Targeting alveolar type II cell dysfunction in idiopathic pulmonary fibrosis: Molecular mechanisms and emerging therapeutic strategies (Review)

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a fatal and progressive form of interstitial lung pathology. It is characterized by the relentless replacement of functional alveolar epithelium by aberrant fibroblasts and excessive extracellular matrix deposition, resulting in respiratory failure. Currently, the treatment options for this disease are limited. Approved antifibrotic agents primarily slow disease progression by inhibiting fibroblast proliferation and downstream fibrotic pathways; however, they do not halt or reverse the underlying pathology. Recent studies have elucidated the proliferation and differentiation characteristics of type II alveolar epithelial (AT2) cells, identifying them as facultative stem cells of the distal lung with significant therapeutic potential in IPF. However, there are certain limitations in clinical translation. This review comprehensively summarizes the regulatory pathways governing AT2 proliferation and differentiation, and investigates key pathogenic drivers of IPF, including cellular senescence and mechanical tension. Furthermore, it evaluates current treatment strategies and methods to facilitate safer, more effective clinical delay or even reversal of pulmonary fibrosis by identifying or improving existing therapies.

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Abbreviations: α-SMA, α-smooth muscle actin; AT1, type I alveolar epithelial cells; BASCs, bronchoalveolar stem cells; BLM, bleomycin; BMP, bone morphogenetic protein; D, Dasatinib; Dlk1, Delta like non-canonical Notch ligand 1; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; H_2S, hydrogen sulfide; IAAPs, injury-activated alveolar progenitor cells; ILDs, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; MDM2, murine double minute 2; PFD, pirfenidone; Q, quercetin; SASP, senescence-associated secretory phenotype; SCAP, senescent cell anti-apoptotic pathways; SnCs, senescent cells; SP, surfactant protein; TGF-β, transforming growth factor β; Tom^{High}, high tdTomato level; Tom^{Low}, low tdTomato level

Key words: type II alveolar epithelial cells, cell senescence, epithelial-mesenchymal transition, idiopathic pulmonary fibrosis, mechanical tension

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1. Introduction

Diffuse parenchymal lung disorders, clinically categorized as interstitial lung diseases (ILDs) or idiopathic interstitial pneumonias, represent a heterogeneous spectrum of age-associated pulmonary conditions (1). The interstitial space is typically the site of inflammation or fibrosis in the majority of ILDs, resulting in dyspnea, reduced exercise tolerance and a diminished quality of life by impairing gas exchange (2). Idiopathic pulmonary fibrosis (IPF), the most prevalent severe fibrotic ILD, has a poor prognosis with a median survival of 3-5 years post-diagnosis (1,3). The global prevalence of IPF was estimated to range from 0.33 to 4.51 per 10,000 individuals by 2021, indicating an upward trend (4,5).

IPF is characterized by altered lung parenchymal cellular composition, dysfunctional resident and immune cells, patchy

dense fibrosis and frequent honeycomb cyst formation (6). Epidemiological studies have suggested that the primary risk factors for IPF include aging, long-term environmental stimulation and genetic susceptibility (3,7). These factors cause repetitive micro-injuries that induce chronic inflammation, resulting in the activation and depletion of alveolar epithelial cells. These cells secrete multiple profibrotic growth factors, cytokines and coagulants, thereby stimulating the proliferating fibroblasts and myofibroblasts in the lung parenchyma to produce collagen in active areas of fibrosis known as fibroblastic foci. These areas are characterized by excessive accumulation of extracellular matrix (ECM) (8). Therefore, the primary objective of IPF therapy is to effectively inhibit fibroblast activation and proliferation pathways while restoring normal alveolar epithelial physiology and repair function.

The alveolar epithelium includes alveolar type I (AT1) and type II (AT2) cells. AT1 facilitates gas exchange and ion transport, while AT2 acts as the primary progenitor stem cell, secreting surfactant, maintaining fluid balance, regulating immune responses and supporting lung homeostasis, repair and regeneration, and plays a pivotal role in pulmonary fibrosis (9). Currently, the primary approach is to use drugs, including pirfenidone (PFD) and nintedanib, to exert anti-inflammatory effects and block the activation and proliferation of certain profibrotic factors and fibroblasts, thereby slowing the epithelial-mesenchymal transition (EMT) process (10,11). However, neither PFD nor nintedanib can completely inhibit or reverse fibrosis. This review aims to provide a comprehensive conceptual framework for IPF pathogenesis centered on AT2 dysfunction. It was explored how initial stimuli, including endoplasmic reticulum (ER) stress and metabolic dysfunction, drive AT2 cellular senescence. The study further delineated how senescent AT2 cells orchestrate a profibrotic microenvironment through senescence-associated secretory phenotypes (SASP) and EMT signaling. Finally, it was discussed how the resulting ECM deposition generates pathological mechanical tension, creating a feed-forward loop that further impairs AT2 regenerative capacity. The theoretical basis and feasibility of current and emerging therapeutic strategies was investigated by integrating these interconnected mechanisms, thereby providing new insights into safe and efficient reversal of pulmonary fibrosis.

2. Regeneration and differentiation of AT2 cells

AT2 cells are cuboidal, polarized, multifunctional epithelial cells of endodermal origin that function as the primary endogenous facultative progenitor cells in the distal adult mammalian lung (12-14). In homeostasis, the lung epithelium is inactive, with AT2 cells maintaining physiological functions including surfactant secretion, sodium/fluid transport and immune regulation (9,15). The potential of AT2 stem cells to regenerate and repair lung tissue is activated in response to injury caused by specific physicochemical stimuli (15,16). The function and differentiation capacity of AT2 vary among subpopulations and are influenced by injury factors and ECM modifications (17).

