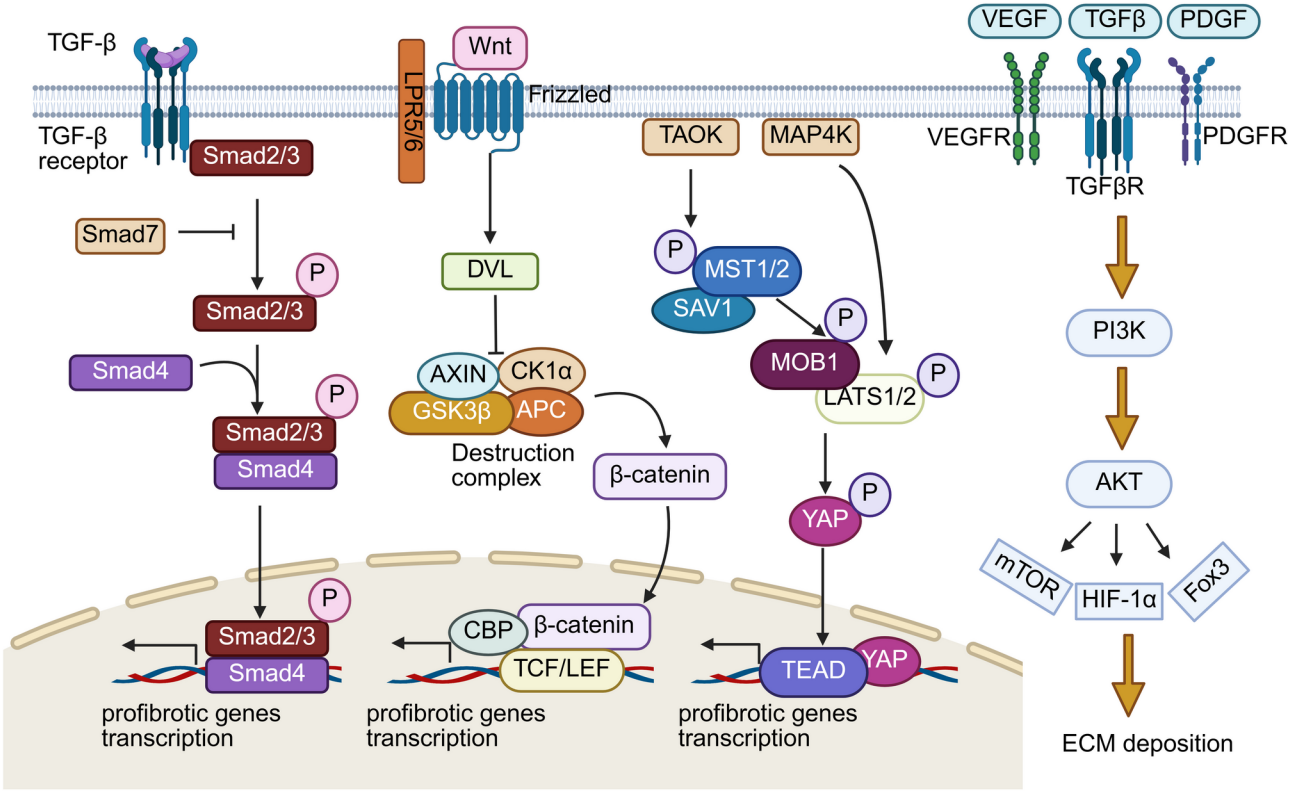

Fig. 2 Summary of the key effector cells in the initiation of PF. Following profibrotic factors stimulus, macrophages respond and produce inflammatory cytokines. Cytokines attract more immune cells, such as monocytes and neutrophils, which in turn produce more cytokines, creating a cycle of inflammation that damages the lung cells. In addition, activated fibroblasts (including those that originated from EMT and EndoMT) stimulate the production of myofibroblasts as well as excessive ECM deposition which undergoes pathologic remodeling. Image Created in https://BioRender.com

cells in the lungs, comprising approximately 70% of the immune cell population, macrophages have significant modulatory roles in the fibrogenic process at various locations or stages of PF [93]. The lungs contain two distinct groups of macrophages: interstitial macrophages (IMs), located within the lung parenchyma, and alveolar macrophages (AMs), found in the airways [94]. Based on their activation status, macrophages can be polarized into two major subsets: classically activated macrophages (M1), which produce pro-inflammatory cytokines and can be activated by lipopolysaccharide (LPS), and activated macrophages (M2), which dampen inflammation, promote wound healing and can be activated by IL-4 [95, 96]. In fibrotic lungs, both M1 and M2 macrophages contribute to disease progression and regulate the production of inflammatory mediators (such as IL-1, inducible nitric oxide synthase (iNOS), and IL-6) and fibrogenic mediators (such as IL-4, arginase 1 (Arg-1), and IL-13) [97].

In the current paradigm of PF pathogenesis, inflammation is recognized as an initiating pathological feature and triggers aberrant wound repair responses throughout the progression of the disease [98]. During the early inflammatory stage, M1 macrophages activate and then produce extracellular matrix metalloproteinases (MMPs), which lead to the degradation of the ECM. Notably, the inhibition of histone methyltransferase enhancer of zeste homolog 2 (EZH2) has been shown to attenuate lung inflammation and fibrosis by modulating macrophage polarization in an LPS-induced acute respiratory distress syndrome (ARDS)-associated PF mouse model [99].

M2 macrophages are thought to regulate the progression of fibrotic lung disease by decreasing inflammatory factors and increasing the production of chemokines, MMPs, TIMPs, and fibronectin [100, 101]. Animal studies have also indicated that M2 macrophages could serve as therapeutic targets for the treatment of PF [102, 103]. However, it is noted that M2 macrophages may exacerbate PF by producing amounts of transforming growth factor-beta 1(TGF-β1) and platelet-derived growth factor (PDGF), which induce fibroblast proliferation and differentiation [104]. In summary, macrophages are implicated in the fibrotic remodeling of organs and play a crucial role in the pathogenesis of PF.

Fibroblasts

Fibroblast-to-myofibroblast transition (FMT) is characterized by excessive ECM deposition in the lung parenchyma and plays a central role in the pathogenesis of PF [105]. TGF-β1 is the primary stimulating factor driving the FMT process. Myofibroblasts are key effector cells of PF and are crucial for the reconstruction of the ECM during the wound healing repair process. After the repair process is completed, the number of myofibroblasts decreases, along with their presence in remodeled areas, which ultimately contributes to the progression of chronic lung diseases [106].

