



Cellular Senescence as a Pathogenic Hub Driving Mechanistic Networks and Reversal Strategies in Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive, ultimately fatal interstitial lung disease for which current antifibrotic therapy — pirfenidone and nintedanib — can slow but not reverse the underlying scarring process, leaving median survival at only three to five years. Over the past several years, the field's understanding of IPF has shifted from a chronic-inflammatory model toward one centered on epithelial injury and, more specifically, on the pathological accumulation of senescent cells within the alveolar niche. This review set out to synthesize that literature systematically, tracing how cellular senescence is generated, sustained, and might eventually be reversed in the fibrotic lung. Using a structured, PubMed-anchored search strategy supplemented by citation-chasing, we reviewed preclinical and clinical studies addressing senescent alveolar epithelial cells (particularly AEC2 progenitors and their KRT8⁺ and KRT5⁺/KRT17⁺ transitional states), heterogeneous CTHRC1⁺ myofibroblast populations, and the intracellular signaling networks — PTEN/Akt/mTOR/NF- κ B, Sirt1/HSF1/HSPs, and the senescence–autophagy axis — that govern their behavior. We found converging evidence, across independent injury models, that senescent epithelial and mesenchymal cells sustain fibrogenesis through a persistent senescence-associated secretory phenotype

(SASP), reinforced by glycolytic metabolic reprogramming and matrix-stiffness-driven mechanotransduction that together lock the tissue into a self-perpetuating fibrotic state. Emerging senotherapeutic strategies — senolytics (dasatinib plus quercetin), senomorphics (EF24, semaglutide, curculigoside, ISRIB), and, notably, autologous basal cell transplantation — showed encouraging, if still largely preclinical or early-phase, evidence of reducing senescent burden and, in limited pilot data, improving functional outcomes. We conclude that cellular senescence functions as a mechanistic hub linking epithelial failure to mesenchymal activation in IPF, offering a biologically coherent rationale for combination senotherapeutic and regenerative strategies, though substantial translational gaps — disease-specific biomarkers, aging-relevant models, and targeted delivery — remain before these approaches can be tested definitively in patients.

Keywords

Idiopathic pulmonary fibrosis; Cellular senescence; Senescence-associated secretory phenotype (SASP); Senotherapeutics; Alveolar epithelial regeneration; Autophagy–senescence axis; Myofibroblast heterogeneity

Significance | Cellular senescence organizes IPF pathogenesis across cell types, positioning senotherapeutics and regenerative cell therapy as biologically grounded strategies for reversing, not merely slowing, fibrosis.

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1. Introduction

There is something almost paradoxical about idiopathic pulmonary fibrosis. The lung, an organ built for elasticity and exchange, slowly turns into something closer to scar tissue — stiff, airless, and, in most patients, unresponsive to anything medicine currently has to offer. IPF is a chronic, progressive, and relentlessly fatal interstitial lung disease marked by irreversible scarring of the lung parenchyma, collapse of alveolar architecture, and a severe restrictive ventilatory defect (Lederer & Martinez, 2018; Raghu et al., 2022). Patients do not experience this abstractly. They experience it as breathlessness that creeps into ordinary tasks, a dry cough that will not resolve, and a slow slide into hypoxemia that eventually ends in respiratory failure (Lederer & Martinez, 2018; Raghu et al., 2022).

Age is not incidental to this story — it may, in fact, be the story. IPF predominantly strikes older adults, with a demographic peak between the sixth and eighth decades of life, and its incidence and prevalence appear to roughly double every ten years beyond age fifty (Raghu et al., 2022; Torres-Machorro et al., 2025). That pattern hints that IPF is not simply a lung disease that happens to occur in older people; it may be, at least in part, a disease of aging biology expressed in lung tissue. The numbers that follow diagnosis are sobering: median survival hovers at only three to five years, a prognosis that is, remarkably, worse than that of many solid malignancies (Lederer & Martinez, 2018; Min et al., 2026). Against this backdrop, the therapeutic arsenal remains thin — two FDA-approved antifibrotics, pirfenidone and nintedanib, can slow the decline in forced vital capacity (FVC) by roughly half but neither halts nor reverses established fibrosis, and both carry meaningful toxicity, including hepatotoxicity and gastrointestinal disturbance (Qian et al., 2026; Raghu et al., 2022). We can decelerate decline, modestly; we cannot yet change the disease's fundamental trajectory. That gap motivates much of what follows.