AT2 cells exhibit diverse origins, differentiation pathways and robust self-renewal capacity. Recent single-cell RNA sequencing and lineage tracing studies in murine models suggest that self-renewal and transformation of bronchoalveolar stem cells (BASCs) and club cells are the primary modes of AT2 regeneration. The dominant regeneration mode varies under different environments and stimuli (18). Under steady-state conditions and in injury induced by physical factors, including pneumonectomy, the regeneration of AT2 cells primarily depends on self-renewal, while in the bleomycin (BLM)-induced injury model, club cells and BASC regeneration are the primary sources of AT2 (18,19). These lineage-tracing experiments robustly define progenitor hierarchies in mice; however, translating these pathways directly to human pathology requires additional research. Human single-cell transcriptomic data from IPF lung tissue indicates a significant increase in basal cells, goblet cells, ciliated cells and club cells, as well as a significant decrease in AT1 and AT2 cells compared to healthy controls (20). However, whether these expanded bronchiolar lineages in humans effectively transdifferentiate into functional AT2 cells *in vivo* to repair the alveoli, or merely contribute to dysplastic bronchiolization in the fibrotic niche, remains a critical unresolved difference between the murine BLM model and human IPF.

The heterogeneity of AT2 cells has been independently characterized in both human patients with IPF and murine injury models; however, species-specific mapping remains complex. In humans, single-cell RNA sequencing by Yang *et al* (21) classified AT2 cells from IPF lungs into 11 putative subpopulations using repeated t-distributed stochastic neighbor embedding analysis. Conversely, in experimental murine models, dynamic AT2 states are typically defined using stem cell surface markers [cluster of differentiation 44 (CD44)] or genetic lineage tracing (15,22-26). By permanently labeling the surfactant protein-C (SP-C) with fluorescent probes (tdTomato), AT2 cells of mice can be divided into two subpopulations: Low tdTomato level (Tom^{Low}) and high tdTomato level (Tom^{High}) (23,24). Tom^{High} AT2s comprise ~80% of lineage-traced AT2s. This subpopulation comprises mature AT2s, which can highly express AT2 differentiation markers [SP-C, SP-B, SP-A, fibroblast growth factor (FGF) receptor 2b and ETS variant transcription factor 5], achieve self-renewal and secrete SP to maintain the physiological function of the alveolar epithelium under steady-state conditions (23). Tom^{Low} AT2s, also known as injury-activated alveolar progenitor cells (IAAPs), are immature AT2s that are activated only in response to injury (24,25). This subpopulation highly expresses the programmed cell death 1 ligand 1, the immunomodulator CD300LF and the adhesion protein CD33. IAAPs rapidly expand to replenish depleted Tom^{High} AT2s after injury, gaining self-renewal and differentiation capacity (24,27). Therefore, Tom^{Low} AT2s are considered a specialized subpopulation primed for post-injury tissue repair. Additionally, ~3% of AT2 cells express high CD44, preferentially localize near capillaries and exhibit upregulated transcription/proliferation, enhanced AT1 differentiation and superior alveolosphere-forming capacity (26). The clinical data support a significant exhaustion of the functional progenitor pool; however, establishing exact one-to-one homologs between murine IAAPs and human IPF AT2 subsets is challenging. In human IPF lung tissue, the number of mature $SP\text{-}C^{+}$ AT2 cells and the expression of proSP-C are significantly downregulated, and are replaced by non-AT2 epithelial cells (28).