Activated myofibroblasts are characterized by high expression of α-SMA, accompanied by collagen deposition and migrating and the formation of fibrotic foci [107]. In a comprehensive analysis using multicolor clonal cell labeling, Ting Xie et al. reported a significant population of fibroblasts in the lungs of mice with PF, including those expressing α-SMA, Col1α1, vimentin, desmin, (platelet-derived growth factor receptor, alpha polypeptide) Pdgfrα, and (platelet-derived growth factor receptor, beta polypeptide) Pdgfrβ [108]. These fibroblasts develop contractile properties similar to those of smooth muscle cells (SMCs), leading to increased mechanical stress and matrix stiffness, ultimately resulting in a feed-forward mechanism of progressive fibrotic remodeling [109]. Therefore, targeting fibroblasts or FMT progression may represent novel therapeutic targets for the treatment of PF.

Endothelial Cells.

In the process of PF, loss of pulmonary microvascular endothelial cells (PMVECs) and dysregulation of angiogenesis are recognized as significant pathological changes [110, 111]. Additionally, endothelial cells serve as a source of myofibroblasts through the endothelial-to-mesenchymal transition (EndoMT) process [112, 113]. During EndoMT, endothelial cells undergo a phenotypic shift to acquire mesenchymal characteristics, resulting in a myofibroblast-like phenotype marked by high expression of α-SMA and vimentin, alongside low expression of vascular endothelial cadherin (VE-cadherin) [113, 114]. Recent studies by Zhang et al. have demonstrated that the FDA-approved antifibrotic drug Pirfenidone mitigates LPS-induced PF by inhibiting EndoMT through the Hedgehog signaling pathway [115]. Furthermore, a subpopulation of $Cxcl12^{+}$ endothelial cells expands in the lungs of mice treated with BLM and is closely associated with pro-fibrotic processes, including the regulation of angiogenesis, collagen binding, and chemokine activity [116]. Collectively, these findings suggest that endothelial cells play a crucial role in the pathogenesis of PF.

The pathogenesis of PF hinges on intricate cellular crosstalk, yet critical ambiguities persist. A critical gap remains in understanding how epithelial injury, macrophage plasticity, fibroblast activation, and endothelial dysfunction synergize across disease stages. Future research needs to consider the role of intercellular crosstalk in PF.

Molecular pathways in PF

Numerous molecular signaling pathways, including TGF-β, Wnt, phosphoinositol-3 kinase (PI3K)-Akt, and Hippo, have been extensively studied for their roles in regulating the progression of PF. This section primarily focuses

on the contributions of these signaling pathways to the pathophysiology of PF (Fig. 3).

TGF-β Signaling

TGF-β plays a multifaceted role in regulating inflammation responses, cell proliferation, and wound healing of fibrotic tissues [117, 118]. There are three isoforms of TGF-βs, termed TGF-β1, TGF-β2, and TGF-β3 [119]. TGF-β1 is primarily expressed in endothelial, hematopoietic, and connective tissue cells, while TGF-β2 is predominantly found in epithelial and neuronal cells. TGF-β3 is mainly expressed in mesenchymal cells [120, 121]. Notably, among various pro-fibrotic factors, TGF-β1 stands out as the most critical contributor to the fibrogenic process. TGF-β1 regulates fibrotic diseases through both canonical (Smad-based) and non-canonical (non-Smad-based) signaling pathways, leading to myofibroblast activation and ECM deposition [122].

In the canonical signaling pathway, TGF-β1 binds to its receptors, TβRI and TβRII, resulting in the phosphorylation of Smad2 and Smad3 [123]. Smad7 acts as a negative

