BIOCELL

Tech Science Press

http://doi.org/10.32604/biocell.2026.078898

REVIEW

Research on Alveolar Type II Epithelial Cell Senescence in Idiopathic Pulmonary Fibrosis

Lichun Zhong[1,#], Dijia Wu[2,#], Sirui Zhang[2], Wenjing Liu[2], Faping Wang[3,*] and Fengming Luo[3,*]

[1]Laboratory of Pulmonary Immunology and Inflammation, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China
[2]West China School of Clinical Medicine, West China Hospital, Sichuan University, Chengdu, China
[3]Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China
*Corresponding Authors: Faping Wang. Email: wangfpscu@gmail.com; Fengming Luo. Email: fengmingluo@outlook.com
#These authors contributed equally to this work

Received: 10 January 2026; Accepted: 11 May 2026; Published: 26 August 2026

ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is an age-associated, progressive fibrotic interstitial lung disease with limited disease-modifying therapies and poor long-term outcomes. Increasing evidence indicates that senescence of alveolar type II epithelial (AT2) cells is not merely a bystander phenomenon but a central driver of epithelial dysfunction, failed alveolar regeneration, and fibrotic remodeling. In this narrative review, we summarize recent mechanistic, single-cell, epigenetic, and translational studies that have reshaped the epithelial-centered model of IPF. We first outline normal AT2 biology and the regenerative AT2-to-AT1 trajectory, and then discuss how telomere dysfunction, endoplasmic reticulum stress, mitochondrial injury, DNA damage signaling, and aberrant mechanotransduction promote AT2 senescence. We further examine how senescence-associated secretory phenotype (SASP), maladaptive transitional epithelial states, and epithelial-stromal crosstalk sustain fibrosis. Finally, we review emerging therapeutic approaches, including senolytics, senomorphics, pathway-directed interventions, and RNA or epigenetic strategies, while emphasizing current limitations in model systems, biomarker development, delivery, safety, and patient stratification. Together, the available evidence supports AT2 senescence as a pathogenic and potentially targetable axis in IPF.

KEYWORDS: Idiopathic pulmonary fibrosis; alveolar type II epithelial cells; cellular senescence; signaling pathways; anti-senescence therapy

1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown etiology, characterized histopathologically by honeycombing and thickening of the alveolar septa [1]. It is associated with cough, dyspnea, and impaired quality of life. If left untreated, IPF has a median survival of 3 years [2]. In the US, the annual incidence of IPF (incidence per 10,000 people) ranges from 6.6–8.8 to 16.3–17.4; In Europe, the range is 0.22 to 2.8; In Australia, it is 10.4 to 11.2 [3], and the global burden is increasing. Currently, only the antifibrotic agents nintedanib, pirfenidone, and nerandomilast are approved by the U.S. Food and Drug Administration for IPF treatment [4,5]; these therapies slow the rate of lung function decline but do not reverse established fibrosis or substantially improve survival. Lung transplantation can be life-prolonging, but access is limited, and the 5-year survival rate remains 60% [6].

Alveolar type II epithelial cells (AT2 cells) are increasingly recognized as central initiators of IPF pathogenesis [7]. Repetitive epithelial injury, apoptosis, and impaired regeneration of the alveolar epithelium promote aberrant wound-healing responses, fibroblast activation, and extracellular matrix deposition [8]. Beyond maintaining alveolar architecture, AT2 cells synthesize and recycle surfactant, regulate alveolar fluid homeostasis, and contribute to innate immune defense and immune modulation.

IPF is a strongly age-associated disease. Individuals older than 70 years have approximately a seven-fold higher risk than those around 40 years of age [9]. Consistent with this epidemiology, lungs from patients with IPF exhibit molecular hallmarks of aging [10]. Cellular senescence—defined by durable cell-cycle arrest accompanied by metabolic and secretory remodeling—has emerged as a key epithelial aging phenotype in IPF. Senescent AT2 cells accumulate in IPF lungs, and experimental depletion of senescent cells attenuates pulmonary fibrosis [11]. In human IPF tissue, senescence markers such as p16 and p21 are increased in AT2 cells, and single-cell sequencing studies report expansion of senescence-associated epithelial states that correlate with fibrotic severity [12]. These findings support an epithelial-centered model in which repeated microinjury, impaired AT2 renewal/differentiation, and chronic wound-healing signals converge on progressive scarring.

This review summarizes normal AT2 biology and repair programs, synthesizes mechanistic evidence linking specific stress pathways to AT2 senescence, and evaluates the translational landscape of anti-senescence interventions in IPF. Although this review focuses on epithelial dysfunction, other pathogenic models also contribute to the current understanding of IPF. Mesenchymal-centered frameworks emphasize fibroblast and myofibroblast activation as core drivers of matrix accumulation, whereas immune-centered models highlight aberrant inflammatory and immune signaling. These mechanisms likely interact with, rather than oppose, epithelial injury and failed repair [13].

For clarity, several key concepts should be defined. The senescence-associated secretory phenotype (SASP) refers to the bioactive program adopted by senescent cells, characterized by the secretion of pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes that can reshape the local microenvironment and promote fibrosis [14]. Transitional epithelial states refer to intermediate epithelial cell states that emerge during alveolar repair, typically between alveolar type II (AT2) and alveolar type I (AT1) cell identities [15]. While these states may be transient and adaptive during normal regeneration, their persistence or maladaptive accumulation has been linked to impaired epithelial differentiation and fibrotic remodeling in IPF [16].

2 Scope and Approach of This Review

This article is a narrative expert review rather than a formal systematic review. To improve transparency, we surveyed PubMed and Web of Science for English-language literature published primarily between January 2010 and January 2026 using combinations of terms including “idiopathic pulmonary fibrosis”, “alveolar type II cells”, “senescence”, “KRT8 transitional cells”, “single-cell”, “spatial transcriptomics”, “epigenetics”, “senolytics”, and “organoids”. We prioritized mechanistic experimental studies, single-cell and spatial profiling studies, translational reports, and selected seminal earlier publications necessary for context. Human tissue studies, lineage-tracing mouse models, organoid systems, and interventional studies were emphasized. We excluded articles that were not directly relevant to AT2 biology or the senescence-fibrosis axis, while acknowledging that the narrative format inherently introduces some selection bias.

3 Functions of AT2 Epithelial Cells

3.1 Definition of AT2 Cells

AT2 cells are multifunctional, polarized epithelial cells derived from the endoderm and located in the distal lungs of adult mammals. AT2 cells are interspersed with AT1 cells to form alveolar sacs and maintain the integrity of the gas-exchange surface. Although AT2 cells cover only ~7% of the alveolar surface area, they constitute ~16% of parenchymal cells [17,18]. AT2 cells secrete pulmonary surfactant to reduce alveolar surface tension and participate in inflammation, immune responses, extracellular matrix (ECM) regulation, and injury repair [17].

3.2 Secretion of Surfactant

AT2 cells contain numerous electron-dense secretory granules—osmiophilic lamellar bodies—within the apical cytoplasm. Lamellar bodies store surfactant components, including phospholipids and proteins, which are released into the alveolar space via exocytosis [19]. Pulmonary surfactant is a complex lipid-protein mixture, and dipalmitoyl phosphatidylcholine (DPPC) is its principal surface-active phospholipid. The surfactant protein B released by AT2 cells can promote the rapid adsorption and spreading of phospholipids (such as DPPC) at the gas-liquid interface, forming a monolayer. This special structure enables it to effectively reduce the surface tension of the alveolus. Surface tension naturally promotes alveolar collapse; however, the surfactant protein B and C facilitate adsorption, spreading, and dynamic reorganization of the phospholipid film; the surfactant film lowers surface tension and helps prevent end-expiratory alveolar collapse [20].

3.3 Immune Functions

Multiple components within pulmonary surfactant contribute to the lung's innate immune response. Among these, surfactant proteins A (SP-A) and D (SP-D) are key glycoproteins that recognize pathogen-associated molecular patterns (PAMPs) such as bacterial lipopolysaccharides and viral glycoproteins [21]. When pathogens enter the alveolar cavity, SP-A and SP-D bind to them, promoting aggregation via agglutination. This aggregation facilitates phagocytosis by alveolar macrophages. SP-A and SP-D simultaneously activate macrophage phagocytic activity, enhancing the body's ability to clear pathogens.