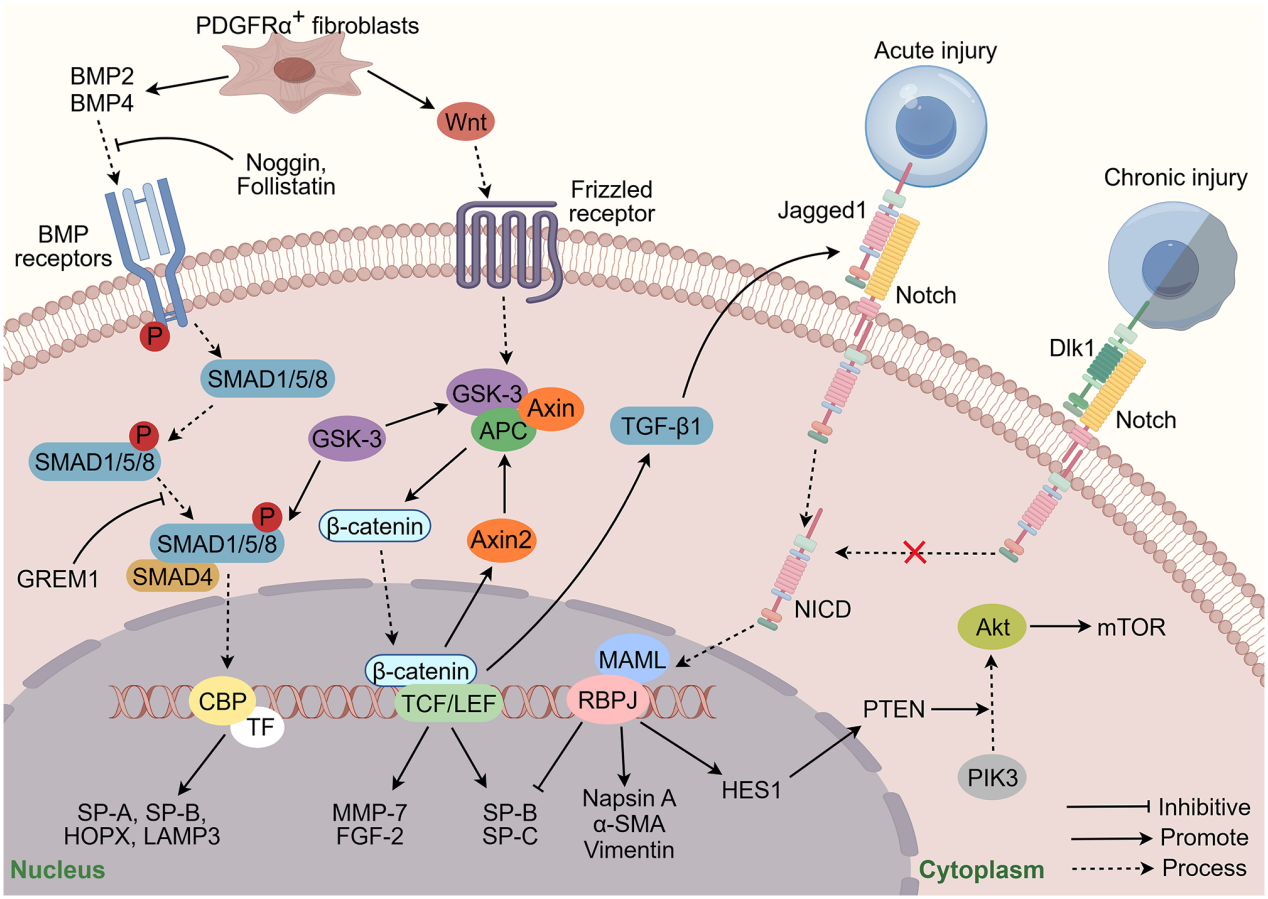

Figure 1. Signaling regulatory pathways of type II alveolar epithelial cells. Akt, protein kinase B; APC, adenomatous polyposis coli; α-SMA, α-smooth muscle actin; BMP, bone morphogenetic protein; CBP, CREB-binding protein; Dlk1, delta-like non-canonical Notch ligand 1; FGF-2, fibroblast growth factor 2; GREM1, gremlin 1; GSK-3, glycogen synthase kinase 3; HES1, hairy and enhancer of split-1; HOPX, HOP homeobox; LAMP3, lysosomal associated membrane protein 3; MAML, mastermind-like protein; MMP-7, matrix metalloproteinase-7; mTOR, mammalian target of rapamycin; NICD, Notch intracellular domain; P, phosphate; PDGFRα, platelet-derived growth factor receptor α; PIK3, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RBPJ, recombination signal binding protein for immunoglobulin kappa J region; SMAD, small mothers against decapentaplegic; SP, surfactant protein; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TF, transcription factor; TGF-β1, transforming growth factor β1; Wnt, wingless-related integration site.

3. Signaling pathways regulating AT2 physiology and repair

The physiological and repair functions of AT2 are fundamental to lung epithelial homeostasis. The repair process for lung epithelial damage involves both the proliferation and renewal of the epithelium and its transformation into mature AT1 cells (29). These processes are intricately regulated by pathways including Wnt/β-catenin, Notch and bone morphogenetic protein (BMP) (30) (Fig. 1).

Canonical Wnt/β-catenin signaling is a significant pathway that promotes AT2 cell transcription and expansion in homeostasis and after lung injury, and is currently a major area of research. During the alveolar epithelial injury and repair stage, the Wnt pathway is significantly upregulated to induce Wnt-responsive AT2 regeneration (31,32). Mechanistically, Wnt ligands secreted by the neighboring platelet-derived growth factor receptor alpha fibroblast niche stabilize intracellular β-catenin, facilitating its nuclear translocation and interaction with T cell factor/lymphoid enhancer factor family (33). Furthermore, this transcriptional program robustly activates target genes required for AT2 proliferation and the maintenance of stemness; however, it paradoxically restricts AT2-to-AT1 differentiation (34). This is accomplished by actively suppressing the genetic programs required for the squamous AT1 morphotype (33,34). Therefore, successful alveolar repair depends on a spatial gradient: Expanding SP-C$^+$ AT2 cells must physically migrate away from the Wnt-secreting fibroblast niche (33). The spatial Wnt downregulation alleviates transcriptional repression, facilitating the critical transition to functional AT1 cells.

Furthermore, Notch signaling exerts significant, but highly context- and time-dependent, control over alveolar regeneration. Early after acute injury, transient activation of canonical Notch signaling is highly advantageous, as it rapidly increases the distal lung progenitor pool and prevents premature differentiation before tissue architecture is stabilized (35). However, persistent canonical Notch activation in IPF is significantly pathogenic (36). In part, the chronically active transforming growth factor (TGF)-β/SMAD family member 3 (Smad3) axis is responsible for sustained Notch signaling that locks transitioning club cells, BASCs and AT2 cells in an aberrant intermediate state. This stalls the essential AT2-to-AT1 transition and stimulates the accumulation of dysplastic intermediate cells (18,37). Studies have indicated that Notch induces alveolar

epithelial proliferation, impairs pro-surfactant processing and promotes EMT (35,38). This pathological arrest is mitigated by non-canonical Notch signaling. Unlike canonical ligands, non-canonical ligands, including delta-like non-canonical Notch ligand 1 (Dlk1), lack the structural domains required to completely activate the Notch receptor (37). Notably, Dlk1 functions as a competitive antagonist, effectively inhibiting canonical Notch signaling (37). This precise inhibition serves as a molecular switch that releases the differentiation block, enabling the stalled progenitor cells to finalize their transformation into AT1 cells and complete alveolar repair.