To understand why senescence has become such a focal point, it helps to trace how the field's conceptual model of IPF has shifted. For years, IPF was framed largely as a chronic inflammatory disorder, with fibrosis positioned as an unfortunate downstream byproduct. That framing has given way, more decisively in recent years, to a rather different model — IPF as an epithelial-driven disorder of maladaptive tissue repair (Gao et al., 2025). Under this newer framework, disease begins with repeated, often

subclinical, micro-injuries to a vulnerable alveolar epithelium, which in genetically susceptible individuals triggers an exaggerated and ultimately self-defeating wound-healing response (Gao et al., 2025; Lederer & Martinez, 2018). What is striking, and central to this review, is that at the heart of this dysregulated repair process sits the premature, persistent accumulation of senescent cells within the pulmonary microenvironment, directly tying the biology of cellular aging to fibrotic remodeling (Torres-Machorro et al., 2025; Yao et al., 2021).

It is worth pausing on what senescence actually is, since the term is often used loosely. Cellular senescence refers to a state of stable, essentially irreversible cell-cycle arrest triggered by stressors such as DNA damage, telomere attrition, mitochondrial dysfunction, and chronic oxidative stress (Juan et al., 2026; Min et al., 2026). Crucially, senescent cells do not simply shut down — they remain metabolically active, sometimes hyperactive, while undergoing substantial morphologic and functional change even as they permanently stop dividing (Juan et al., 2026). Their hallmark is the senescence-associated secretory phenotype (SASP): a complex secretome of pro-inflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases (Juan et al., 2026; Min et al., 2026). In healthy tissue, senescence can serve protective purposes; in the fibrotic lung, however, senescent cells persist rather than being cleared, and their sustained SASP output converts a transient, localized injury signal into a chronic, non-resolving inflammatory and fibrogenic microenvironment (Min et al., 2026).

This process is not confined to a single cell type, which is part of what makes it difficult to target. Alveolar type II (AEC2) epithelial cells — the lung's endogenous stem cell reservoir — appear particularly susceptible to stress-induced premature senescence (Min et al., 2026; Yao et al., 2021). Repeated insults drive genomic instability and telomere shortening, ultimately locking these cells into permanent arrest via the p53-p21 (CDKN1A) and p16 (CDKN2A)/Rb pathways (Min et al., 2026; Yao et al., 2021). The result is a "regenerative bottleneck": senescent AEC2s can no longer differentiate into gas-exchanging alveolar type I (AEC1) cells, leaving injured septa denuded and prone to collapse, while their SASP output — TGF-1, IL-6, PAI-1 — pushes neighboring fibroblasts toward a contractile, matrix-producing myofibroblast phenotype (Min et al., 2026; Rana et al., 2020; Yao et al., 2021).

Fibroblasts, in turn, are not passive recipients of these signals; they undergo their own senescence program, marked by apoptosis resistance, glycolytic dependence, and largely autonomous production of pro-fibrotic matrix (Melo-Narváez et al., 2024; Min et al., 2026). The resulting stiffness feeds back onto resident cells through mechanotransduction, forming a self-reinforcing mechanical-pathological loop (Min et al., 2026; Torres-Machorro et al., 2025).

Underneath these cellular phenomena sit several interconnected signaling networks that represent plausible intervention points. The PTEN/Akt/mTOR/NF-B axis functions as a central hub: PTEN loss activates Akt/mTOR signaling, driving NF-B-mediated SASP gene transcription, while hyperactive mTOR simultaneously suppresses autophagy and mitophagy, amplifying reactive oxygen species and DNA damage (Li et al., 2023; Min et al., 2026; Zhang et al., 2024). Protective pathways move in the opposite direction — the Sirt1/HSF1/HSPs axis, which normally supports protein quality control and mitochondrial integrity, is markedly downregulated in fibrotic lung tissue (Qian et al., 2026).