3.4 Regenerative Functions

AT2 cells exhibit stem cell characteristics and serve as progenitor cells within the alveolar epithelium. Following lung injury, AT2 cells proliferate and differentiate into type I AT cells, restoring alveolar structure and maintaining normal lung function [15]. Under homeostatic conditions, alveolar epithelial turnover is slow; however, after injury, AT2 cells function as facultative stem cells and rapidly expand and differentiate. This process is regulated by multiple factors and signaling pathways, including Wnt/β-catenin and Notch. Dysregulation of these pathways can impair AT2 cell renewal and differentiation, compromising alveolar repair and predisposing to fibrosis [22]. This distinction is essential when interpreting IPF. Transitional epithelial states characterized by markers such as keratin 8 (KRT8), Claudin-4 (CLDN4), or stress-response genes have been found in fibrotic lungs and in experimental systems [23]. These cells may represent stalled or maladaptive regeneration, but they should not be conflated with senescence. A transitional cell can still be dynamic and fate-competent, whereas a senescent cell is defined by durable growth arrest and broader molecular remodeling. In practice, however, there can be partial overlap: prolonged stress, DNA damage,

persistent TGF-β exposure, or abnormal matrix stiffness may trap AT2-lineage cells in a state that combines transitional features with senescence-associated signaling [24].

Beyond their classical roles, AT2 cells function as a key signaling node that senses mechanical stretch, hypoxia, and inflammatory mediators and then adjusts the alveolar microenvironment. AT2-derived factors can influence local fibroblasts [25], endothelial cells [26], and immune populations [27], thereby shaping extracellular matrix turnover and vascular integrity. In homeostasis, niche signals (including WNT, FGF, and EGFR ligands) help preserve AT2 "stemness," whereas dysregulated niche cues after injury can bias AT2 cells toward aberrant transitional phenotypes [28,29]. Appreciating these niche dynamics is important for interpreting experimental models, as subtle shifts in culture conditions or injury context can markedly alter AT2 fate decisions and downstream fibrotic outcomes. The AT2 functions are summarized in Fig. 1.

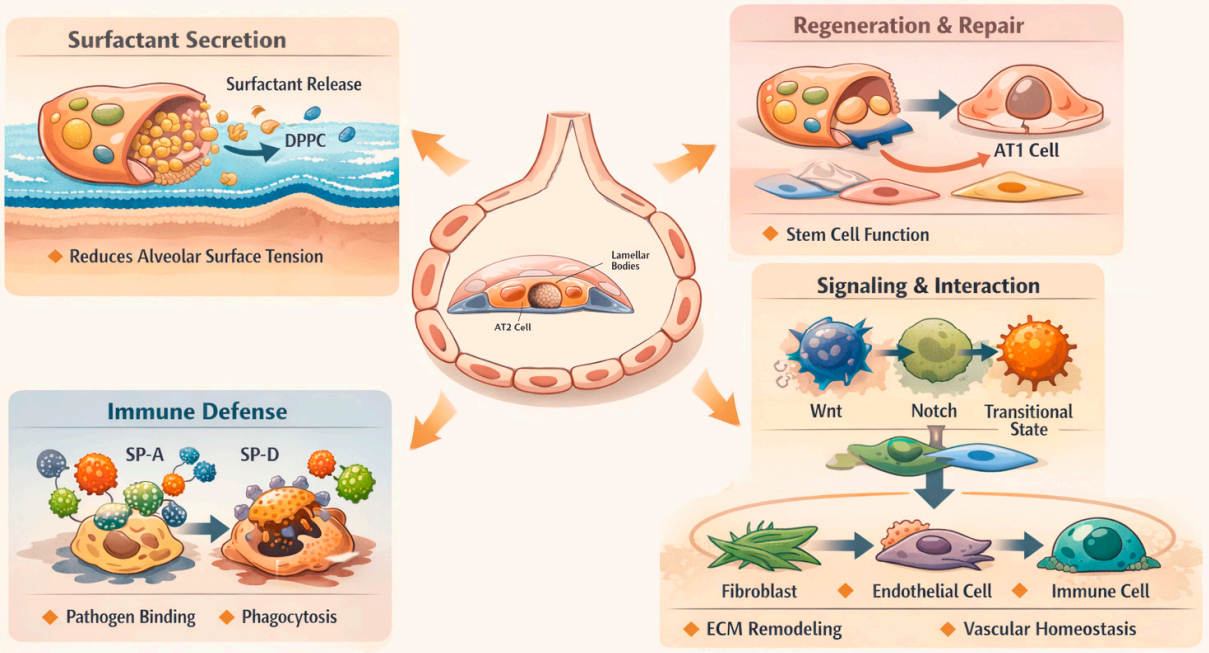

Figure 1: Functional schematic of AT2 epithelial cells. Schematic overview of the key structural and functional roles of AT2 cells in the distal lung. AT2 cells contain lamellar bodies that store and secrete pulmonary surfactant, including phospholipids such as DPPC, which reduces alveolar surface tension and prevents alveolar collapse. AT2 cells also contribute to innate immune defense through surfactant proteins (e.g., SP-A and SP-D), facilitating pathogen recognition, aggregation, and macrophage-mediated phagocytosis. In addition, AT2 cells function as facultative progenitor cells, capable of self-renewal and differentiation into AT1 cells during alveolar repair. Beyond these classical roles, AT2 cells act as key signaling hubs, integrating pathways such as Wnt and Notch to regulate transitional epithelial states and coordinate interactions with fibroblasts, endothelial cells, and immune cells, thereby influencing extracellular matrix remodeling and vascular homeostasis. (Figure created with BioRender.com and ChaptGPT).

4 Role of AT2 Senescence in Pulmonary Fibrosis

4.1 Impact of AT2 Senescence on Pulmonary Fibrosis

4.1.1 Endoplasmic Reticulum Stress

Endoplasmic reticulum stress (ERS) plays a considerable role in pulmonary fibrosis by modulating AT cell dysfunction and aberrant fibroblast activation [27]. ERS is an adaptive response triggered by disruptions in endoplasmic reticulum homeostasis, caused by stimuli such as hypoxia, oxidative damage, or excessive

protein folding demands [30]. ER stress is coordinated mainly through the unfolded protein response (UPR), whereas endoplasmic reticulum-associated degradation (ERAD) and autophagy are complementary proteostatic mechanisms that remove misfolded proteins and damaged organelles.

Aging cells show reduced expression and activity of molecular chaperones or an altered protein-folding environment in the endoplasmic reticulum. Glucose-regulated protein 78 (GRP78), a critical molecular chaperone, is essential for maintaining protein folding within the endoplasmic reticulum. In senescent AT2 cells, reduced GRP78 expression increases ERS [31]. ERAD serves as a quality control mechanism by identifying and degrading unfolded or misfolded proteins, alleviating protein overload in the endoplasmic reticulum. This process recognizes misfolded proteins, retrotranslocates them to the cytoplasm, and degrades them via the ubiquitin-proteasome system [32]. Autophagy is an intracellular degradation pathway that encapsulates organelles, protein aggregates, or other cellular components within autophagosomes, which fuse with lysosomes for degradation. During ERS, autophagy is activated to clear misfolded proteins and damaged organelles accumulated in the endoplasmic reticulum, reducing stress levels [33].

Human relevance is supported by the observation that surfactant-related gene defects and abnormal alveolar proteostasis are linked to familial or sporadic fibrotic lung disease. Nevertheless, ER stress should not be understood as a singular pathway. It encompasses distinct branches with different outputs, and their relative contribution may vary with age, genotype, and stage of disease. This heterogeneity is one reason why broad anti-ER-stress therapy has not yet translated directly into routine clinical use.

4.1.2 Telomere Dysfunction

In familial pulmonary fibrosis and IPF, shortened telomeres in AT2 cells result from genetic abnormalities and/or age-related DNA damage susceptibility [34]. Mouse models with conditional telomere dysfunction in AT2 cells demonstrate that telomere shortening induces AT2 cell senescence and spontaneous fibrosis, whereas telomere dysfunction in fibroblasts does not [35]. Additionally, F-box and WD repeat domain-containing 7-dependent degradation of telomere protection protein 1 (TPP1) promotes telomere uncapping, AT2 senescence, and pulmonary fibrosis [36]. Krüppel-like factor 4 overexpression preserves or increases telomerase reverse transcriptase (TERT) expression and reduces AEC/AT2 senescence and bleomycin-induced fibrosis [37]. These findings identify telomere dysfunction as a key risk factor for AT2 senescence and fibrosis. Whether telomere attrition contributes to the accumulation and/or senescence of PATS cells remains unclear.

This line of evidence is among the strongest arguments that AT2 senescence can be causal rather than merely consequential. Clinical extrapolation is limited by patient heterogeneity and by the fact that not all IPF cases show overt telomere-related disease. Moreover, telomere dysfunction may predispose to a broad state of epithelial fragility rather than a single uniform senescence program.