Besides, BMP, a member of the TGF-β superfamily, regulates lung development and adult homeostasis by signaling through Smad-dependent or independent pathways (39). BMP signaling suppresses stem cell proliferation and promotes differentiation, thereby maintaining AT2 quiescence and identity under homeostasis (40). The capacity of IPF AT2 cells to convert AT2-to-AT1 is limited because they express only half the typical levels of BMP2/3 receptors (41). Additionally, the fibrotic niche is characterized by the robust upregulation of endogenous BMP antagonists (Gremlin), which physically bind to BMP ligands in the extracellular space, thereby preventing them from interacting with their cognate receptors (41). This intense extracellular antagonism induces a localized BMP-deficient state that not only exacerbates AT2 differentiation failure but also eliminates the natural brakes on aberrant proliferation, thereby further promoting progressive fibrotic remodeling of the lung architecture.

4. Dysregulated epithelial-mesenchymal crosstalk and partial EMT drive fibrogenesis

EMT is a highly conserved biological process that is indispensable for growth, development and tissue repair (42). During EMT, alveolar epithelial cells and other epithelial cells undergo reprogramming, suppressing epithelial gene markers, including E-cadherin, and acquire invasive mesenchymal phenotypes characterized by the expression of vimentin and α-smooth muscle actin (α-SMA) (43,44). The International EMT Association classifies EMT associated with tissue regeneration and organ fibrosis as type 2 EMT (43). However, the precise quantitative contribution of complete type 2 EMT to the myofibroblast pool in human IPF has been a subject of intense scientific debate. Early *in vitro* hypotheses suggested that AT2 cells undergoing complete EMT were the direct precursors of most myofibroblasts; however, recent rigorous lineage-tracing and single-cell sequencing studies have fundamentally changed this paradigm (45,46). It is now well-established that the massive accumulation of ECM is primarily induced by the excessive activation and proliferation of resident interstitial fibroblasts, lipofibroblasts and perivascular pericytes, rather than epithelial cells that have completely transitioned into a mesenchymal state (45,47).

The transition of these diverse mesenchymal precursor cells into hyperactive, α-SMA$^+$/fibroblast-specific protein 1$^+$ myofibroblasts is the core effector mechanism of pulmonary fibrosis (48,49). Multiple overlapping signaling networks intricately regulate this activation. Foremost among these is the TGF-β pathway. TGF-β1 potently induces myofibroblast differentiation through the canonical Smad2/3 pathway, directly driving the transcription of profibrotic genes (50). The activation of fibroblasts, in addition to TGF-β, is intricately associated with mechanotransduction. In the stiffened fibrotic microenvironment, the Yes-associated protein and transcriptional coactivator with PDZ-binding motif detect altered ECM mechanical tension. Upon mechanical stimulation, they translocate to the nucleus to induce the massive synthesis of collagen (types I and III) and ECM cross-linking enzymes, including lysyl oxidase-like 2 (51). This cross-linking further stiffens the lung matrix, establishing a pathological feed-forward loop that chronically maintains fibroblast activation independently of initial inflammatory cues.

Notably, the primary understanding of the role of EMT in IPF is based on 'partial EMT' and aberrant epithelial-mesenchymal crosstalk. Instead of fully converting to myofibroblasts, damaged AT2 cells undergo partial EMT, losing their regenerative capacity while initiating a robust profibrotic autocrine and paracrine signaling loop (52). These dysfunctional epithelial cells secrete a potent cocktail of cytokines, Wnt ligands and Sonic hedgehog in response to EMT-inducing transcription factors (zinc finger E-box binding homeobox 1/2, snail family transcriptional repressor 1 and twist family bHLH transcription factor 1) and TGF-β exposure (53-55) (Fig. 2). This epithelial secretome serves as the critical upstream catalyst that continuously recruits and hyper-activates the underlying resident fibroblasts (56).

In summary, complete EMT is no longer considered the primary source of myofibroblasts; however, partial EMT and the resulting dysregulated epithelial-fibroblast crosstalk are clinically significant drivers of IPF pathogenesis. Current approved antifibrotic therapies, including nintedanib and PFD, exert their clinical benefits precisely by targeting this downstream mesenchymal effector phase, thereby disrupting excessive fibroblast proliferation and activation, and slowing disease progression.

5. The vicious cycle of AT2 senescence and mechanical tension in progressive fibrosis

Aging is a significant risk factor for IPF, an age-associated disease with a median age of onset of 65-70 years (57). IPF has been characterized as an aberrant repair response to repetitive alveolar injury in genetically predisposed aged individuals (58). Cells from IPF lungs, especially AT2 cells, exhibit significant senescence: High p21/p53 expression, shortened telomeres and aberrantly activated senescence pathways (59,60). Multiple studies suggest that the characteristic manifestations of aging in AT2 cells, including SASP, ER stress, mitochondrial dysfunction, as well as metabolic and regenerative disorders, are important factors in IPF development. These aging pathways can establish a microenvironment that directly impairs the lung's intrinsic repair system and relentlessly activates resident fibroblasts, in addition to promoting EMT (58,61,62).