Given how centrally senescence orchestrates epithelial dysfunction, fibroblast activation, and fibrogenesis, it has become a genuinely promising therapeutic frontier (Juan et al., 2026; Torres-Machorro et al., 2025). Senolytics selectively eliminate senescent cells by exploiting their anti-apoptotic dependencies (e.g., dasatinib plus quercetin, fisetin, EF24), while senomorphics suppress the pro-fibrotic SASP without killing the cell (e.g., semaglutide, curculigoside, resveratrol) (Juan et al., 2026; Qian et al., 2026; Zhang et al., 2024). A complementary approach targets proteostasis directly, through enhanced autophagic flux (rapamycin, metformin) or mitigation of integrated stress responses (ISRIB), with encouraging preclinical efficacy already reported (Li et al., 2023; Min et al., 2026). Whether these strategies can be translated into meaningful clinical reversal of fibrosis — rather than mere deceleration — is the central question this review sets out to address.

To compile, analyze, and systematically evaluate the rapidly expanding body of literature surrounding cellular senescence in IPF, this review is organized around four core objectives. The first is to synthesize the cellular and molecular mechanisms of cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis, delineating the cell-type-specific roles of senescent alveolar epithelial

cells (particularly AEC2 progenitors) and lung fibroblasts in driving maladaptive tissue repair. The second is to outline the key signaling pathways and regulatory networks that govern the senescent phenotype in the fibrotic lung, with particular focus on the integration of the Sirt1/HSF1, PTEN/Akt/NF-B, and TGF-1/Smad signaling axes, as well as the reciprocal crosstalk within the senescence–autophagy axis. The third is to critically evaluate emerging therapeutic reversal strategies targeting cellular senescence in IPF, analyzing the preclinical efficacy, molecular targets, and translational potential of diverse senotherapeutics, including senolytics, senomorphics, autophagy/mitophagy restorers, and integrated stress response inhibitors. The fourth and final objective is to discuss critical translational challenges and future directions in the clinical application of senescence-targeted therapies, addressing key bottlenecks such as the lack of disease-specific longitudinal biomarkers, the necessity of aging-relevant experimental animal models, and cell-type-specific drug delivery systems.

2. Cellular Senescence in Idiopathic Pulmonary

Fibrosis: Pathogenic Networks and Reversal

Strategies

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive interstitial lung disease of older adults that leads to irreversible destruction of alveolar architecture and fatal respiratory failure. While historically viewed as a chronic inflammatory disorder, contemporary research has redefined IPF as a cellular-systems problem driven by repetitive epithelial microinjury, aberrant mesenchymal activation, and compromised cellular quality-control networks. At the epicenter of this pathogenesis is cellular senescence, a state of permanent cell-cycle arrest that actively orchestrates remodeling of the lung parenchyma. This literature review adopts a multiscale conceptual mind map framework to dissect the pathogenic networks of cellular senescence in IPF. We trace how microinjuries and genetic susceptibilities trigger aberrant, senescent progenitor states—such as the KRT8 alveolar differentiation intermediate (ADI) and KRT5/KRT17 aberrant basaloid cells—which disrupt the epithelial stem cell niche and lock cells in regenerative arrest. We explore the bidirectional mechanical and metabolic crosstalk between senescent epithelial cells and a heterogeneous fibroblast landscape, showing how metabolic reprogramming (aerobic glycolysis) and mechanical memory drive persistent myofibroblast activation.

Furthermore, we examine the reciprocal regulation of the senescence-autophagy axis, detailing how disabled macroautophagy and mitophagy fuel reactive oxygen species (ROS) accumulation and stabilize senescent phenotypes. Finally, we review emergent senotherapeutic and regenerative reversal strategies---encompassing selective senolytic clearance, senomorphic modulation of the pro-fibrotic secretome, and autologous basal cell transplantation---as pioneering roadmaps to move the clinical management of IPF beyond palliative deceleration toward structural and functional restoration. This organization is summarized conceptually in Figure 1, which maps the four thematic branches synthesized below and their convergence on a shared, self-reinforcing pathogenic network.

2.1 Branch 1: Reprogrammed Epithelial Trajectories and Alveolar Regeneration Failure

The classical paradigm of idiopathic pulmonary fibrosis (IPF) as a linear, passive tissue response to chronic inflammation has been substantially reshaped by single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (Deng et al., 2026). The contemporary consensus establishes IPF as an epithelial-driven, aberrant wound-healing disorder initiated by recurrent, subclinical microinjuries to the alveolar epithelium (Baurzhan et al., 2026; Torres-Machorro et al., 2025). In genetically susceptible individuals, these microinjuries---compounded by environmental toxicants such as silica dust, particulate matter, and tobacco smoke---drive alveolar type II (AEC2) progenitor cells into states of persistent regenerative arrest and cellular senescence (Gao et al., 2025; Jones et al., 2025).