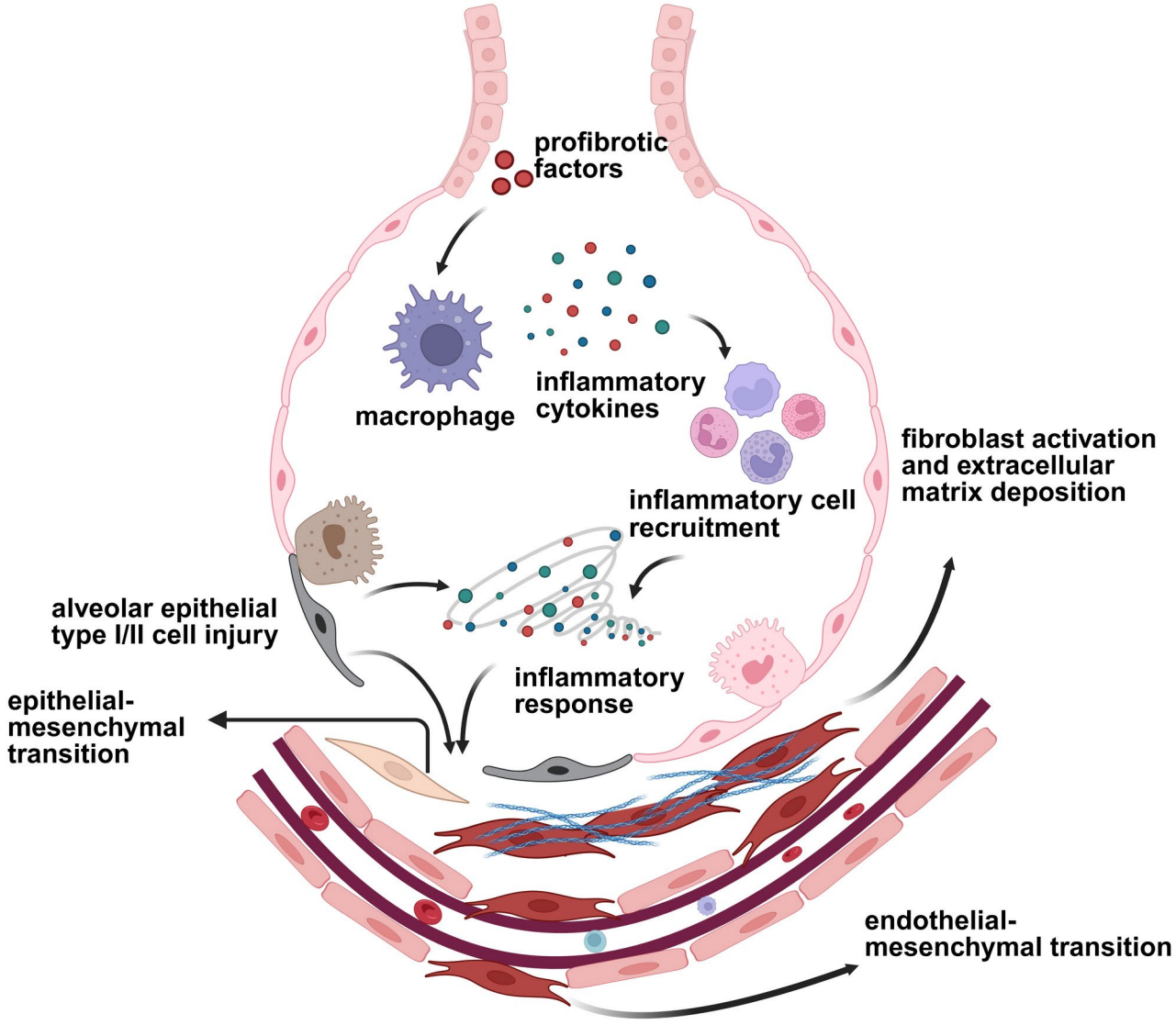

Fig. 3 Overview of molecular signaling pathways in PF. In the TGF-β signaling, TGF-β binding to TGF-βRs activates the TGF-β-Smad signalings. In the Wnt signaling, activated DVL inhibits the destruction complex and then allows β-catenin accumulation to enter the nucleus where it can act together with either p300 or CBP as a transcriptional co-activator for TCF/LEF to activate Wnt-related fibrotic genes. In the Wnt signaling, MAP4K and TAOK families of kinases phosphorylate and activate LATS1/2. Meanwhile, YAP activity is regulated by the LATS1/2 kinases, which promote YAP nucleus accumulation and bind to several transcription factors, such as the TEAD family, eventually changing profibrotic gene expression. In the PI3K-Akt signaling, PI3Ks can be activated by various growth factors like VEGF, PDGF, and TGF-β. The common downstream of receptor-mediated PI3K activation is Akt, which regulates the activity of mTOR, HIF-1α, and Fox3 to involve cell proliferation, differentiation, and ECM deposition in PF. Image Created in https://BioRender.com

regulator of the TGF-β1/Smad pathway. Phosphorylated Smad2 and Smad3 then associate with Smad4 and translocate into the nucleus, where they regulate the expression of downstream target genes [124, 125]. Besides, the cellular homolog of the avian Sloan-Kettering virus (SKI) encodes the SKI proto-oncogene protein and is commonly regarded as a negative regulator of the canonical TGF-β signaling pathway [126]. The SKI protein complex plays a critical role in regulating fibroblast activation and EMT by modulating TGF-β1/Smad signaling. The inhibition of SKI significantly suppresses TGF-β1-induced fibroblast proliferation, highlighting its importance in cellular activation processes [127]. Additionally, SKI acts as a key negative regulator of EMT by antagonizing Smad-dependent signaling, as evidenced by its ability to reverse the process of EMT [128]. These findings underscore SKI's dual function in both fibroblast proliferation and EMT regulation, positioning it as a central player in TGF-β1-mediated cellular responses.

In the non-canonical signaling pathway, TGF-β interacts with ALK1, leading to the activation of Smad1/5, which is implicated in tissue disease [129]. During the process of PF, TGF-β can be released by alveolar epithelial cells, macrophages, or regulatory T cells following injury. It subsequently recruits and activates circulating fibrocytes and fibroblasts, resulting in ECM production and deposition [130, 131]. Furthermore, TGF-β inhibits the production of anti-fibrotic molecules, such as prostaglandin E2, thereby exacerbating the progression of PF [132].

Wnt Signaling

The Wnt signal pathways are critically recognized as important pathways for the development and homeostasis of organs and tissue [133, 134]. Wnt genes encode proteins that are highly conserved throughout evolution. These pathways are involved in various biological functions, including cell proliferation, polarity, and differentiation [135]. Moreover, sustained activation of Wnt signaling is implicated in wound repair and the pathogenesis of fibrosis, including lung, kidney, and liver fibrosis [136, 137].

Wnt signaling pathways are principally characterized by two classes: the canonical Wnt pathway and the non-canonical Wnt/calcium pathway [138]. The canonical Wnt signaling, also referred to as Wnt/β-Catenin signaling, is typically initiated by its central effector, β-Catenin. The transcription activity of β-Catenin is generally regulated by canonical Wnt proteins (Wnt1, Wnt2, Wnt3, Wnt3a, Wnt8b, Wnt10a, and Wnt10b) [139, 140]. In the "WNT ON state" (Wnt ligands exit), the formation of the destruction complex (composed by AXIN, CK1α, GSK3β, and APC, which phosphorylates β-catenin) is inhibited, leading to the nuclear translocation of β-catenin. Conversely, in the "WNT OFF state" (in the absence of Wnt ligands), the destruction complex facilitates the ubiquitin-proteasomal degradation of β-Catenin [141].

Recent literature has demonstrated that aberrant activation of Wnt signaling is observed in PF, along with persistent expression of the β-Catenin-dependent gene. Notably, nuclear accumulation of β-Catenin has been found to increase proliferative epithelial lesions and fibroblastic foci in the lungs of patients with PF [142]. Additionally, the expression of Wnt1, Wnt7b, and Wnt10b was significantly elevated in PF [143]. Furthermore, various studies have shown that Wnt signaling can regulate tissue remodeling by MMPs and vascular endothelial growth factor (VEGF) [144, 145]. Overall, it is evident that Wnt signaling plays a crucial role in the development of PF.

PI3K-Akt Signaling

Recent studies have shown that the PI3K/Akt signaling pathway serves as a master regulator in PF by influencing cell growth, differentiation, apoptosis, and angiogenesis [146, 147]. PI3K functions as a lipid kinase and is classified into three classes based on its molecular structure [148]. Among these, Class I PI3K is the most extensively studied in various diseases [149]. Following the activation of receptor tyrosine kinases, PI3K translocates from the cytoplasm to the plasma membrane. This translocation activates its catalytic subunit (p110α) and promotes the phosphorylation of phosphoinositides, leading to the formation of a complex consisting of PI3,4-bisphosphate and PI3,4,5-trisphosphate that binds to the pleckstrin-homology domain of Akt [150]. Moreover, serine 473 and threonine 308 residues of Akt are phosphorylated by pyruvate dehydrogenase kinase 1 (PDK1) and pyruvate dehydrogenase kinase 2 (PDK2), respectively, resulting in the activation of downstream signaling molecules. Key downstream targets of the PI3K/Akt signaling pathway implicated in fibrotic diseases include mTOR, Hif-1α, GSK-3, Forkhead box proteins O (FoxOs, such as FoxO3), and nitric oxide synthase (NOS) [151].