Senescent cells (SnCs) remain metabolically active, secreting a unique, cell- and context-dependent SASP, including chemokines (C-C motif chemokine ligand 2), interleukins, growth factors (TGF-β), bioactive lipids (leukotrienes), matrix metalloproteinases, extracellular vesicles and non-coding nucleic acids (63). SASP is the primary mediator of SnC within its tissue microenvironment, exerting autocrine

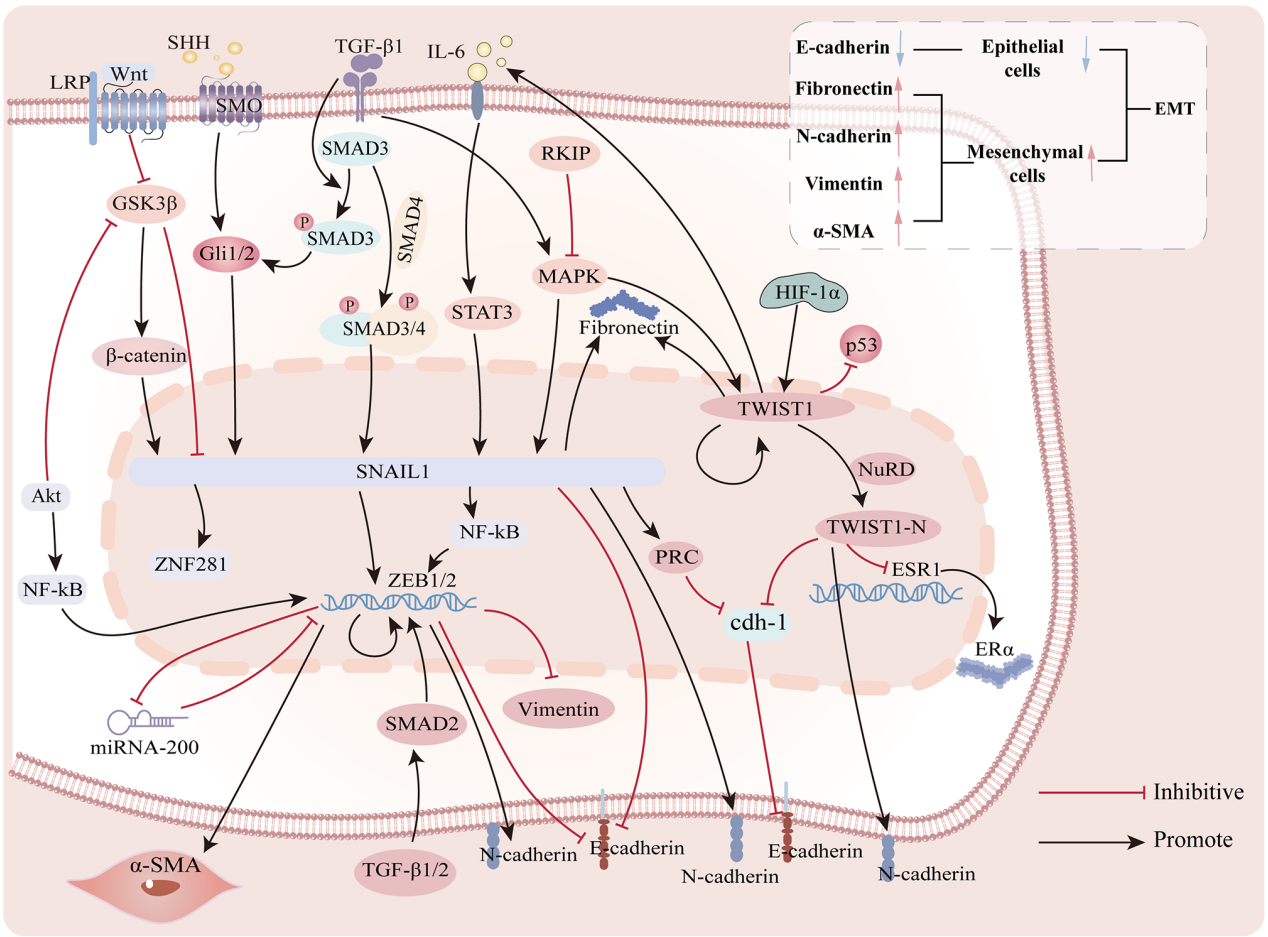

Figure 2. EMT-regulatory miRNA-TF networks. Akt, protein kinase B; α-SMA, α-smooth muscle actin; cdh-1, cadherin-1; E-cadherin, epithelial cadherin; EMT, epithelial-mesenchymal transition; ERα, estrogen receptor α; ESR1, estrogen receptor 1; Gli1/2, glioma-associated oncogene homolog 1/2; GSK3β, glycogen synthase kinase 3β; HIF-1α, hypoxia-inducible factor 1α; IL-6, interleukin 6; LRP, lipoprotein receptor-related protein; MAPK, mitogen-activated protein kinase; miRNA-200, micro ribonucleic acid-200; N-cadherin, neural cadherin; NF-κB, nuclear factor Kb; NuRD, nucleosome remodeling and deacetylase; p53, tumor protein 53; PRC, polycomb repressive complex; RKIP, Raf kinase inhibitor protein; SHH, sonic hedgehog; SMAD, small mothers against decapentaplegic; SMO, smoothened; SNAIL1, snail family transcriptional repressor 1; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta; TWIST1, Twist family bhlh transcription factor 1; Wnt, wingless-related integration site; ZEB1/2, zinc finger E-box binding homeobox 1/2; ZNF281, zinc finger protein 281.

and paracrine effects, that regulates multiple local and systemic biological functions (64). Additionally, other SASP factors also have significant inflammatory properties, which can induce chronic inflammation and fibroblast activation, promote ECM deposition and induce senescence-associated bystander effects, further accelerating the aging of neighboring cells (65).