Rather than undergoing simple apoptotic depletion, injured alveolar progenitors enter a highly active, reprogrammed transitional state. A primary node in this aberrant epithelial trajectory is the accumulation of the KRT8 alveolar differentiation intermediate (ADI) stem cell state (Deng et al., 2026).

This trajectory — summarized schematically in Figure 2 — begins during healthy alveolar repair, where the ADI state represents a transient, developmental bridge through which AEC2 progenitors differentiate into flat, gas-exchanging alveolar type I (AEC1) cells (Jones et al., 2025). In the chronic fibrotic milieu of IPF, however, these cells fail to exit this transitional phase. They become locked in a persistent regenerative bottleneck

characterized by the continuous activation of p53, NF- κ B, and DNA damage response (DDR) pathways (Deng et al., 2026; Longhin et al., 2026). This trajectory arrest is accompanied by the up-regulation of the cellular senescence markers p21 (CDKN1A) and p16 (CDKN2A), converting a physiological repair intermediate into a pathological signaling engine (Baurzhan et al., 2026; Deng et al., 2026).

Spatially segregated at the active borders of fibroblastic foci and within remodeled honeycomb cysts lie ectopic epithelial cells termed aberrant basaloid cells (Deng et al., 2026; Svobodová et al., 2025). Characterized transcriptomically as KRT5/KRT17, these cells co-express markers of senescence (p21, p16, GDF15), epithelial-to-mesenchymal transition (EMT), and extracellular matrix remodeling, including collagen VII (Svobodová et al., 2025). Spatial transcriptomic profiling demonstrates that these aberrant basaloid cells line the highly remodeled epithelial-mesenchymal interface immediately overlying pathological fibroblasts, where they serve as crucial paracrine hubs promoting fibrogenesis (Deng et al., 2026; Jones et al., 2025). Bulk and single-cell transcriptomic analyses indicate that these senescent epithelial populations undergo substantial epigenetic and transcriptional modifications, acquiring an altered, secretory phenotype that further drives tissue stiffness and suppresses healthy stem cell renewal (Melo-Narváez et al., 2024). This epithelial dysfunction extends into the conducting and small airways. Accumulating evidence reveals that small airway ciliary impairment and compromised mucociliary clearance (MCC) are early, active drivers of IPF pathogenesis rather than secondary consequences of parenchymal collapse (Wang et al., 2025). Mature multiciliated cells in the conducting airway epithelium are responsible for clearing inhaled particulates, pathogens, and cellular debris (Wang et al., 2025). In patients with IPF, small airway epithelial cells (SAECs) demonstrate a significant, intrinsic decline in ciliogenesis potency, characterized by a marked reduction in the expression of Forkhead box protein J1 (FOXJ1)---the master transcriptional orchestrator of ciliogenesis---and fewer -IV-tubulin-positive ciliated cells (Wang et al., 2025). When SAECs are subjected to external injuries (such as bleomycin challenge) or serial cell passage, ciliary differentiation is selectively impaired, while mucin production (MUC5AC and MUC5B) remains unaffected