Evidence suggests that the activation of the PI3K/Akt signaling pathway is linked to fibroblast activation, epithelial cell damage, and macrophage polarization. For instance, the PI3K-Akt-mTOR/PFKFB3 pathway has been shown to regulate fibroblast glycolysis and collagen synthesis in LPS-induced PF [152]. Lu et al. demonstrated that BLM can induce lung fibroblast activation by upregulating collagen expression and enhancing cell proliferation through the PI3K/Akt pathway [153]. Besides, increased levels of PI3K have been observed in silica-induced lung fibrosis tissues and epithelial cells; the knockdown of PI3K has been shown to reduce the EMT process and attenuate PF [154]. Furthermore, enhanced PI3K/Akt signaling may worsen PF progression by promoting the M2 polarization of macrophages [155].In

conclusion, PI3K/Akt signaling plays a significant role in the development of PF.

Hippo-YAP Signaling

The Hippo signaling pathway is a critical and evolutionarily conserved regulator of organismal homeostasis, consisting of a three-step cascade involving mammalian sterile 20-like kinases 1 and 2 (MST1/2, also known as STK4/3), Salvador (SAV1), large tumor suppressor 1 and 2 (LATS1/2), MOB kinase activators 1 A and 1B (MOB1a/b), and Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ, also known as WWTR1) [156, 157]. It is well established that the Hippo signaling pathway regulates cellular proliferation, differentiation, and survival through its downstream effector YAP [158, 159]. Mechanistically, YAP interacts with transcription factors such as TEAD1–4 to modulate the expression of fibrotic genes [160].

In the context of PF pathogenesis, the Hippo-YAP signaling pathway plays a multifaceted role by targeting various effector cell types. Liu et al. demonstrated that the Hippo pathway is activated in fibrotic lung tissue. Inhibition of YAP and TAZ was shown to attenuate PF by suppressing collagen synthesis and lung fibroblast proliferation [161]. Furthermore, the downregulation of the Hippo signaling pathway inhibited the expression of Collagen I and Fibronectin in fibroblasts induced by TGF-β1 [162]. It is noteworthy that the Hippo/YAP signaling pathway is involved in normal alveolar development and repair processes. Activated YAP in airway basal cells can lead to hyperplasia and impair terminal differentiation [163]. Additionally, nuclear transcription of YAP is essential for airway epithelial cells to respond effectively to TGF-β. The deletion of TAZ in mouse AEC2 cells resulted in a decrease in AEC1 cell differentiation following BLM-induced lung injury [164]. Therefore, selective activation of the Hippo/YAP pathway in AEC2 cells may promote alveolar regeneration and facilitate tissue repair in PF.

TGF-β, Wnt, PI3K-Akt, and Hippo-YAP pathways drive PF through fibroblast activation, ECM remodeling, and epithelial dysfunction, yet key challenges persist. TGF-β1's dual Smad/non-Smad signaling and SKI's regulatory duality offer therapeutic potential but face hurdles due to TGF-β's pleiotropy. Wnt/β-catenin activation in fibrosis is well-documented, yet the conflicting roles of Wnt isoforms (e.g., Wnt7b vs. Wnt10b) and unclear cell-specific effects limit targeted interventions. PI3K-Akt's broad influence on fibroblast metabolism and macrophage polarization raises off-target risks. Besides, studies often neglect pathway crosstalk (e.g., Wnt-YAP/β-catenin interplay) and spatial dynamics. Finally, using specific inhibitors targeting these signaling pathways may be the potential strategy for the treatment of PF.

Table 1 Comparison of Annual Costs for PF Medications in Europe vs. US

Treatment Type	European Cost (Annual Range)	US Cost (Annual Range)
Traditional Approaches	Healthcare cost in Germany: $3210.84 (€2973)[166]	Inpatient supportive care: $21,732[167]
Pirfenidone	UK: $ 77,227.66 (£59,121.16)[6]	US:113,193[5]
Nintedanib	Beligium: $ 110500.20 (€102315)[168]	US:112,357[5]

Abbreviations: UK, United Kingdom; US, United States

Therapeutic approaches

Traditional approaches to managing PF encompass a range of interventions, including oxygen therapy, pulmonary rehabilitation, symptom management with medications, lifestyle modifications, and eventual lung transplantation [165]. However, as shown in Table 1, there is a significant cost disparity between these conventional therapies and newer-generation agents like pirfenidone and nintedanib, particularly in Europe and the US. This economic consideration highlights the need for cost-effective yet efficacious treatment options.

To better evaluate current therapeutic strategies, Table 2 provides an infographic summarizing the recommended treatments based on guidelines from leading scientific societies (mainly from the ATS/ERS/JRS/ALAT 2011 guideline) [169]. This comparative analysis helps identify evidence-based approaches while underscoring the ongoing demand for novel, affordable anti-fibrotic therapies.

Pharmacological treatment

Current Anti-fibrotic drugs

Current drug therapies for PF include synthetic compounds, natural compounds, and antibody-based treatments. Despite only two drugs having received regulatory approval for PF treatment to date, numerous investigational compounds and antibodies have advanced to clinical trials (Table 3). The following sections will provide a detailed overview of these therapeutic candidates.

Targeting signaling pathways

Current evidence spans the therapeutic agents from preclinical validation to clinical trial evaluation across different signaling pathways (including TGF-β, Wnt, PI3K-Akt, and Hippo-YAP signaling) for PF treatment. There are several effective strategies for inhibiting TGF-β. Preclinical approaches include blocking TGF-β synthesis using antisense oligonucleotides, targeting TGF-β ligands with proteoglycans or soluble TGF-β receptors, inhibiting TGF-β receptors through ALK5 inhibitors, and preventing the activation of latent TGF-β using neutralizing antibodies or small molecule inhibitors [117]. Notably, increased SKI expression effectively

Table 2 Summary of available therapies for PF based on scientific society guidelines