Borok *et al* (66) used the ER stress inhibitor tauroursodeoxycholic acid to downregulate the expression of mesenchymal marker expression in heat shock protein family A *(Hsp70)* member 5-knockout mice. They demonstrated that fibrosis is associated with the accumulation of misfolded proteins caused by impaired ER function. This accumulation of misfolded proteins activates the unfolded protein response and triggers cell apoptosis (66,67). Stem cells consume a significant amount of energy during proliferation and differentiation processes. Extensive mutations and accumulation of mitochondrial DNA damage under oxidant exposure and aging conditions can result in uncoupling of the mitochondrial electron transport chain or calcium imbalance. This can affect cellular metabolism and ATP production and inhibit AT2 proliferation and differentiation into AT1 (68,69). This was confirmed by Watson *et al* (70), who found that the cell density of AT2 in the lungs of 22-month-old mice remained unchanged compared to that of 3-month-old rats; however, the rate of differentiation into AT1 was significantly reduced. Additionally, partial disruption of the cellular respiratory chain increases the production of mitochondrial reactive oxygen species, which can oxidize and activate latent TGF-β1, thereby promoting the recruitment of myofibroblasts (71).

Fibrotic lungs harbor transitional cells along the AT2-AT1 differentiation axis, essential for alveolar regeneration (72). Transitional cells are abundant in IPF lungs, indicating the persistence of a transitional state in fibrosis, in which the differentiation of alveolar progenitor cells may be stagnant (73). During differentiation, transitional cells become highly susceptible to DNA damage induced by excessive mechanical tension. This state is characterized by activation of the TGF-β signaling pathway, upregulated expression of cell-cycle genes, Wnt/β-catenin signaling, NF-κB, and cellular senescence (74). Applying mechanical tension to AT2 cells can directly upregulate its *Tgfb1* expression and activate the TGF-β signaling loop, therefore resulting in the progression of

fibrosis (75). This is consistent with the pathological findings indicating that AT2 aging results in SP reduction, the intercellular matrix replaces normal epithelial cells and fibrosis starts from the edge of the lung lobe towards the center. Additionally, it demonstrates that lung stiffening is not only a consequence of pulmonary fibrosis, but also a contributor to AT2 aging. This physical cycle must be disrupted to facilitate treatment. Targeting mechanical signaling pathways or modulating the ECM could provide new therapeutic avenues to restore lung homeostasis and promote functional tissue repair.

To fully understand the broader pathogenesis of IPF, it is necessary to consider these distinct mechanisms-ER stress, senescence, EMT and mechanical tension-as an integrated, self-perpetuating vicious cycle. Initial ER stress and metabolic exhaustion prime AT2 cells for senescence. These senescent AT2 cells persist and function as profibrotic drivers through the SASP, rather than undergoing appropriate apoptosis. This secretome directly stimulates dysregulated epithelial-mesenchymal crosstalk (partial EMT) and excessive fibroblast activation. The subsequent massive deposition of ECM significantly increases alveolar mechanical stiffness. Notably, this elevated mechanical tension is not merely a downstream structural consequence; it also acts as a potent upstream mechanotransduction signal. The pathological tension causes continuous DNA damage in transitional AT2 cells, thereby impeding their differentiation into functional AT1 cells and accelerating secondary senescence (74,75). This continuous biophysical and biochemical loop elucidates the relentless and progressive nature of IPF. Additionally, it underscores the importance of breaking this complex cycle to identify novel effective therapies, as targeting a single pathway is frequently insufficient.

6. Current IPF therapies

Surgical lung transplantation is currently the only approach to clinically cure pulmonary fibrosis. However, this treatment method cannot be extensively adopted in clinical practice due to the high difficulty of lung transplantation, limited organ sources, large rejection reactions and frequent postoperative complications. Therefore, it can only be treated conservatively with drugs (76). The primary therapeutic rationale for PFD and nintedanib, the commonly used standard-of-care drugs for IPF, is to slow disease progression by targeting the common progressive fibrotic phenotype. These drugs disrupt the downstream effector phase of fibrosis and reduce subsequent massive ECM deposition by significantly inhibiting EMT and the activation, migration and proliferation of multiple fibroblast populations (77). As a synthetic oral agent, PFD exhibits comprehensive antifibrotic efficacy. It is involved in upregulating E-cadherin expression and inhibiting EMT development by inhibiting macrophage polarization, downregulating key profibrotic factors (TGF-β) and suppressing TGF-β1/Smad2/3 and Wnt/glycogen synthase kinase-3β/β-catenin signaling (10,78,79). Nintedanib is an orally active small-molecule tyrosine kinase inhibitor. It has a broad inhibitory effect on the downstream signaling pathways of fibroblasts and myofibroblasts through its multi-pharmacological actions on receptors for profibrotic mediators (platelet-derived growth factor and FGF), and on non-receptor kinases including Sarcoma kinase. Consequently, it inhibits fibroblast proliferation and migration, as well as ECM synthesis and accumulation (80,81). Additionally, nintedanib can upregulate E-cadherin expression and downregulate α-SMA expression by mediating EMT-associated gene expression and the TGF-β/Smad pathway in alveolar epithelial cells (82). PFD and nintedanib have been demonstrated to significantly slow IPF progression, prolong patient survival and slow the decline in lung function in multicenter trials. However, they are unable to cure or reverse fibrosis (83,84). This can be because pulmonary fibrosis involves diverse pathways and intricate regulatory factors, whereas these drugs inhibit only certain fibrotic pathways and do not address the underlying causes of fibrosis.