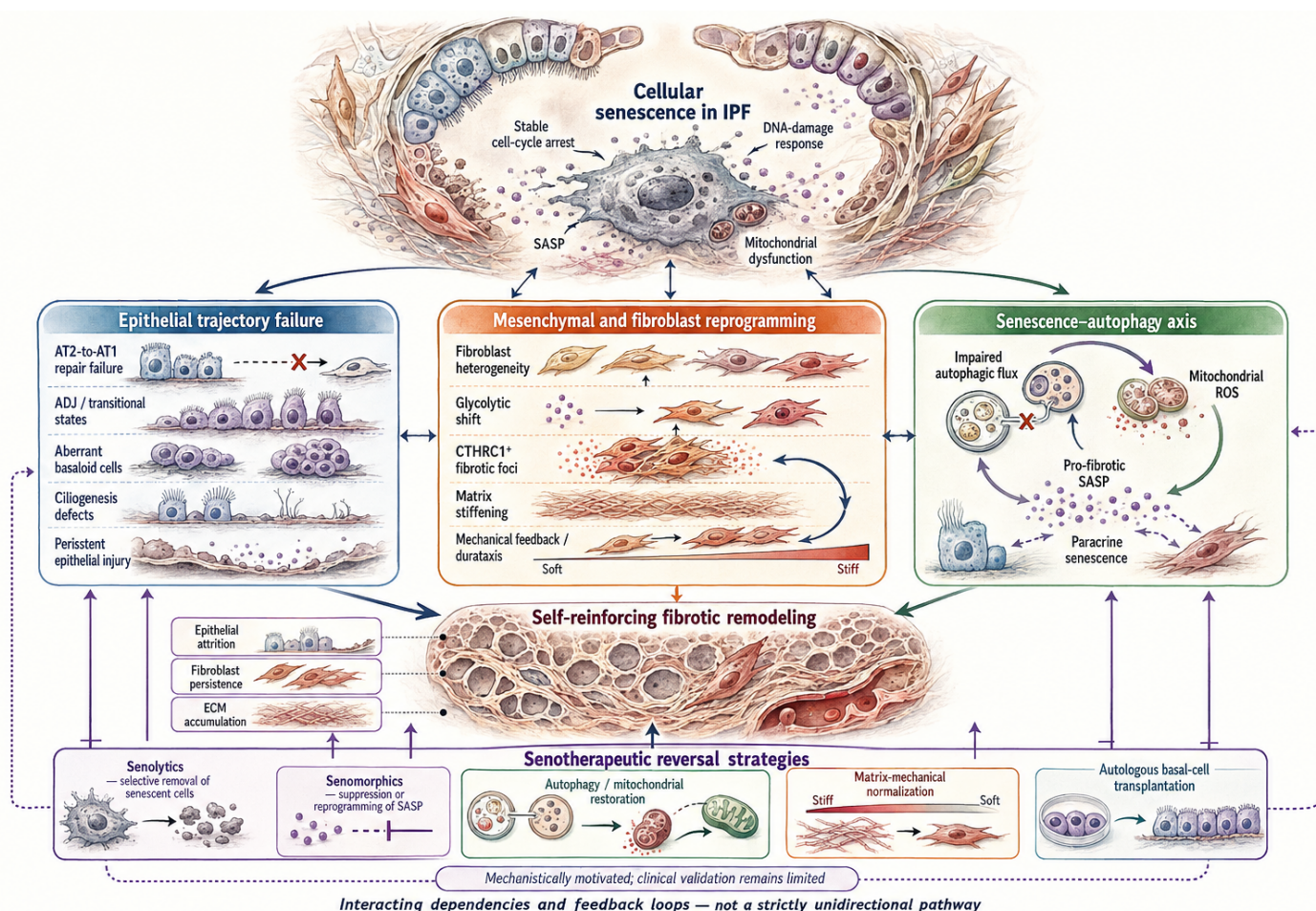


Figure 1 | Conceptual organization of cellular-senescence pathways in idiopathic pulmonary fibrosis. Cellular senescence forms a pathogenic hub characterized by stable cell-cycle arrest, persistent DNA-damage signalling, mitochondrial dysfunction and secretion of the senescence-associated secretory phenotype (SASP). This state interacts with three overlapping mechanistic branches. Epithelial trajectory failure involves unsuccessful alveolar type 2-to-type 1 cell differentiation, accumulation of transitional and aberrant basaloid populations, ciliogenesis defects and persistent epithelial injury. Mesenchymal reprogramming encompasses fibroblast heterogeneity, glycolytic shifts, CTHRC1-positive fibrotic foci and mechanically reinforced migration and activation within stiffened extracellular matrix. The senescence–autophagy axis links impaired autophagic flux with mitochondrial reactive oxygen species, profibrotic SASP signalling and paracrine propagation of senescence. These processes converge on epithelial attrition, fibroblast persistence and extracellular-matrix accumulation, producing self-reinforcing fibrotic remodeling. Potential reversal strategies include senolytics, senomorphics, restoration of autophagy and mitochondrial function, normalization of matrix mechanics and autologous basal-cell transplantation. Arrows represent interacting mechanistic dependencies and feedback relationships rather than strictly unidirectional causation; clinical validation of these therapeutic approaches remains limited.