Line of Treatment	Therapy	Mechanism of Action	Route of Administration	Key Recommendations (ATS/ERS/JRS/ALAT)
First-line	Pirfenidone	Antifibrotic; anti-inflammatory; modulates growth factors (TGF-β, PDGF); inhibits fibroblast proliferation and collagen synthesis, and antioxidant.	Oral	Conditional recommendation for use in PF. Recommended if lung capacity is 50–80% expected.
	Nintedanib	Tyrosine kinase inhibitor targeting PDGF, FGF, and VEGF receptors; inhibits fibroblast proliferation, migration, and differentiation.	Oral	Conditional recommendation for use in PF. Recommended if lung capacity is 50–80% expected.
Supportive care (Throughout)	Oxygen therapy	Supplemental oxygen to alleviate hypoxemia.	Inhalation	Recommended for patients with hypoxemia to improve breathing, exercise tolerance, and potentially reduce complications.
	Pulmonary rehabilitation	Exercise training; breathing techniques; education; nutritional and psychological support.	Program-based	Strongly recommended to improve exercise capacity, reduce breathlessness, and enhance overall well-being.
	Vaccinations (influenza, pneumococcal)	Prevention of respiratory infections.	Injection	Recommended to prevent exacerbations.
	Smoking cessation	Eliminating a major risk factor for lung disease.	Behavioral/Pharmacological	Strongly recommended for current smokers.
	Nutritional support & lifestyle	Maintaining a healthy diet; regular exercise within tolerance, and adequate rest.	Lifestyle modifications	Advised for managing symptoms and maintaining overall health.
Later-Stage/Severe Disease	Lung transplantation	Surgical replacement of diseased lungs with healthy donor lungs.	Surgical	Potential option for selected patients with severe and progressive PF who meet specific criteria. Early referral for evaluation is recommended.
Management of acute exacerbations	Corticosteroids	Anti-inflammatory.	Oral/Intravenous	Recommended for treating acute worsening of symptoms.

Abbreviations: AST, American Thoracic Society; ERS, European Respiratory Society; JRS, Japanese Respiratory Society; ALAT, Latin American Thoracic Association

blocked BLM-induced TGF-β1 signaling activation and exerted an anti-fibrotic action in PF [187], suggesting that SKI modulation could serve as a novel therapeutic strategy for PF treatment. In line with this finding, apigenin suppresses TGF-β1 signaling by downregulating the Ski protein complex expression, which subsequently decreases both total and phosphorylated Smad2/3 levels (p-Smad2/3) [188]. As a result, this mechanism effectively inhibits fibroblast-to-myofibroblast differentiation and reduces ECM deposition. Additionally, the use of antagonists, small interfering RNA, and transcription inhibitors has proven effective in inhibiting Wnt signaling in fibrotic diseases [136, 189]. For the PI3K signaling pathway, targeted inhibitors such as Omipalisib and Rapamycin have been evaluated in clinical trials for PF treatment [172, 190]. In the context of the Hippo-YAP pathway, G-protein-coupled receptor (GPCR) signaling plays a significant role and serves as a promising therapeutic target [191]. Consequently, drugs directed at GPCRs may be utilized for the pharmacological targeting of Hippo-YAP signaling.

Targeting inflammation

Targeted anti-inflammatory therapies have emerged as a promising adjunctive strategy in the treatment of PF, focusing on modulating specific inflammatory mediators and immune pathways that contribute to disease progression. While the role of inflammation in PF has been debated historically, recent evidence has clarified that inflammation plays a significant role in the disease, particularly in the context of acute exacerbations and certain disease subtypes [192]. Key inflammatory mediators, such as cytokines (e.g., IL-13, IL-6), chemokines (e.g., CCL2), and growth factors like TGF-β, have been identified as critical drivers of fibroblast activation and extracellular matrix deposition, making them promising therapeutic targets [193]. Furthermore, recent studies have shown that blocking members of the tumor necrosis factor (TNF) superfamily, such as LIGHT (TNFSF14) and TL1A (TNFSF15), can significantly reverse fibrosis in preclinical models, further supporting the idea of targeting specific inflammatory drivers in PF therapy [194]. However, attempts to broadly suppress inflammation with corticosteroids and immunosuppressants have often been ineffective or even detrimental, underscoring

Table 3 Emerging Anti-Pulmonary fibrosis drugs in clinical development

Drug classification	Agents	Mechanism	The phase of development status	Refs.
synthetic compounds	Pirfenidone	Antifibrotic; anti-inflammatory; modulates growth factors (TGF-β, PDGF); inhibits fibroblast proliferation and collagen synthesis, and antioxidant	Phase III	[170]
	Nintedanib	Tyrosine kinase inhibitor targeting PDGF, FGF, and VEGF receptors; inhibits fibroblast proliferation, migration, and differentiation.	Phase III	[171]
	Omipalisib	PI3K/mammalian target of rapamycin (mTOR) inhibitor; inhibit PI3K signaling; inhibit Akt phosphorylation.	Phase I	[172]
	GSK3008348	Small molecule αvβ6 integrin inhibitor; selective and high affinity binding to the αvβ6 integrin; inhibit TGFβ activation	Phase I	[173]
	GLPG1690	First-in-class ATX inhibitor; suppression of LPA-driven fibrosis; attenuate collagen deposition	Phase II	[174]
	PBI-4050	Inhibit the differentiation of fibroblasts to myofibroblasts; antagonist ligand affinity towards the G-protein coupled receptors GPR40 and GPR84.	Phase II	[175]
	TD139	Small-molecule Galectin-3 inhibitor; selectively binds to the carbohydrate recognition domain (CRD) of Galectin-3.	Phase II	[176]
natural compounds	Curcumin	Inhibit the TGF-β, NF-κB, mitogen-activated protein kinase, TLRs, and PPARγ/PDGFβ signaling pathway; inhibit fibroblast proliferation.	preclinical	[177]
	Resveratrol	Anti-oxidation, antibacterial, anti-inflammatory, growth inhibitory, anti-platelet aggregation, pro-apoptotic.	preclinical	[178]
	Baicalin	Inhibit the NLRP3 inflammasome and TLR4/JNK/ERK/NF-κB pathway; anti-inflammatory, antimicrobia.	preclinical	[179]
	Quercetin	Inhibition of TGF-β/Smad Signaling; anti-Inflammatory; regulation of autophagy & senescence.	Phase I	[180]
	Salvianolic acid B	Relieve peroxide-stress injury; regulate TNF-α and other inflammatory cytokines and fibrosis-related cytokines.	preclinical	[181]
	Celastrol	Suppression of TGF-β/Smad signaling; inhibition of NF-κB and NLRP3 Inflammasome, antioxidant.	preclinical	[182]
Antibodies	Tocilizumab	Blockade of IL-6 signaling; anti-inflammatory effects; inhibition of fibroblast activation.	Phase III	[183]
	Pamrevlumab	Inhibition of CTGF Activity; reduction of ECM accumulation; anti-inflammatory.	Phase II	[184]
	Simtuzumab	Inhibition of LOXL2-mediated ECM crosslinking; suppression of fibroblast activation and TGF-β signaling	Phase II	[185]
	Tralokinumab	Blockade of IL-13 signaling; suppression of fibroblast activation and differentiation	Phase II	[186]

the need for more precise, mechanism-based approaches [195, 196]. Despite the promising preclinical results, the clinical application of combination therapies that integrate both anti-inflammatory and anti-fibrotic strategies faces challenges related to patient selection, the risk of side effects, and the need for sustained, targeted immune modulation [197]. Nonetheless, the growing body of research and these promising findings provide a solid foundation for the future development of personalized, inflammation-targeted treatments for PF.