However, multiple bleomycin-induced mouse models demonstrate fibrosis reversibility (85,86). Recent insights into lung epithelial lineages and IPF drivers provide novel therapeutic avenues. Targeting senescence pathways to limit AT2 senescence, regulate the activity of senescent AT2 cells, promote apoptosis and increase the proliferation of functional AT2 cells can help improve the prognosis and prolong survival of patients with IPF. These emerging strategies, including the use of senolytics to induce apoptosis, anti-senescence agents, cell transplantation and mechanomodulation, along with their specific mechanisms, clinical status and current limitations, are summarized below (Table I). *p53* is a tumor suppressor gene that can regulate cell aging through multiple pathways, including regulating the cell cycle, apoptosis and DNA repair (87). p53 can be activated by phosphorylation or acetylation in response to stimuli. This process further results in the transcription of p21, and induces cell cycle arrest and senescence (88,89). Furthermore, the secretion and composition of SASP are regulated by p53, potentially through NF-κB (90). p53 signaling is one of the primary pathways upregulated during the senescence of IPF AT2 cells (91). Murine double minute 2 (MDM2) is the most well-characterized negative regulator of p53. It acts as an E3 ubiquitin ligase to promote the ubiquitination and proteasomal degradation of p53 and its export to the nucleus (89,92). Nagaraja *et al* (93) developed a caveolin-1 scaffolding domain peptide that improves MDM2-mediated p53 degradation, suppresses p53 in AT2 cells and impedes murine fibrosis. Hydrogen sulfide (H_2S) is a well-recognized gaseous transmitter involved in multiple physiological and pathological processes. Low H_2S concentrations reduce oxidative stress, inflammation and airway remodeling, mitigating stimulus-induced alveolar epithelial senescence (94,95). A recent study has found that H2S can promote p53 degradation by increasing MDM2-mediated ubiquitination, attenuate BLM-induced p53/p21-dependent AT2 cell senescence *in vivo* and *in vitro*, and effectively inhibit fibroblast proliferation and myofibroblast transdifferentiation (96). Furthermore, multiple cell senescence inhibitory drugs, including nitazoxanide and YTH N6-methyladenosine RNA binding protein C1 have been reported to inhibit pulmonary fibrosis (97,98).

SnCs have a series of survival mechanisms, including SnC anti-apoptotic pathways (SCAP), metabolic reprogramming and immune evasion. These mechanisms allow them to resist multiple pro-apoptotic stimuli, including serum withdrawal, ultraviolet irradiation and oxidative stress, thereby resulting in the accumulation of SnCs (99,100). SnC accumulation in the lung can promote inflammation, induce secondary senescence

Table I. Emerging therapeutic strategies targeting AT2 cell dysfunction in IPF.

Therapeutic strategy	Target/mechanism	Representative agents	Clinical status	Key advantages	Current challenges and limitations	(Refs.)
Senolytics	Bcl-2/Bcl-xL inhibition	Navitoclax (ABT-263)	Preclinical	Potently clears senescent AT2 cells; reverses persistent fibrosis in mice	Significant cytotoxicity	(1)
	Targeting SCAP networks	Dasatinib + Quercetin	Phase I	First-in-class human trial; reduces inflammation and fibrosis markers	High incidence of adverse events; unclear long-term efficacy; poor targeting specificity	(2)
	Autophagy enhancement	Roxithromycin	Preclinical	Repurposed drug with known safety profile	Efficacy in human IPF lungs requires further validation	(3)
Anti-senescence	Promoting p53 degradation to prevent cell cycle arrest	Caveolin-1 peptide Hydrogen sulfide	Preclinical	Mitigates p53/p21-dependent senescence; inhibits fibroblast activation	Specificity to AT2 cells *in vivo*; delivery stability of gaseous transmitter	(4) (5)
	Inhibiting EMT and SASP secretion	Pirfenidone Nintedanib	Approved	Slows disease progression and lung function decline	Does not reverse fibrosis; fails to restore lost alveolar epithelium; side effects	(6) (7)
Cell transplantation	Cell replacement and paracrine support	AT2 cells iPSC-derived cells MSCs	Preclinical Clinical	Directly replenishes functional stem cells; reduces mechanical tension; degrades ECM	Source scarcity; low engraftment efficiency; debate over delivery routes; potential rejection	(8) (9)
Mechanomodulation	Targeting the stiffness-driven senescence loop	Cyclic peptide-modified zeolitic imidazolate framework-8 nanoparticles	Preclinical	Restores lung mechanical homeostasis; terminates fibrotic feedback loops	Requires sophisticated delivery systems to target deep lung tissue	(10)

AT2, type II alveolar epithelial cells; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; iPSC, induced pluripotent stem cell; IPF, idiopathic pulmonary fibrosis; MSCs, mesenchymal stem cells; SASP, senescence-associated secretory phenotype; SCAP, senescent cell anti-apoptotic pathways.