4.1.3 Mitochondrial Dysfunction

Aging AT2 cells show mitochondrial abnormalities, impaired mitophagy, redox imbalance, and reduced resilience to stress. The ZIP8/SIRT1 axis has been implicated in maintaining alveolar progenitor renewal, and disruption of this pathway may promote epithelial exhaustion and fibrosis [38]. Mitochondrial dysfunction may amplify senescence through several converging routes, including increased reactive oxygen species, DNA damage, altered nicotinamide adenine dinucleotide (NAD^+) metabolism, poly (ADP-ribose) polymerase 1 (PARP1) activation, and reduced sirtuin activity [39]. Because mitochondrial stress also interacts with ERS and transforming growth factor-β (TGF-β) signaling, it may be difficult to assign unique causal priority to one pathway in human disease; in most cases, the relevant question is how these insults cooperate.

From a therapeutic perspective, mitochondrial dysfunction is attractive because it may be modifiable through interventions that restore redox balance, enhance mitophagy, or improve metabolic resilience. Yet this area also illustrates a broader challenge in IPF: mitochondrial abnormalities are not unique to senescence and are shared across epithelial, stromal, and immune compartments. Because mitochondrial abnormalities occur across epithelial, stromal, and immune compartments, responses to mitochondria-targeted therapy may depend on the timing of treatment and the dominant affected cell type. The major drivers and impact of AT2 Senescence on pulmonary fibrosis are summarized in Fig. 2.

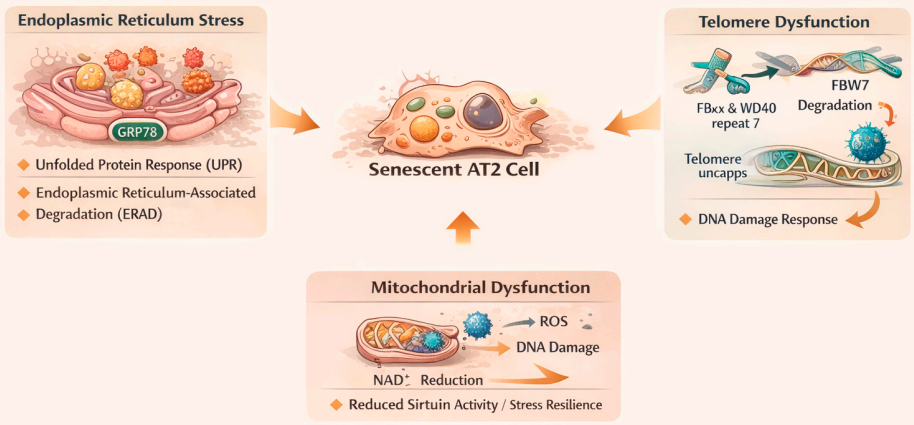

Figure 2: Major drivers and impact of AT2 senescence in pulmonary fibrosis. Schematic illustration of major drivers contributing to AT2 cell senescence. ERS, characterized by activation of the unfolded protein response and endoplasmic reticulum-associated degradation, promotes proteostasis imbalance in AT2 cells. Telomere dysfunction leads to telomere uncapping and activation of the DNA damage response. Mitochondrial dysfunction further amplifies cellular stress through increased reactive oxygen species production, DNA damage, and NAD^+ depletion, resulting in reduced sirtuin activity and impaired stress resilience. (Figure created with BioRender.com and ChatGPT).

4.2 Regulatory Pathways of AT2 Cell Senescence

Regulating cellular senescence involves complex and interconnected pathways modulated by various transcription factors and cell cycle-related genes. For example, specific deletion of Sin3a [40], a transcriptional repressor, in AT2 cells or AT2-restricted expression of mutant Sftpc [41] in mice results in spontaneous pulmonary fibrosis. In models with Sin3a loss-of-function (LOF), "senolytic" cocktail treatment—designed to induce apoptosis in senescent cells and reduce their numbers—alleviates pulmonary fibrosis, confirming the pathogenic role of AT2 senescence in driving fibrosis [40]. The most extensively studied signaling mechanisms regulating senescence in AT progenitor cells are the TP53 and retinoblastoma protein (RB) pathways, which promote and inhibit senescence, respectively. The summarized pathways of AT2 cell senescence are seen in Fig. 3 and Table 1.

4.2.1 TP53 and p21

The TP53-p21 axis is the best-characterized pathway linking epithelial stress to senescence. The transcription factor p53 (TP53), a tumor suppressor highly expressed in senescent cells, is typically maintained in an inactive state. Cellular stress, such as DNA damage or Ras activation, triggers p53 activation, upregulating p21. This inhibits retinoblastoma protein (Rb) phosphorylation, arresting cell growth in the G1 phase [42]. Additionally, p53 mediates selenium-induced pulmonary fibrosis in AT2 cells. Research also [43] reported that p53 regulates the pro-apoptotic receptor expression, with concurrent p21 upregulation in IPF AT cells, which may also induce cell cycle arrest or senescence in specific alveolar

epithelial cells (AECs) subsets. Yao et al. [40] identified senescent characteristics in AT2 cells from IPF lung tissue, with single-cell RNA sequencing revealing substantial p53 signaling pathway activation in both IPF AT2 cells and Sin3a knockout mouse lungs. Furthermore, Disayabutr et al. [44] proposed that p53 activation regulates AT2 cell senescence in patients with IPF by upregulating miR-34, which downregulates key cell cycle target genes (e.g., E2F1, c-Myc, and CCNE2), contributing to pulmonary fibrosis development.

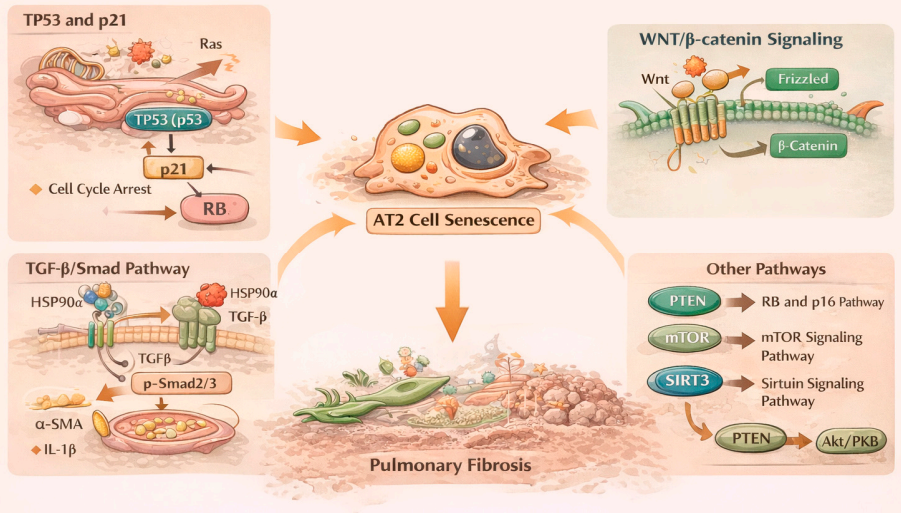

Figure 3: The regulatory signaling pathways of AT2 cell senescence. Activation of the TP53/p21 pathway induces cell cycle arrest through inhibition of retinoblastoma (RB) phosphorylation, promoting senescence. WNT/β-catenin signaling, while involved in epithelial maintenance and regeneration, can drive senescence when persistently activated. The TGF-β/Smad pathway, including extracellular HSP90α-mediated activation, enhances Smad2/3 phosphorylation and promotes pro-fibrotic responses, such as increased α-SMA expression and inflammatory cytokine production (e.g., IL-1β). Additional modulatory pathways, including PTEN/Akt, mTOR, and sirtuin signaling, further influence cellular senescence and metabolic regulation. (Figure created with BioRender.com and ChatGPT).

An additional complexity is that p53 activation can have very different biological meanings depending on context. In some circumstances, it coordinates DNA repair and preserves epithelial integrity; in others, it tips the balance toward senescence or apoptosis. Therefore, the presence of p53-pathway activation in human tissue is informative but not by itself sufficient to infer an identical functional outcome across all AT2 populations.

4.2.2 WNT/β-Catenin Signaling Pathway

Wnt proteins are secreted glycoproteins essential for embryonic development and tissue regeneration, regulated by a transcriptional complex composed of DNA-binding factors (e.g., lymphoid enhancer factor/T-cell factor) and β-catenin [45]. Although Wnt/β-catenin signaling is ubiquitous across tissues, the genes it activates vary depending on cell type and environment. WNT signaling has dual roles in the injured alveolus. Short-term activation may support progenitor maintenance and early repair, but prolonged or dysregulated activation can contribute to aberrant epithelial remodeling and senescence [28]. Lehmann et al. reported elevated Wnt/β-catenin activity in AT2 cells of aged mice, with chronic activation for 7 days triggering senescence [46]. Chronic Wnt/β-catenin signaling in lung epithelial cells has been shown to induce senescence-like programs, and LRP5-dependent WNT signaling contributes to pulmonary fibrosis in experimental models [47].