Drug delivery strategies

In the past decade, various drug delivery strategies and systems have been explored for the treatment of PF to minimize side effects (Fig. 4). Effective targeted delivery routes and technologies should possess several desirable characteristics, including reduced side effects, appropriate biodegradability, high bioavailability, and optimal drug efficacy [198]. Consequently, there has been a growing interest in the development of therapeutic approaches utilizing pulmonary drug delivery systems.

Nanoparticle delivery system

Currently, conventional drug delivery approaches, such as oral administration, intravenous injection, nasal delivery, inhalation, and intratracheal administration, face significant limitations. Notably, certain routes (e.g., oral delivery) subject drugs to hepatic first-pass metabolism, reducing systemic bioavailability and impairing their therapeutic potential upon reaching target tissues like the lungs [199, 200]. To address these challenges, nanotechnology-based delivery systems have emerged as a transformative solution. By encapsulating therapeutics within engineered nanomaterials, these platforms significantly enhance drug stability, bioavailability, and targeted accumulation at disease sites [201, 202]. Among the most promising nanocarriers are liposomes, polymer-based nanoparticles, and mesoporous silica nanoparticles, each offering unique advantages for controlled release, tissue-specific targeting, and improved therapeutic outcomes in pulmonary and systemic diseases [203, 204]. The following describes various nanomaterial-based delivery approaches.

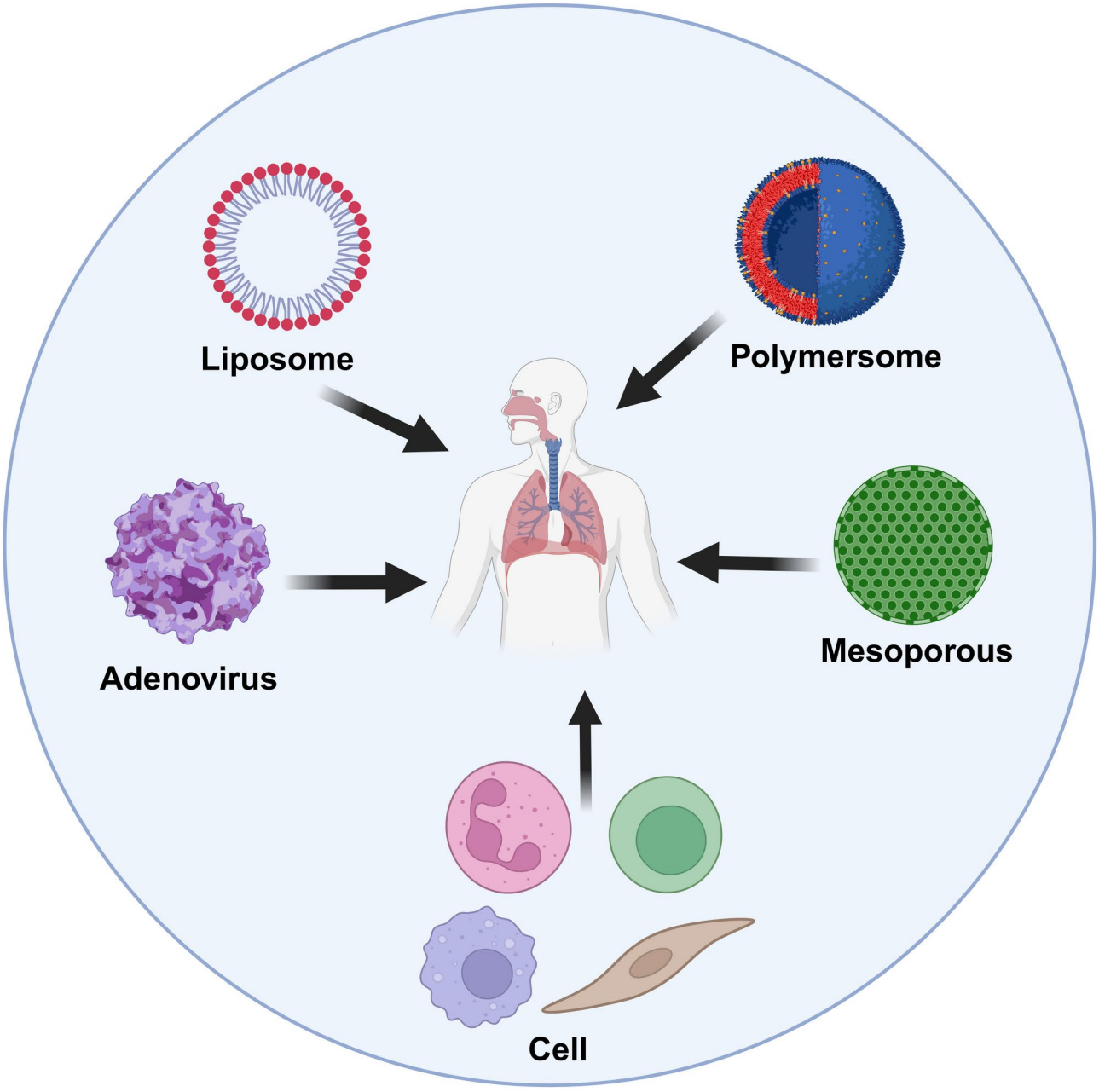

Fig. 4 Drug delivery strategies for PF treatment. Drug delivery strategies of various therapeutic modalities (including nanoparticle delivery system, cell-mediated delivery system, and adeno-associated virus vectors-mediated delivery system) for the treatment of PF. Image Created in https://BioRender.com

Liposomal Nanoparticles Delivery

Lipid nanoparticles are submicron capsules characterized by a homogeneous lipid core that is surrounded and stabilized by lipid layers [205, 206]. In recent years, they have emerged as a promising platform for drug delivery, with various liposomal formulations being utilized in a wide range of pharmaceutical applications [207, 208]. Notably, liposomes exhibit favorable properties, including reasonable biodegradability, excellent biocompatibility, and high encapsulation efficiency [209]. These nanoparticles can serve as effective delivery vehicles for oligonucleotides, peptides, and siRNA in the treatment of various diseases. In 2018, the U.S. FDA approved the first siRNA drug formulated with liposomes. Previous studies have shown that siRNA-loaded liposomes represent a promising strategy for siRNA-based therapy targeting PF [210, 211]. Furthermore, liposomes co-decorated with collagen-binding peptides and collagenase have the potential to specifically target fibrotic lung tissues and help restore normal lung architecture [212]. Thus, lipid nanoparticles have emerged as one of the most

prominent nanocarriers, particularly important for the delivery of peptides and siRNAs.