of neighboring cells and result in fibrosis through its unique metabolic properties and gene expression (61,65). Therefore, reducing the metabolic activity of SnCs or inducing apoptosis to reduce their accumulation in the lungs can be a potential therapeutic approach for IPF. Senolytics are a class of drugs that selectively eliminate SnCs. Currently, most senolytics promote SnC apoptosis by targeting key enzymes in the SCAP pathway, including Bcl-2 family proteins, Akt, PI3K and p53 (101,102). Dasatinib (D) and quercetin (Q) were first identified to exhibit senolytic activity in 2015 by targeting specific anti-apoptotic pathways (103). D is a tyrosine kinase inhibitor that can inhibit cell proliferation and migration and induce apoptosis. Q is a naturally occurring flavonoid that can interact with PI3K isoforms and Bcl-2 family members to inhibit SCAP (103). In IPF, the combined use of Q+D can more effectively target SCAPs, induce apoptosis of senescent AT2, downregulate the expression of fibrosis markers and upregulate the expression of epithelial cell markers. It has exhibited good tolerability and compliance in small-scale clinical trials; however, more non-serious adverse events have been reported (104,105). Navitoclax (ABT-263) can reverse PF by selectively killing senescent AT2 cells through inhibition of BCL-2 and BCL-XL. However, it has not yet entered clinical trials due to its cytotoxicity (106). The frequently used macrolide drug, roxithromycin, has been reported to exhibit senolytic activity. This can reduce senescent AT2 cells and fibroblasts by improving autophagy and alleviate the progression of pulmonary fibrosis by degrading specific oxidase through proteasomes (107). At present, the rapid identification of novel molecules with senolytic activity and their subsequent screening using novel methods, including single-cell sequencing and cell viability assays, is facilitated by integrating transcriptomic analysis, gene co-expression networks and network pharmacology with substantial data and high-performance computing. Multiple new molecules have been identified that require further verification (101,103).

Li *et al* (108) constructed cyclic peptide-modified zeolitic imidazolate framework 8 nanoparticles to target and repair abnormal mechanical tension levels in pathological lungs. They successfully restored lung mechanical homeostasis and terminated the fibrotic process in bleomycin-induced fibrotic mice, suggesting that reducing mechanical tension can treat pulmonary fibrosis. Cell transplantation is one method to increase the number and activity of functional AT2 cells, to stimulate stemness, to maintain normal lung epithelial physiology and to reduce mechanical tension (109). Transplantation of AT2 cells or of pluripotent stem cells, including club cells or BASCs, to induce AT2 derivation, can effectively reverse bleomycin-induced pulmonary fibrosis by replacing damaged AT2 cells, producing AT1 cells, promoting the synthesis and secretion of pulmonary surfactant and altering the local microenvironment (85,110,111). Mesenchymal stem cells do not differentiate into alveolar epithelial cells; however, MSC transplantation can enhance the body's immune response through paracrine effects, degrade ECM and promote the regeneration of endogenous distal lung stem cells. MSC transplantation at high cumulative doses has demonstrated safety and efficacy in clinical studies (112,113). However, the source and extraction of cells, the selection of traditional intravenous administration and intratracheal transplantation, the adjustment of dosing frequency and individual differences in rejection reactions and transplantation effects are all issues that must be addressed before this treatment is widely used in clinical practice (114,115).

7. Summary and outlook

The complexity and diversity of regulatory pathways involved in pulmonary fibrosis present significant challenges for its treatment, as no drug currently exists that can address all fibrotic pathways. The breakthrough point in the treatment of pulmonary fibrosis has shifted as a result of a more comprehensive understanding of the AT2 cell lineage and the mechanisms underlying IPF. IPF is driven by AT2 cell senescence and aberrant responses to mechanical tension; therefore, targeting these upstream mechanisms is a promising approach to inhibit EMT at its source. A potential breakthrough in pulmonary fibrosis therapy is using epithelial plasticity to reverse these pathogenic processes. Among them, anti-aging drugs have certain theoretical feasibility in disease prevention and long-term control for individuals with high-risk factors, including family history. However, their short-term inhibitory and reversal effects on patients with progressive pulmonary fibrosis are not satisfactory. Furthermore, cell transplantation demonstrates significant performance in IPF; however, this therapy remains in the preclinical stage. There are certain challenges in selecting stem cell sources, the route of administration and techniques to increase the *in vivo* active survival time of stem cells. Given their strong theoretical rationale and research progress, senolytics are considered promising therapeutics with relatively high clinical potential for treating IPF. Clinical trials of Q+D have demonstrated the efficacy and feasibility of these drugs in treating IPF to some extent; however, certain adverse reactions have been observed. In the future, improvements in computational power and the continued optimization of artificial intelligence are expected to accelerate the identification and screening novel senolytic drugs with fewer side effects and a greater ability to target and clear SnCs. Furthermore, combining multiple treatment strategies, including SnC scavengers, stem cell transplantation and antifibrotic drugs, can exhibit synergistic effects, thereby improving short- and long-term clinical outcomes for patients. Determining how to effectively integrate these treatments into clinical practice through diverse research approaches and interdisciplinary collaboration is crucial for developing more effective therapies.

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Authors' contributions

HD and JZ designed the structure of the article. TX and SP performed the literature search. TX and KH wrote the manuscript. XT and HH created the figures and tables. HD and JZ made revisions and proofread the manuscript. Data authentication is not applicable. All authors have read and agreed to the published version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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