The interpretation is context-dependent: WNT signaling may support early repair but may become pathogenic when sustained or uncoupled from resolution signals. Pathways required for regeneration can become pathogenic when sustained or uncoupled from normal resolution signals. This has practical implications for drug development. A treatment that suppresses chronic WNT signaling may be beneficial in a lung already dominated by persistent aberrant epithelial states, but the same treatment could be harmful if given too early and if it blocks a required regenerative response.

4.2.3 TGF-β/Smad Pathway

Increasing evidence positions TGF-β as a central mediator in IPF. Extracellular heat shock protein 90α activates TGF-β signaling via phosphorylation of the Smad complex, which subsequently binds to p53 and p21 promoters, initiating their transcription. This process mediates fibroblast senescence and contributes to mitochondrial dysfunction in IPF [48]. In epithelial cells, TGF-β can induce growth arrest, oxidative stress, and senescence-related phenotypes; in stromal compartments, it drives myofibroblast differentiation and matrix production [49]. Minagawa and colleagues provided early evidence that accelerated epithelial senescence occurs in IPF and that SIRT6 can restrain TGF-β-induced senescence responses [50]. TGF-β also interacts with transitional-state biology, as persistent signaling can lock AT2-lineage cells into maladaptive intermediate states that fail to resolve [25]. Thus, TGF-β acts both upstream and downstream of epithelial senescence. In the fibrotic lung, TGF-β is both an epithelial stress signal and a stromal execution signal. Senescent or transitional epithelial cells can help activate it, and activated fibroblasts can feed back additional TGF-β, further locking epithelial cells into maladaptive states.

4.2.4 NF-κB Signaling Pathway

Nuclear factor kappa B (NF-κB) is an inducible transcription factor complex composed of five DNA-binding proteins (NF-κB1, NF-κB2, p65/RelA, RelB, and c-Rel), capable of forming various homodimers and heterodimers. NF-κB is a core regulator of inflammatory transcription and has been strongly linked to SASP control [51]. PTEN loss has been linked to alveolar epithelial senescence through both Akt-dependent and NF-κB-dependent mechanisms [52]. These findings suggest that sustained NF-κB activation is associated with and enhances cellular senescence. This supports the concept that NF-κB functions not merely as a bystander inflammatory pathway but as a stabilizer of the senescent/SASP program that links epithelial injury to persistent fibrotic remodeling.

4.2.5 Other Pathways

PTEN exhibits significant anti-tumor functions by negatively regulating the protein kinase B (Akt) signaling pathway, which plays a key role in modulating cell growth and survival across various systems [53]. PTEN loss is associated with Akt activation and increased senescence markers, including $P21^{WAF1}$ and SA-β-gal. Conversely, PTEN restoration or pharmacological Akt inhibition attenuates epithelial senescence and reduces experimental pulmonary fibrosis, suggesting that AEC senescence triggers IPF and identifies the PTEN/Akt pathway as a promising therapeutic target [54]. Additional pathways potentially regulating AT2 senescence include the retinoblastoma protein (RB) and p16 pathway [55]. Sirtuin-dependent pathways [38] and the mechanistic target of rapamycin (mTOR) signaling pathway also play a role in regulating AT2 senescence [56].

These signaling pathways are tightly interconnected and frequently reinforce one another. For example, p53/p21-driven cell-cycle arrest can cooperate with NF-κB to promote SASP gene expression, while TGF-β signaling can enhance oxidative stress and mitochondrial dysfunction that further stabilizes

senescence [49,57] WNT/β-catenin activity may support short-term progenitor expansion after injury, but when prolonged, can contribute to aberrant epithelial remodeling and mesenchymal activation. Additional pathways such as mTOR, Hippo-YAP/TAZ, Notch, and integrin-FAK mechanotransduction likely function as context-sensitive amplifiers that integrate matrix stiffness, TGF-β, and inflammatory signals into durable transcriptional programs that sustain epithelial dysfunction and fibrotic remodeling [58]. Mapping these interactions helps explain why single-node inhibition can be insufficient and supports combination or sequential approaches. Epigenetic regulation may shape maladaptive AT2-cell fate during pulmonary fibrosis. Xiong et al. showed that AT2-specific deletion of HDAC3 protects against bleomycin-induced pulmonary fibrosis, suggesting that histone deacetylation programs contribute to fibrotic epithelial remodeling [59]. Seasock et al. further demonstrated that let-7 restrains an epigenetic circuit in AT2 cells, preventing the emergence of fibrogenic intermediate states, indicating that epigenetic–post-transcriptional regulation helps maintain AT2 identity and limit profibrotic transition [60].

Table 1: Representative pathways involved in AT2 cell senescence and fibrosis.

Pathway/Process	Representative Evidence	Putative Consequence in IPF	Translational Implication
TP53-p21	Human IPF AT2 cells and Sin3a-deficient mouse models show activation of senescence programs [40,44]	Durable growth arrest, impaired regeneration, fibrogenic signaling	Timing-sensitive target; systemic inhibition may impair tumor suppression
WNT-β-catenin	Chronic epithelial WNT activation can induce senescence-like programs [45,46]	Stalled repair and abnormal epithelial remodeling	Context-dependent; may be harmful if broadly or chronically inhibited
TGF-β-Smad	Central pathway in epithelial-stromal crosstalk and senescence induction [25,48,49]	Fibroblast activation, transitional-state persistence, matrix accumulation	Attractive but pleiotropic target
Other pathways (PTEN-AKT; RB-p16; Sirtuin et al.)	PTEN loss and inflammatory amplification promote senescence-associated fibrosis [53,54]	Stabilize AT2 senescence, SASP reinforcement, and stromal activation	Combination strategies targeting may be more effective for preventing maladaptive AT2 fate and fibrotic progression

5 Epigenetic Changes in AT2 Promote Lung Fibrosis

5.1 Multi-Omics Evidence for Maladaptive AT2 States in IPF

Multi-omics studies increasingly support the idea that maladaptive AT2 states are a central feature of IPF rather than a secondary epiphenomenon. Single-cell transcriptomic analyses first showed that injured AT2 cells can enter transitional programs marked by genes such as KRT8 and CLDN4; although such states may be transient during normal regeneration, they persist abnormally in fibrotic lungs and are linked to defective AT2-to-AT1 differentiation [61]. More recent spatial transcriptomic work has refined this model by showing that, in human IPF, AT2 cells branch toward either AT1 differentiation or aberrant epithelial programs, including $KRT5^{-}/KRT17^{+}$ aberrant basaloid states. These maladaptive states occupy fibrotic niches enriched for ECM remodeling and disease-associated cell-cell interactions [62]. Integrated transcriptomic—epigenomic analyses of purified IPF AT2 cells further demonstrate that these cells undergo genome-wide molecular reprogramming, including enhancer remodeling and activation of epithelial plasticity regulators such as thyroid receptor interactor 13, supporting the concept that maladaptive

AT2 behavior is encoded at both transcriptional and chromatin levels [63]. Finally, broader multi-omics integration of lung tissue has identified progression-associated signatures involving surfactant defects, epithelial—mesenchymal transition, mitochondrial dysfunction, and altered differentiation programs, consistent with a model in which stressed AT2 cells become trapped in persistent, non-resolving repair states that promote fibrosis progression [64].

5.2 Epigenetic Regulators Linking AT2 Stress Responses to Fibrosis

Mechanistically, these cell-state shifts are increasingly understood as epigenetically stabilized programs rather than transient injury responses. AT2 senescence is a key upstream driver: conditional disruption of chromatin-associated repressors (e.g., Sin3a) in AT2 cells triggers SASP, progressive fibrosis, and loss of effective epithelial regeneration *in vivo* [40]. Multi-omics analyses further suggest that chromatin accessibility and histone modification landscapes in AT2-lineage intermediates enable sustained expression of profibrotic ligands, integrins, and stress-response transcriptional modules. For example, an organoid-based lung fibrosis model using mouse and human tissues demonstrated that DNA damage and p53 activation in AT2-lineage cells can elicit a transition-like, SASP-associated state that activates fibroblasts via TGF-β and is maintained by an autocrine TGF-β positive-feedback loop [25]. Epigenetic enzymes appear to act as 'state keepers' in this setting. AT2-specific deletion of histone deacetylase 3 (HDAC3) attenuates bleomycin-induced fibrosis, consistent with HDAC3-dependent maintenance of inflammatory and profibrotic gene expression programs during epithelial injury responses [59]. More recently, loss of the let-7 microRNA cluster in AT2 cells was shown to unleash an oncogenic–epigenetic circuit (including chromatin regulators such as Enhancer of Zeste Homolog 2 [EZH2]) that promotes accumulation of $KRT8^{+}$ fibrogenic intermediates and progressive fibrosis, supported by integrated Argonaute 2-enhanced Cross-Linking and ImmunoPrecipitation (AGO2-eCLIP), RNA-seq, and chromatin profiling [60].