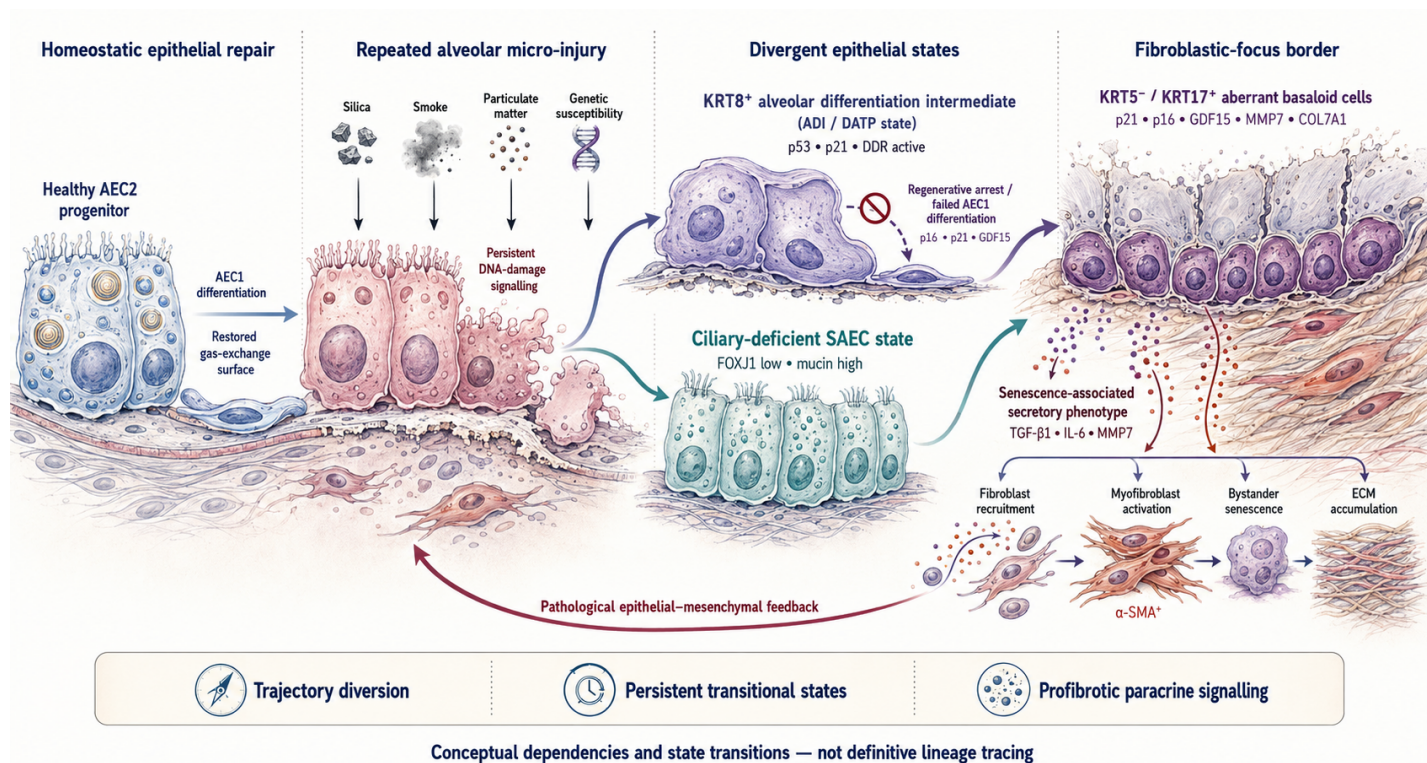


Figure 2 | Reprogrammed epithelial trajectories following alveolar micro-injury. Under homeostatic conditions, alveolar epithelial type 2 (AEC2) progenitors differentiate into flattened alveolar type 1 (AEC1) cells to restore the gas-exchange surface. Repeated injury associated with inhaled particulates, smoke, silica or genetic susceptibility disrupts this regenerative program and sustains DNA-damage signalling. Injured progenitors are consequently diverted into persistent KRT8-positive alveolar differentiation intermediate or damage-associated transient progenitor states and ciliary-deficient small-airway epithelial states characterized by low FOXJ1 and increased mucin expression. Regenerative arrest prevents completion of AEC1 differentiation and promotes the accumulation of KRT5-negative/KRT17-positive aberrant basaloid cells at the epithelial–fibroblastic-focus interface. These persistent epithelial populations express senescence-associated markers and release SASP mediators, including TGF-1, IL-6 and MMP7, which recruit fibroblasts, promote myofibroblast differentiation, propagate bystander senescence and increase extracellular-matrix deposition. The resulting epithelial–mesenchymal feedback reinforces tissue injury and fibrotic remodeling. Arrows denote conceptual state transitions and mechanistic dependencies rather than definitive lineage tracing.