Polymeric Nanoparticles Delivery

Polymeric nanoparticles are colloidal and offer enhanced drug loading efficiency and improved drug solubility [213]. These nanoparticles can either chemically conjugate active compounds or adsorb them onto their surface, functioning as either a reservoir (by dissolving or dispersing the actives) or a matrix (by entrapping the actives) [214]. However, several challenges must be addressed for effective pulmonary delivery of polymeric nanoparticles, including particle characteristics (such as size, shape, and surface charge), mucociliary clearance, and cellular internalization [215, 216]. A recent study conducted by Lee et al. utilized inhaled tacrolimus-loaded chitosan-coated poly nanoparticles in a mouse model of BLM-induced PF [217]. The surface modification of PLGA nanoparticles with chitosan offers several pharmaceutical advantages, including reduced burst effects of drug release and improved tissue retention and permeation. Another study demonstrated that GSE4-loaded PLGA nanoparticles could serve as a potential therapy for BLM-induced fibrosis by enhancing telomerase activity and reducing cell apoptosis and DNA damage [218]. These findings indicate that polymeric nanoparticles represent a promising strategy for the treatment of PF.

Mesoporous Silica nanoparticles Delivery

Mesoporous silica nanoparticles, characterized by their amorphous structure and lack of distinct geometric shape, are primarily composed of silicon dioxide. These nanoparticles are widely utilized in various applications, particularly in drug delivery, due to their exceptional biocompatibility, large surface area, and tunable particle size [219]. The use of mesoporous silica nanoparticles in drug delivery systems offers enhanced stability and presents a promising alternative to traditional delivery mechanisms [220]. Typically, the particle size and surface modifications of mesoporous silica nanoparticles play critical roles in influencing cellular uptake and therapeutic efficacy during targeted drug delivery processes [221, 222]. For instance, a nanosystem composed of Janus Au/mesoporous silica core/shell nanoparticles is designed for effective therapeutic and real-time tracing of pirfenidone in PF therapy [223]. Additionally, the intelligent nanodrug based on dendritic mesoporous silica nanoparticles loaded with the sonosensitizer protoporphyrin IX (PpIX) demonstrated significant anti-pulmonary fibrosis efficacy [224]. These findings underscore the significant potential of mesoporous silica nanoparticles in advancing biomedical sciences, particularly in the development of targeted drug delivery systems for PF treatment.

Cell-mediated delivery system

Recently, cell-mediated drug-delivery targeting systems have emerged as a significant area of research due to their therapeutic specificity in addressing various diseases [225]. These systems leverage the natural circulation of blood and the presence of surface ligands, which enhance therapeutic efficacy while minimizing side effects [226]. In the context of PF treatment, various types of cells can serve as effective drug carriers. By utilizing the unique properties of these cells, researchers aim to improve the precision of drug delivery, ensuring that therapeutic agents are effectively transported to the targeted sites of action. This approach not only holds promise for enhancing treatment outcomes but also for reducing the systemic exposure and associated adverse effects commonly seen with conventional drug delivery methods.

Macrophages-mediated Delivery

Macrophages, which are natural immune cells and antigen-presenting cells within the leukocyte lineage, originate from monocytes and play crucial roles as regulators of the innate immune system [227, 228]. They are integral to various biological processes, including responses to pathogens, the resolution of inflammation, and tissue repair [229]. Due to their long circulation time in the bloodstream and their ability to phagocytose foreign particles [230], macrophages present a promising platform for drug delivery systems aimed at treating diseases. Recent studies have demonstrated the use of macrophages to deliver dexamethasone, enhancing the therapeutic outcomes for PF by modulating the immune microenvironment [231]. In summary, macrophages represent a viable and effective vehicle for drug delivery, offering significant potential for improving therapeutic strategies in various diseases.

Neutrophil-mediated Delivery

Neutrophils are vital effector cells of the immune system and serve as the first line of defense against pathogens during inflammation and immune responses [232, 233]. They play a significant role in various chronic respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), and PF. In the progression of these diseases, neutrophils can undergo profound infiltration and activation, triggering a cascade of inflammatory responses and cytokine release that ultimately leads to tissue remodeling and damage [234]. Similar to other immune cells, neutrophils possess the capability to facilitate targeted drug delivery. For instance, therapeutic nanoparticles combined with denatured bovine serum albumin (BSA) can be internalized by activated neutrophils, allowing them to migrate across blood vessels and deliver the therapeutic agents to inflamed tissues [235]. While neutrophil-mediated drug delivery has shown promise in targeting inflammatory diseases, current literature reveals no reported studies specifically investigating

this approach for PF treatment. Given neutrophils' natural tropism for fibrotic lesions and their demonstrated utility as drug carriers in other pathological contexts, this represents an unexplored therapeutic opportunity. Future research should evaluate: (1) neutrophil-hitchhiking strategies for antifibrotic agents (e.g., pirfenidone, nintedanib), (2) biomimetic neutrophil-membrane-coated nanoparticles for lung targeting, and (3) combination approaches leveraging neutrophils' innate immune functions with precision drug delivery.

Stem Cell-mediated Delivery

Stem cells possess the unique ability to self-renew and differentiate into various specialized cell types [236]. Traditionally, stem cells are classified into two main categories based on their origin and plasticity: embryonic stem cells and somatic stem cells [237]. Recent research indicates that stem cells can produce a range of bioactive factors, including cytokines, chemokines, and antioxidant molecules, as well as angiogenic and antifibrotic agents during tissue repair processes [238–240]. Given these capabilities, stem cells represent a promising strategy for targeted drug delivery. For instance, Lata G. Menon et al. demonstrated the use of human bone marrow-derived mesenchymal stromal cells (hMSCs) as cellular vehicles for delivering tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to glioma tumors [241]. Additionally, the administration of hMSCs engineered to produce interferon-beta (IFN-β) has been shown to inhibit the growth of pulmonary metastases through the systemic release of IFN-β at cancer sites [242]. In conclusion, stem cells may serve as a valuable platform for the targeted delivery of therapeutic agents, offering significant potential for enhancing treatment outcomes in various diseases.