5.3 Non-Coding RNAs and RNA-Based Therapeutic Opportunities

Non-coding RNAs are therefore not only biomarkers but also mechanistic levers in epithelial-driven fibrosis. Among candidate antifibrotic RNAs, the miR-29 family is particularly notable because it suppresses extracellular matrix gene networks and is reduced in fibrotic lungs. A lung-targeted, peptide-conjugated miR-29 mimic (MRG-229) decreases collagen production and profibrotic gene expression across *in vitro* and *in vivo* models, and shows preclinical tolerability in larger animals—supporting its translational development for IPF [65]. Conversely, miR-21 is a pro-fibrotic microRNA implicated in both fibroblast activation and epithelial injury responses; lung-targeted delivery of anti-miR-21 via cationic liposomes suppresses myofibroblast differentiation and reduces fibrosis progression in experimental models [66]. These studies highlight a therapeutically attractive logic: rather than targeting a single cytokine, RNA therapeutics may 'reset' coordinated gene programs that are epigenetically reinforced in AT2 intermediates and their neighboring stromal compartments.

5.4 Organoids and Lineage-Informed Experimental Systems

Organoid and induced pluripotent stem cell-derived alveolar systems have become useful complements to animal models because they permit controlled perturbation of epithelial programs in a human genetic context [67]. Profibrotic cytokine exposure can drive alveolar organoids toward persistent transitional phenotypes, offering tractable platforms for testing whether epithelial states are reversible [67]. Enomoto and colleagues further showed, using mouse and human organoid systems together with *in vivo* experiments, that autocrine TGF-β-positive feedback in profibrotic AT2-lineage cells is sufficient to sustain non-inflammatory

fibrogenesis [25]. These models are most useful for mechanistic perturbation and drug prioritization, while *in vivo* and human tissue validation remain essential.

At the same time, organoids simplify the tissue context. They often lack full immune, endothelial, neural, and mechanical inputs and may display culture-induced artifacts. Thus, their greatest value lies in mechanistic dissection and drug prioritization rather than in complete disease recapitulation. These systems also enable more precise discussion of evidence strength. Human tissue datasets are strong for association and relevance, mouse lineage models are strongest for causal inference, and organoids are strongest for mechanistic tractability and perturbation screening. No single model class is sufficient on its own. Robust conclusions about AT2 senescence should ideally be supported across at least two of these levels.

5.5 Translational Strategies and Clinical Outlook

Clinically, epithelial epigenetic targeting remains early-stage but is rapidly maturing. Interventions that reduce AT2 senescence or clear senescent cells could indirectly mitigate epigenetically fixed profibrotic states; a pilot study of senolytics (dasatinib plus quercetin) in IPF demonstrated feasibility [68]. Epigenetic enzyme inhibitors are conceptually attractive, but cell-type specificity and off-target effects will be key constraints; AT2-specific genetic evidence for HDAC3 [59] and the let-7 chromatin circuit [60] helps prioritize mechanisms and biomarkers for such approaches. Finally, lung-targeted RNA therapeutics (miR-29 replacement or miR-21 inhibition) offer a pragmatic translational bridge and can be aligned with multi-omics-defined epithelial states for patient stratification [65,66]. Together, these advances support a model in which AT2 epigenetic reprogramming is a driver of persistent fibrogenic intermediates and a promising axis for disease-modifying therapy. A key emerging theme is that epigenetic remodeling may encode a form of "memory" in AT2 cells, whereby transient insults produce sustained changes in chromatin accessibility and transcription factor occupancy. Spatial and single-cell multi-omics are beginning to resolve how these epigenetic states align with anatomical gradients of fibrosis and with specific stromal or immune neighborhoods. However, therapeutic targeting of epigenetic regulators raises challenges: many chromatin enzymes are broadly required across tissues, and systemic inhibition can cause off-target toxicity. Future progress will likely rely on lung-selective delivery (e.g., inhaled formulations, targeted nanoparticles) and on identifying epigenetic dependencies that are most specific to maladaptive AT2 states. Integrating patient-derived organoids with perturbation screens may accelerate prioritization of such targets for clinical translation.

6 Intervention Strategies for AT2 Cell Senescence

Currently, therapies for fibrotic diseases target senescent cells via two main strategies: (1) inducing or inhibiting cellular senescence based on its underlying mechanisms and its specific regulatory effects on fibrosis progression; (2) eliminating profibrotic SASP factors produced by senescent cells. The interventions are summarized in Table 2.

6.1 Anti-Senescence Therapy

Yao et al. [40] showed that inhibiting the p53 signaling pathway mitigates pulmonary fibrosis in Sin3a knockout mice, suggesting that early targeting of senescent cells can treat pulmonary fibrosis in murine models. Bleomycin-induced lung fibrosis in rats activates the Wnt/β-catenin signaling pathway, with increased expression of Wnt components, including Wnt3a, β-catenin, and phosphorylated glycogen synthase kinase-3β (pGSK-3β), during IPF development, alongside reduced GSK-3β expression in fibrotic mouse lungs [69]. Chen et al. [70] similarly demonstrated that inhibiting the Wnt/β-catenin pathway

attenuates IPF. SIRT6, a member of the sirtuin family, suppresses epithelial-mesenchymal transition in IPF, preventing TGF-β1-induced myofibroblast differentiation by inhibiting the TGF-β1/Smad2 and NF-κB signaling pathways [71]. Plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor with antiprotease activity, is essential for fibrinolysis and wound healing. Depleting or inhibiting PAI-1 in AT2 cells nearly completely blocks TGF-β1-induced AT2 senescence, profibrotic mediator secretion, and SASP-mediated macrophage stimulation [72]. The PAI-1 inhibitor TM5275 reduces TGF-β1-induced pulmonary fibrosis and AT2 senescence in mice [73]. Furthermore, the combination of the pan-tyrosine kinase inhibitor dasatinib and the natural flavonoid quercetin reduces levels of senescence markers p16 and β-galactosidase [74].

6.2 Suppression of SASP Factors from Senescent Cells

Targeting the NF-κB signaling pathway can mitigate inflammatory responses. Fisetin, a novel dietary flavonoid from various plants, fruits, and vegetables, ameliorates lung inflammation by downregulating p-STAT-1 and NF-κB signaling via heme oxygenase-1, effectively reducing oxidative stress-induced lung damage [75]. Fisetin delays AT cell senescence by inhibiting NF-κB, improving the SASP profile of senescent cells, and reducing fibroblast-to-myofibroblast differentiation and collagen deposition [76]. Human efficacy and long-term safety in IPF remain unproven; fisetin should be described as a preclinical candidate rather than an established therapeutic option.

Protein Tyrosine Phosphatase Receptor Type J (CD148) expression is downregulated in IPF lungs and fibroblasts. In fibroblasts lacking CD148, overactivation of the PI3K/Akt/mTOR signaling pathway, reduced autophagy, and increased p62 accumulation trigger NF-κB activation and profibrotic gene expression. *In vivo* administration of SDC2-pep reduces pulmonary fibrosis and suppresses IPF-derived fibroblast activation. This suggests that targeting the interaction between CD148 phosphatase and its activating ligand, such as SDC2-pep, could potentially serve as a promising therapeutic strategy for IPF [77].

Table 2: Representative therapeutic strategies targeting the AT2 senescence axis.

Strategy	Drug/Target	Evidence	Evidence Stage	Potential Strength	Realistic Risk-Benefit Evaluation
Senomorphics/ pathway modulators	PAI-1 inhibition, SIRT-related approaches, WNT or TGF-β modulation	*In vivo* bleomycin mice model [71–73]	Preclinical	May preserve viable epithelial cells and modulate upstream senescence circuitry without indiscriminate cell depletion.	Biologically attractive but not yet clinically ready. Off-target effects; timing is critical; pathway inhibition may impair normal repair if misapplied.
Senolytics	Dasatinib plus quercetin; fisetin	A two-center, open-label study, 14 treatment patients [67]; phase I RCT pilot trial, 6 placebo, 6 treatment patients [74]	Early clinical feasibility	Removes pathogenic senescent cells rather than merely suppressing their secretome.	Conceptually powerful but still high-risk/ high-uncertainty. Efficacy on FVC, exacerbations, or survival has not been demonstrated.