(Wang et al., 2025).

Importantly, conditioned medium harvested from SAECS with defective ciliogenesis or silenced FOXJ1 potently stimulates healthy lung fibroblasts to differentiate into -smooth muscle actin (-SMA)-positive and fibronectin-positive myofibroblasts, demonstrating that ciliary impairment mediates pro-fibrotic epithelial-mesenchymal crosstalk (Wang et al., 2025). This deficiency is further compounded by the gain-of-function MUC5B promoter variant (rs35705950), the strongest genetic risk factor for IPF, which drives massive mucin accumulation in the distal bronchioles and alveoli, triggering chronic endoplasmic reticulum (ER) stress and further stabilizing the senescent, basaloid state (Deng et al., 2026).

2.2 Branch 2: Fibroblast Heterogeneity, Glycolytic Reprogramming, and Biomechanical Feedback

The mesenchymal compartment of the IPF lung exhibits profound cellular heterogeneity, containing distinct subpopulations of fibroblasts that occupy different pathological niches (Deng et al., 2026), summarized across their markers, metabolic programs, and apoptotic sensitivity in Table 2. Single-cell transcriptomics has identified that the active core of the fibroblastic focus---the primary site of active matrix deposition---is dominated by a highly specialized, collagen-producing fibroblast subpopulation marked by the expression of Collagen Triple Helix Repeat Containing 1 (CTHRC1) (Deng et al., 2026; Melo-Narváez et al., 2024). CTHRC1 fibroblasts exhibit extreme invasiveness, apoptotic resistance, and robust collagen synthesis, representing the primary engine of structural scarring (Deng et al., 2026; Melo-Narváez et al., 2024). Spatiomics and lineage-tracing studies describe a dynamic cellular trajectory wherein quiescent lung fibroblasts and lipid-storing lipofibroblasts undergo a phenotypic switch toward these pathogenic, CTHRC1 myofibroblasts under the influence of local biochemical and biophysical cues (Deng et al., 2026; Shanmugasundaram et al., 2024).

The persistence and aggressiveness of these activated mesenchymal populations are tightly regulated by metabolic reprogramming and biomechanical feedback loops (Alvarado-Vasquez et al., 2024; Zhang et al., 2022). In the fibrotic lung, myofibroblasts shift their primary energy production from oxidative phosphorylation to aerobic glycolysis, a metabolic phenomenon analogous to the Warburg effect in cancer cells (Alvarado-Vasquez et

al., 2024). This glycolytic reprogramming is driven by the up-regulation of rate-limiting enzymes, including 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) and hexokinase 2 (HK2), which are induced downstream of transforming growth factor-beta 1 (TGF-1) signaling (Alvarado-Vasquez et al., 2024). Elevated glycolysis results in the excessive accumulation and extracellular secretion of lactic acid, which establishes a local acidic microenvironment (Alvarado-Vasquez et al., 2024). This extracellular acidity further activates latent, matrix-bound TGF-1, creating a self-sustaining, pro-fibrotic feed-forward circuit (Alvarado-Vasquez et al., 2024).

Concurrently, this metabolic shift is reinforced by a highly altered biomechanical microenvironment (Zhang et al., 2022). As myofibroblasts deposit disorganized fibrillar collagens and matricellular proteins, the mechanical stiffness of the extracellular matrix (ECM) increases exponentially (Svobodová et al., 2025; Zhang et al., 2022). This local stiffening is sensed by cell-surface mechanoreceptors, which transduce physical forces into intracellular biochemical signals (such as the MRTF-actin and YAP/TAZ axes), a process known as mechanotransduction (Zhang et al., 2022).

Stiff substrates persistently stimulate lung fibroblasts to remain in an activated, contractile, and synthetic state (Zhang et al., 2022). Over time, fibroblasts exposed to stiff environments acquire a "mechanical memory" through chromatin remodeling and stable epigenetic modifications (such as altered histone acetylation and DNA methylation), allowing them to maintain their pro-fibrotic, senescent state even if they are removed from the stiff microenvironment (Zhang et al., 2022). Consequently, the integration of mechanical forces with glycolytic reprogramming locks the mesenchymal compartment into an irreversible, self-perpetuating fibrotic state that resists physiological resolution (Alvarado-Vasquez et al., 2024; Zhang et al., 2022).