Fibroblast-mediated Delivery

Targeting fibroblast and drug delivery has emerged as a promising therapeutic strategy against PF. For example, Sun et al. developed the clodronate-loaded liposomal and fibroblast-derived exosomal hybrid system as an available drug delivery strategy for PF treatment [243]. Also, researchers have engineered a core-shell microneedle platform for stable fibroblast delivery, featuring a cell-encapsulating gelatin methacryloyl hydrogel core surrounded by a protective polylactic-co-glycolic acid (PLGA) sheath. This minimally invasive design combines cellular viability preservation with structural robustness, providing a clinically adaptable solution for targeted fibroblast delivery [244]. Another promising strategy involves fibroblast-targeting dual siRNA-loaded micelles (including siPTPN13 and siNOX4), which offers a potential strategy with promising prospects in PF therapy [245]. Given the pivotal role of activated fibroblasts in pulmonary fibrogenesis, there is an urgent need to develop more targeted drug delivery strategies to effectively intervene in disease progression.

Adeno-associated Vectors-mediated delivery system

Gene therapy for PF has garnered attention with the advancement of viral vector technologies, particularly adeno-associated viruses (AAVs) and adenoviral vectors (AdVs). AAVs, such as AAV9 and AAV1, are favored due to their ability to target specific lung cells, including alveolar epithelial cells, fibroblasts, and endothelial cells, which are involved in the disease's pathogenesis. AAVs are known for their low immunogenicity, which enables long-term gene expression and sustained therapeutic effects in chronic diseases like PF. Preclinical studies have shown that AAV9, used to overexpress sphingosine-1-phosphate lyase (SGPL1), reduces lung fibrosis by modulating pro-fibrotic pathways like TGF-β [246]. Additionally, AAV2/9-mediated delivery of LIM domain-only protein 7 (Lmo7) shRNA significantly ameliorated the progression of BLM-induced PF [247]. In contrast, AdVs offer high transduction efficiency and the ability to deliver larger genes but are limited by high immunogenicity, leading to transient expression and inflammation. New-generation adenoviral vectors, such as helper-dependent adenoviral vectors (HDAds), have been engineered to reduce immune responses and improve transgene persistence, showing promise in targeting key pathways like TGF-β signaling [248]. Despite these advancements, challenges such as efficient vector delivery, sustained expression, and overcoming immune responses remain. Moreover, no clinical trials have been published yet for AAVs or new-generation AdVs in PF treatment. Nonetheless, preclinical successes and the application of AAVs in other lung diseases, such as cystic fibrosis, provide a strong foundation for future clinical trials.

Conclusion and future perspective

While the understanding of its pathophysiology and potential therapeutic options have advanced in recent years, there remains no effective intervention to halt or cure PF. A variety of risk factors, including air pollution, smoking, aging, occupational exposure, environmental pollutants exposure, and microbial infections contribute to the progression of PF. Currently, only two drugs, pirfenidone and nintedanib, have been approved by the FDA for the treatment of PF. However, numerous other pharmacological agents targeting different aberrant signaling pathways are under development in clinical trials. Furthermore, the challenges posed by the low solubility and poor specificity of fibrosis-related therapeutic agents necessitate the creation of reliable delivery systems to enhance their efficacy. In summary, the current landscape of PF treatment highlights the urgent need for

further research into the underlying pathogenic mechanisms, the identification of novel therapeutic targets, and the development of effective delivery systems for anti-fibrotic drugs.

Abbreviations

ARDS	Acute respiratory distress syndrome
AAVs	Adeno-associated viruses
AdVs	Adenoviral vectors
Ams	Alveolar macrophages
AST	American Thoracic Society
Arg-1	Arginase 1
α-SMA	αsmooth muscle actin
BaP	Benzo[a]pyrene
BLM	Bleomycin
BSA	Bovine serum albumin
COPD	Chronic obstructive pulmonary disease
M1 macrophage	Classically activated macrophages
CMV	Cytomegalovirus
EndoMT	Endothelial-to-mesenchymal transition
EMT	Epithelial-mesenchymal transition
EBV	Epstein–Barr virus
ERS	European Respiratory Society
ECM	Extracellular matrix
FPF	Familial pulmonary fibrosis
FMT	Fibroblast-to-myofibroblast transition
FoxOs	Forkhead box proteins O
FDA	Food and Drug Administration
GPCR	G-protein-coupled receptor
GWAS	Genome-wide association studies
HDAds	Helper-dependent adenoviral vectors
HIV	Human immunodeficiency virus
HTLV	Human T-cell leukemia virus
Ims	Interstitial macrophages
IFN-β	Interferon-beta
iNOS	Inducible nitric oxide synthase
JRS	Japanese Respiratory Society
ALAT	Latin American Thoracic Association
Lmo7	LIM domain-only protein 7
MST1/2	Mammalian sterile 20-like kinases 1 and 2
MMPs	Matrix metalloproteinases
MOB1a/b	MOB kinase activators 1 A and 1B
NOX4	NADPH oxidase 4
NO	Nitrogen oxides
PM	Particularly particulate matter
PI3K	Phosphoinositol-3 kinase
PDGF	Platelet-derived growth factor
Pdgfrα	Platelet-derived growth factor receptor alpha polypeptide
Pdgfrβ	Platelet-derived growth factor receptor, beta polypeptide
PLGA	Polylactic-co-glycolic acid
PS-NPs/PS-MPs	Polystyrene nano- and microplastics
PpIX	Protoporphyrin IX
PF	Pulmonary fibrosis
PMVECs	Pulmonary microvascular endothelial cells
PDK1	Pyruvate dehydrogenase kinase 1
PDK2	Pyruvate dehydrogenase kinase 2
ROS	Reactive oxygen species
SAV1	Salvador 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SGPL1	Sphingosine-1-phosphate lyase
SMCs	Smooth muscle cells
SKI	Sloan-Kettering virus
TGF-β1	Transforming growth factor-beta 1
TAZ	Transcriptional co-activator with PDZ-binding motif
AEC1	Tumor necrosis factor (TNF), Type-1 alveolar epithelial
AEC2	Type-2 alveolar epithelial
VE-cadherin	Vascular endothelial cadherin
VEGF	Vascular endothelial growth factor
YAP	Yes-associated protein
EZH2	Zeste homolog 2

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Declarations

Competing interests
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