Table 2: *Cont.*

Strategy	Drug/Target	Evidence	Evidence Stage	Potential Strength	Realistic Risk-Benefit Evaluation
SASP-directed approaches	NF-κB-related suppression; stromal interaction modifiers such as CD148 signaling	*In vivo* bleomycin mice model [77]	Preclinical	Reduces harmful paracrine signaling and may dampen profibrotic amplification loops.	Potentially useful as an adjunct strategy. May not eliminate persistent dysfunctional cells; broad inflammatory pathway inhibition may reduce specificity. unlikely to be sufficient alone if the senescent-cell burden remains high.
RNA/epigenetic therapeutics	miR-29 mimic, anti-miR-21, HDAC or let-7-related targeting	*In vivo* bleomycin mice model [59,60,65,66]	Preclinical	Can reset coordinated gene networks and may more directly address epithelial state programs.	High mechanistic appeal but still investigational. Delivery, tissue specificity, durability, immune/off-target effects, and biomarker selection remain major hurdles.

7 Limitations

Much of the causal evidence for AT2 senescence comes from mouse models such as bleomycin injury, genetic telomere dysfunction, or inducible epithelial knockout systems. These models are indispensable but imperfect. Bleomycin fibrosis is often partially reversible and may not recapitulate the chronic spatially heterogeneous remodeling of human usual interstitial pneumonia. Genetic models may overrepresent single pathways. Therefore, although they strongly support biological plausibility, they cannot by themselves prove that the same pathway hierarchy operates in all patients with IPF.

Species differences in alveolar repair, immune tone, lifespan, and matrix remodeling are additional reasons for caution. Mouse models are powerful experimental tools, but they compress time scales and simplify exposures in ways that may not mirror the decades-long evolution of human IPF. This is why convergence between human tissue, organoid, and animal evidence is particularly valuable.

Another unresolved issue is the distinction among senescence, apoptosis, exhaustion, dedifferentiation, and transitional epithelial states. In the literature, these are sometimes treated interchangeably, which risks conceptual inflation. Causal claims should be reserved for experiments showing that specific manipulation of senescence pathways in AT2 cells alters fibrotic outcomes, as in targeted telomere or Sin3a models. By contrast, many single-cell and pathology studies show a strong association but not direct causality. This does not diminish their importance; rather, it defines what kind of inference can be made from each dataset.

More precise phenotyping will therefore be critical. Future studies should combine lineage information, cell-cycle status, chromatin features, spatial context, and secretory readouts rather than relying on a single marker or transcriptomic label. This will help prevent the field from assigning a single pathological identity to biologically heterogeneous epithelial populations. The field also contains apparently conflicting observations. WNT signaling can be regenerative or senescence-promoting depending on timing. TGF-β can support normal repair but also drive pathological persistence. Some senescent stromal populations may aid wound healing in certain tissues, whereas epithelial senescence appears harmful in the fibrotic lung.

From a clinical standpoint, the major barriers are biomarker scarcity, delivery to the distal lung, long-term safety, and uncertainty regarding treatment timing. It is still unclear whether anti-senescence strategies should be given early to preserve regenerative reserve, later to interrupt feed-forward fibrosis, or

both. Combination strategies with approved antifibrotics may be necessary. Precision approaches based on epithelial-state profiling, spatial biomarkers, and patient-derived models are therefore especially promising.

8 Conclusion

In conclusion, accumulating evidence supports AT2 senescence as a central pathogenic axis in IPF. Rather than being a passive consequence of chronic injury, senescent AT2 cells integrate multiple upstream stresses—including telomere dysfunction, endoplasmic reticulum stress, mitochondrial injury, DNA-damage signaling, and aberrant mechanotransduction—and translate them into persistent epithelial dysfunction. These maladaptive epithelial states are characterized by impaired regenerative capacity, transitional arrest, and senescence-associated secretory phenotypes, which together amplify fibroblast activation, extracellular matrix deposition, and progressive architectural distortion. Human tissue studies, single-cell and spatial transcriptomics, organoid systems, and lineage-informed animal models collectively indicate that AT2 senescence is closely linked to failed alveolar repair and sustained epithelial–stromal crosstalk in IPF. From a therapeutic perspective, currently approved antifibrotics slow disease progression but do not directly restore epithelial competence or reverse senescence. Emerging approaches, including senolytics, senomorphics, pathway-directed interventions, and RNA/epigenetic therapeutics, offer promising mechanistic strategies, but their clinical translation remains limited by challenges in biomarker selection, treatment timing, delivery specificity, and long-term safety. Overall, the AT2 senescence framework provides a coherent model that links aging, epithelial injury, and fibrosis, and highlights a future therapeutic goal beyond simply slowing decline: restoring alveolar regenerative capacity through precise modulation of maladaptive epithelial cell states.

Acknowledgement: All the Figures were generated with the assistance of BioRender.com and ChatGPT.

Funding Statement: This work was supported by the National Natural Science Foundation of China grant (NSFC No. 82400084) and the Sichuan Science and Technology Program (No. 2024NSFSC1530).

Author Contributions: The authors confirm contribution to the paper as follows: study conception and design: Faping Wang, Fengming Luo; draft manuscript preparation: Lichun Zhong, Dijia Wu, Sirui Zhang, Wenjing Liu; review and editing: Faping Wang, Fengming Luo, Dijia Wu; visualization: Lichun Zhong, Dijia Wu; supervision: Faping Wang, Fengming Luo. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

IPF	Idiopathic pulmonary fibrosis
AT2	Alveolar type II epithelial cells
AT1	Alveolar type I epithelial cells
AECs	Alveolar epithelial cells
ECM	Extracellular matrix
DPPC	Dipalmitoylphosphatidylcholine
SP-A	Surfactant protein A
SP-D	Surfactant protein D

PAMPs	Pathogen-associated molecular patterns
KTR8	Keratin 8
SDC2	Syndecan-2
FGF	Fibroblast Growth Factor
EGFR	Epidermal Growth Factor Receptor
ERS	Endoplasmic Reticulum Stress
UPR	Unfolded protein response
ERAD	Endoplasmic Reticulum-Associated Degradation
GRP78	Glucose-regulated protein 78
TERT	Telomerase reverse transcriptase
PARP1	Poly(ADP-ribose) polymerase 1
NAD^+	Nicotinamide adenine dinucleotide
SIRT1	Sirtuin 1
Bmi-1	B-cell-specific Moloney murine leukemia virus insertion site 1
LOF	Loss of function
RB	Retinoblastoma protein
SASP	Senescence-associated secretory phenotype
PDGF-AA	Platelet-derived growth factor AA
TP53	Transcription factor p53
TGF-β	Transforming growth factor-β
α-SMA	α-smooth muscle actin
NF-κB	Nuclear factor kappa B
PTEN	Phosphatase and tensin homolog
mTOR	Mechanistic target of rapamycin
LRP5	Low-Density Lipoprotein Receptor-Related Protein 5
E2F1	E2F transcription factor 1
c-Myc	cellular Myelocytomatosis oncogene
CCNE2	Cyclin E2
P21	Cyclin-Dependent Kinase Inhibitor 1A
P53	Tumor Protein 53
SIRT6	Sirtuin 6
CLDN4	Claudin 4
KRT5	Keratin 5
KRT17	Keratin 17
HDAC3	histone deacetylase 3
EZH2	Enhancer of Zeste Homolog 2
AGO2-eCLIP	Argonaute 2-enhanced Cross-Linking and ImmunoPrecipitation
RNA-seq	RNA sequencing
pGSK-3β	phosphorylated glycogen synthase kinase-3β
PAI-1	Plasminogen activator inhibitor-1
CD148	Protein Tyrosine Phosphatase Receptor Type J
P16	Cyclin-dependent kinase inhibitor 2A

References

1. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017;389(10082):1941–52. [CrossRef].
2. Zheng Q, Cox IA, Campbell JA, Xia Q, Otahal P, de Graaff B, et al. Mortality and survival in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. ERJ Open Res. 2022;8(1):591–2021. [CrossRef].
3. Spagnolo P, Guler SA, Chaudhuri N, Udwadia Z, Sesé L, Kaul B, et al. Global epidemiology and burden of interstitial lung disease. Lancet Respir Med. 2025;13(8):739–55. [CrossRef].
4. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192(2):e3–19. [CrossRef].
5. Brown MB. Nerandomilast: first approval. Drugs. 2026;86(4):557–63. [CrossRef].

6. Valapour M, Lehr CJ, Schladt DP, Swanner K, Poff K, Handarova D, et al. OPTN/SRTR 2023 annual data report: lung. Am J Transplant. 2025;25(2):S422–89. [CrossRef].
7. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–23. [CrossRef].
8. Olajuyin AM, Zhang X, Ji HL. Alveolar type 2 progenitor cells for lung injury repair. Cell Death Discov. 2019;5:63. [CrossRef].
9. O'Hare M, Amarnani D, Whitmore HAB, An M, Marino C, Ramos L, et al. Targeting runt-related transcription factor 1 prevents pulmonary fibrosis and reduces expression of severe acute respiratory syndrome coronavirus 2 host mediators. Am J Pathol. 2021;191(7):1193–208. [CrossRef].
10. Meiners S, Eickelberg O, Königshoff M. Hallmarks of the ageing lung. Eur Respir J. 2015;45(3):807–27. [CrossRef].
11. Hecker L, Logsdon NJ, Kurundkar D, Kurundkar A, Bernard K, Hock T, et al. Reversal of persistent fibrosis in aging by targeting Nox4-Nrf2 redox imbalance. Sci Transl Med. 2014;6(231):231ra47. [CrossRef].
12. Lehmann M, Korfei M, Mutze K, Klee S, Skronska-Wasek W, Alsafadi HN, et al. Senolytic drugs target alveolar epithelial cell function and attenuate experimental lung fibrosis *ex vivo*. Eur Respir J. 2017;50(2):1602367. [CrossRef].
13. Habermann AC, Gutierrez AJ, Bui LT, Yahn SL, Winters NI, Calvi CL, et al. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. Sci Adv. 2020;6(28):eaba1972. [CrossRef].
14. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010;5:99–118. [CrossRef].
15. Aspal M, Zemans RL. Mechanisms of ATII-to-ATI cell differentiation during lung regeneration. Int J Mol Sci. 2020;21(9):3188. [CrossRef].
16. Wang F, Ting C, Riemondy KA, Douglas M, Foster K, Patel N, et al. Regulation of epithelial transitional states in murine and human pulmonary fibrosis. J Clin Investig. 2023;133(22):e165612. [CrossRef].
17. Beers MF, Moodley Y. When is an alveolar type 2 cell an alveolar type 2 cell? a conundrum for lung stem cell biology and regenerative medicine. Am J Respir Cell Mol Biol. 2017;57(1):18–27. [CrossRef].
18. Zhang J, Liu Y. Epithelial stem cells and niches in lung alveolar regeneration and diseases. Chin Med J Pulm Crit Care Med. 2024;2(1):17–26. [CrossRef].
19. Martínez-Calle M, Olmeda B, Dietl P, Frick M, Pérez-Gil J. Pulmonary surfactant protein SP-B promotes exocytosis of lamellar bodies in alveolar type II cells. FASEB J. 2018;32(8):4600–11. [CrossRef].
20. Baritussio AG, Magoon MW, Goerke J, Clements JA. Precursor-product relationship between rabbit type II cell lamellar bodies and alveolar surface-active material. Surfactant turnover time. Biochim Biophys Acta. 1981;666(3):382–93. [CrossRef].
21. Guillot L, Nathan N, Tabary O, Thouvenin G, Le Rouzic P, Corvol H, et al. Alveolar epithelial cells: master regulators of lung homeostasis. Int J Biochem Cell Biol. 2013;45(11):2568–73. [CrossRef].
22. Hernandez BJ, Cain MP, Lynch AM, Flores JR, Tuvim MJ, Dickey BF, et al. Intermediary role of lung alveolar type 1 cells in epithelial repair upon Sendai virus infection. Am J Respir Cell Mol Biol. 2022;67(3):389–401. [CrossRef].
23. Kobayashi Y, Tata A, Konkimalla A, Katsura H, Lee RF, Ou J, et al. Persistence of a regeneration-associated, transitional alveolar epithelial cell state in pulmonary fibrosis. Nat Cell Biol. 2020;22(8):934–46. [CrossRef].
24. Hoffman ET, Shah A, Barboza WR, Rodriguez LR, Dherwani R, Dooley PE, et al. Aberrant intermediate alveolar epithelial cells promote pathogenic activation of lung fibroblasts in preclinical fibrosis models. Nat Commun. 2025;16:8710. [CrossRef].
25. Enomoto Y, Katsura H, Fujimura T, Ogata A, Baba S, Yamaoka A, et al. Autocrine TGF-β-positive feedback in profibrotic AT2-lineage cells plays a crucial role in non-inflammatory lung fibrogenesis. Nat Commun. 2023;14(1):4956. [CrossRef].
26. Bärnthaler T, Maric J, Platzer W, Konya V, Theiler A, Hasenöhrl C, et al. The role of PGE2 in alveolar epithelial and lung microvascular endothelial crosstalk. Sci Rep. 2017;7:7923. [CrossRef].
27. Gschwend J, Sherman SPM, Ridder F, Feng X, Liang HE, Locksley RM, et al. Alveolar macrophages rely on GM-CSF from alveolar epithelial type 2 cells before and after birth. J Exp Med. 2021;218(10):e20210745. [CrossRef].
28. Nabhan AN, Brownfield DG, Harbury PB, Krasnow MA, Desai TJ. Single-cell Wnt signaling niches maintain stemness of alveolar type 2 cells. Science. 2018;359(6380):1118–23. [CrossRef].

29. Brownfield DG, de Arce AD, Ghelfi E, Gillich A, Desai TJ, Krasnow MA. Alveolar cell fate selection and lifelong maintenance of AT2 cells by FGF signaling. Nat Commun. 2022;13:7137. [CrossRef].
30. Marciniak SJ, Chambers JE, Ron D. Pharmacological targeting of endoplasmic reticulum stress in disease. Nat Rev Drug Discov. 2022;21(2):115–40. [CrossRef].
31. Borok Z, Horie M, Flodby P, Wang H, Liu Y, Ganesh S, et al. Grp78 loss in epithelial progenitors reveals an age-linked role for endoplasmic reticulum stress in pulmonary fibrosis. Am J Respir Crit Care Med. 2020;201(2):198–211. [CrossRef].
32. Vembar SS, Brodsky JL. One step at a time: endoplasmic reticulum-associated degradation. Nat Rev Mol Cell Biol. 2008;9(12):944–57. [CrossRef].
33. Yorimitsu T, Nair U, Yang Z, Klionsky DJ. Endoplasmic reticulum stress triggers autophagy. J Biol Chem. 2006;281(40):30299–304. [CrossRef].
34. van Batenburg AA, Kazemier KM, van Oosterhout MFM, van der Vis JJ, Grutters JC, Goldschmeding R, et al. Telomere shortening and DNA damage in culprit cells of different types of progressive fibrosing interstitial lung disease. ERJ Open Res. 2021;7(2):691–2020. [CrossRef].
35. Naikawadi RP, Disayabutr S, Mallavia B, Donne ML, Green G, La JL, et al. Telomere dysfunction in alveolar epithelial cells causes lung remodeling and fibrosis. JCI Insight. 2016;1(14):e86704. [CrossRef].
36. Wang L, Chen R, Li G, Wang Z, Liu J, Liang Y, et al. FBW7 mediates senescence and pulmonary fibrosis through telomere uncapping. Cell Metab. 2020;32(5):860–77.e9. [CrossRef].
37. Wang H, Xu H, Lyu W, Xu Q, Fan S, Chen H, et al. KLF4 regulates TERT expression in alveolar epithelial cells in pulmonary fibrosis. Cell Death Dis. 2022;13(5):435. [CrossRef].
38. Liang J, Huang G, Liu X, Taghavifar F, Liu N, Wang Y, et al. The ZIP8/SIRT1 axis regulates alveolar progenitor cell renewal in aging and idiopathic pulmonary fibrosis. J Clin Investig. 2022;132(11):e157338. [CrossRef].
39. Zank DC, Bueno M, Mora AL, Rojas M. Idiopathic pulmonary fibrosis: aging, mitochondrial dysfunction, and cellular bioenergetics. Front Med. 2018;5:10. [CrossRef].
40. Yao C, Guan X, Carraro G, Parimon T, Liu X, Huang G, et al. Senescence of alveolar type 2 cells drives progressive pulmonary fibrosis. Am J Respir Crit Care Med. 2021;203(6):707–17. [CrossRef].
41. Nureki SI, Tomer Y, Venosa A, Katzen J, Russo SJ, Jamil S, et al. Expression of mutant Sftpc in murine alveolar epithelia drives spontaneous lung fibrosis. J Clin Investig. 2018;128(9):4008–24. [CrossRef].
42. Gire V, Dulic V. Senescence from G2 arrest, revisited. Cell Cycle. 2015;14(3):297–304. [CrossRef].
43. Rana T, Jiang C, Banerjee S, Yi N, Zmijewski JW, Liu G, et al. PAI-1 regulation of p53 expression and senescence in type II alveolar epithelial cells. Cells. 2023;12(15):2008. [CrossRef].
44. Disayabutr S, Kim EK, Cha SI, Green G, Naikawadi RP, Jones KD, et al. miR-34 miRNAs regulate cellular senescence in type II alveolar epithelial cells of patients with idiopathic pulmonary fibrosis. PLoS One. 2016;11(6):e0158367. [CrossRef].
45. Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, et al. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther. 2022;7(1):3. [CrossRef].
46. Lehmann M, Hu Q, Hu Y, Hafner K, Costa R, van den Berg A, et al. Chronic WNT/β-catenin signaling induces cellular senescence in lung epithelial cells. Cell Signal. 2020;70:109588. [CrossRef].
47. Lam AP, Herazo-Maya JD, Sennello JA, Flozak AS, Russell S, Mutlu GM, et al. Wnt coreceptor Lrp5 is a driver of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190(2):185–95. [CrossRef].
48. Zhong W, Chen W, Liu Y, Zhang J, Lu Y, Wan X, et al. Extracellular HSP90α promotes cellular senescence by modulating TGF-β signaling in pulmonary fibrosis. FASEB J. 2022;36(8):e22475. [CrossRef].
49. Massagué J, Sheppard D. TGF-β signaling in health and disease. Cell. 2023;186(19):4007–37. [CrossRef].
50. Minagawa S, Araya J, Numata T, Nojiri S, Hara H, Yumino Y, et al. Accelerated epithelial cell senescence in IPF and the inhibitory role of SIRT6 in TGF-β-induced senescence of human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2011;300(3):L391–L401. [CrossRef].
51. Christian F, Smith EL, Carmody RJ. The regulation of NF-κB subunits by phosphorylation. Cells. 2016;5(1):12. [CrossRef].
52. Tu M, Wei T, Jia Y, Wang Y, Wu J. Molecular mechanisms of alveolar epithelial cell senescence and idiopathic pulmonary fibrosis: a narrative review. J Thorac Dis. 2023;15(1):186–203. [CrossRef].

53. Choudhury AD. PTEN-PI3K pathway alterations in advanced prostate cancer and clinical implications. Prostate. 2022;82(S1):S60–S72. [CrossRef].
54. Qiu T, Tian Y, Gao Y, Ma M, Li H, Liu X, et al. PTEN loss regulates alveolar epithelial cell senescence in pulmonary fibrosis depending on Akt activation. Aging. 2019;11(18):7492–509. [CrossRef].
55. Safwan-Zaiter H, Wagner N, Wagner KD. P16INK4A-more than a senescence marker. Life. 2022;12(9):1332. [CrossRef].
56. Jung SH, Hwang HJ, Kang D, Park HA, Lee HC, Jeong D, et al. mTOR kinase leads to PTEN-loss-induced cellular senescence by phosphorylating p53. Oncogene. 2019;38(10):1639–50. [CrossRef].
57. Chien Y, Scuoppo C, Wang X, Fang X, Balgley B, Bolden JE, et al. Control of the senescence-associated secretory phenotype by NF-κB promotes senescence and enhances chemosensitivity. Genes Dev. 2011;25(20):2125–36. [CrossRef].
58. Liu F, Lagares D, Choi KM, Stopfer L, Marinković A, Vrbanac V, et al. Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. Am J Physiol Lung Cell Mol Physiol. 2015;308(4):L344–57. [CrossRef].
59. Xiong R, Geng B, Jiang W, Hu Y, Hu Z, Hao B, et al. Histone deacetylase 3 deletion in alveolar type 2 epithelial cells prevents bleomycin-induced pulmonary fibrosis. Clin Epigenetics. 2023;15(1):182. [CrossRef].
60. Seasock MJ, Shafiquzzaman M, Ruiz-Echartea ME, Kanchi RS, Tran BT, Simon LM, et al. Let-7 restrains an epigenetic circuit in AT2 cells to prevent fibrogenic intermediates in pulmonary fibrosis. Nat Commun. 2025;16:4353. [CrossRef].
61. Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, et al. Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis. Nat Commun. 2020;11(1):3559. [CrossRef].
62. Franzén L, Olsson Lindvall M, Hühn M, Ptasinski V, Setyo L, Keith BP, et al. Mapping spatially resolved transcriptomes in human and mouse pulmonary fibrosis. Nat Genet. 2024;56(8):1725–36. [CrossRef].
63. St Pierre L, Berhan A, Sung EK, Alvarez JR, Wang H, Ji Y, et al. Integrated multiomic analysis identifies TRIP13 as a mediator of alveolar epithelial type II cell dysfunction in idiopathic pulmonary fibrosis. Biochim Biophys Acta BBA Mol Basis Dis. 2025;1871(3):167572. [CrossRef].
64. Pattaroni C, Begka C, Cardwell B, Jaffar J, Macowan M, Harris NL, et al. Multi-omics integration reveals a nonlinear signature that precedes progression of lung fibrosis. Clin Transl Immunol. 2024;13(1):e1485. [CrossRef].
65. Chioccioli M, Roy S, Newell R, Pestano L, Dickinson B, Rigby K, et al. A lung targeted miR-29 mimic as a therapy for pulmonary fibrosis. eBioMedicine. 2022;85:104304. [CrossRef].
66. Yan L, Su Y, Hsia I, Xu Y, Vincent-Chong VK, Mojica W, et al. Delivery of anti-microRNA-21 by lung-targeted liposomes for pulmonary fibrosis treatment. Mol Ther Nucleic Acids. 2023;32:36–47. [CrossRef].
67. Ptasinski V, Monkley SJ, Öst K, Tammia M, Alsafadi HN, Overed-Sayer C, et al. Modeling fibrotic alveolar transitional cells with pluripotent stem cell-derived alveolar organoids. Life Sci Alliance. 2023;6(8):e202201853. [CrossRef].
68. Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. EBioMedicine. 2019;40:554–63. [CrossRef].
69. Lv Q, Wang J, Xu C, Huang X, Ruan Z, Dai Y. Pirfenidone alleviates pulmonary fibrosis *in vitro* and *in vivo* through regulating Wnt/GSK-3β/β-catenin and TGF-β1/Smad2/3 signaling pathways. Mol Med. 2020;26(1):49. [CrossRef].
70. Chen X, Shi C, Meng X, Zhang K, Li X, Wang C, et al. Inhibition of Wnt/β-catenin signaling suppresses bleomycin-induced pulmonary fibrosis by attenuating the expression of TGF-β1 and FGF-2. Exp Mol Pathol. 2016;101(1):22–30. [CrossRef].
71. Zhang Q, Tu W, Tian K, Han L, Wang Q, Chen P, et al. Sirtuin 6 inhibits myofibroblast differentiation via inactivating transforming growth factor-β1/Smad2 and nuclear factor-κB signaling pathways in human fetal lung fibroblasts. J Cell Biochem. 2019;120(1):93–104. [CrossRef].
72. Rana T, Jiang C, Liu G, Miyata T, Antony V, Thannickal VJ, et al. PAI-1 regulation of TGF-β1-induced alveolar type II cell senescence, SASP secretion, and SASP-mediated activation of alveolar macrophages. Am J Respir Cell Mol Biol. 2020;62(3):319–30. [CrossRef].
73. Huang WT, Vayalil PK, Miyata T, Hagood J, Liu RM. Therapeutic value of small molecule inhibitor to plasminogen activator inhibitor–1 for lung fibrosis. Am J Respir Cell Mol Biol. 2012;46(1):87–95. [CrossRef].

74. Nambiar A, Kellogg D, Justice J, Goros M, Gelfond J, Pascual R, et al. Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. eBioMedicine. 2023;90:104481. [CrossRef].
75. Hussain T, Al-Attas OS, Alamery S, Ahmed M, Odeibat HAM, Alrokayan S. The plant flavonoid, fisetin alleviates cigarette smoke-induced oxidative stress, and inflammation in Wistar rat lungs. J Food Biochem. 2019;43(8):e12962. [CrossRef].
76. Zhang L, Tong X, Huang J, Wu M, Zhang S, Wang D, et al. Fisetin alleviated bleomycin-induced pulmonary fibrosis partly by rescuing alveolar epithelial cells from senescence. Front Pharmacol. 2020;11:553690. [CrossRef].
77. Tsoyi K, Liang X, De Rossi G, Ryter SW, Xiong K, Chu SG, et al. CD148 deficiency in fibroblasts promotes the development of pulmonary fibrosis. Am J Respir Crit Care Med. 2021;204(3):312–25. [CrossRef].