2.3 Branch 3: The Senescence-Autophagy Axis, Mitochondrial ROS, and the SASP Secretome

At the molecular scale, cellular senescence and macroautophagy are best conceptualized as intertwined components of a single, disrupted cellular quality-control network (Min et al., 2026); the principal signaling axes underlying this network, including their mechanobiological and autophagy-regulatory effects, are catalogued in Table 3. Autophagy is a critical homeostatic mechanism

Table 1. Epithelial cell states, metaplasia, and regenerative arrest in idiopathic pulmonary fibrosis. This table catalogues the major senescent and transitional epithelial cell phenotypes identified across single-cell and spatial transcriptomic studies of the IPF lung, including aberrant basaloid cells, alveolar differentiation intermediates (ADI/DATP), metaplastic airway basal cells, and ciliary-deficient small airway epithelial cells. For each phenotype, the table lists defining molecular markers, spatial localization within the alveolar or airway niche, presumed cellular origin and lineage trajectory, the senescence pathway(s) activated, the dominant SASP secretory profile, and the resulting functional impact on the surrounding alveolar microenvironment, with supporting citations.

Epithelial Cell Phenotype / Subtype	Key Molecular Markers	Primary Spatial Localization	Cellular Origins & Lineage Trajectories	Senescence Pathways Activated	SASP Secretory Profile & Cytokines	Functional Impact on Alveolar Microenvironment	Grounding References (APA Style)
Aberrant Basaloid Cells (AbBa / KRT5/KRT17)	KRT17, TP63, LAMB3, LAMC2, CDH2, VIM, FN1, COL1A1, GDF15, MMP7	Located at the direct borders/edges of active fibroblastic foci, adjacent to diseased stroma, and lining honeycomb cysts.	Failed or ectopic differentiation path originating from mature alveolar type II (AT2) cells and SCGB3A2 airway secretory lineages.	Co-expression of stable cell-cycle arrest pathways governed by CDKN1A (p21) and CDKN2A (p16).	Robust secretion of stroma-remodeling matrix metalloproteinases (MMP7), GDF15, TGF-1, IL-6, and IL-1.	Drives fibroblast-to-myofibroblast transition (FMT), induces paracrine "bystander" senescence, and deposits pathological fibrillar ECM.	Adams et al. (2020); Habermann et al. (2020); Mayr et al. (2024); Svobodová et al. (2025)
Alveolar Differentiation Intermediate (ADI) Cells	KRT8, CLDN4, YAP1, TAZ	Preserved alveolar regions with fibrotic septa and at the margins of collapsing alveoli.	Arise from injured mature AT2 cells or distal small airway Scgb1a1 club cell progenitors during aberrant repair.	Persistent, non-mitotic arrest characterized by chronic p53 activation, DNA damage responses (DDR), and telomere attrition.	Secretes high levels of TGF-1, IL-6, and various pro-inflammatory SASP chemokines.	Locks alveolar regeneration, failing to transition into gas-exchanging AT1 cells, and promotes chronic tractional alveolar collapse.	Jones et al. (2026); Min et al. (2026); Svobodová et al. (2025)
Metaplastic Airway Basal Cells (KRT17 ^{high} / PTEN ^{low})	KRT17, p63, GPR87	Dilated distal bronchioles and lining the pseudostratified epithelium of pathological honeycomb cysts.	Proximal cartilaginous airway basal stem cells undergoing aberrant distal migration and expansion ("bronchiolization").	Replicative senescence marked by severe down-regulation of PTEN and loss of normal ciliary-fate program.	High release of IL-6, IL-8, and macrophage-activating factors such as osteopontin (SPP1).	Directly stimulates mesenchymal proliferation, recruits neutrophils and monocytes, and impairs local mucociliary clearance.	Deng et al. (2026); Jones et al. (2026); Svobodová et al. (2025)
Activated Airway Club Cells (Club_MMP1 ^{hi} Subpopulation)	KRT17, CC10 (SCGB1A1), MMP1	First-line epithelial barrier of remodeled bronchioles and terminal conducting small airways.	Homeostatic ciliated club cells undergoing injury-induced activation and basaloid metaplasia.	Stress-induced premature senescence (SIPS) driven by environmental inhaled toxicants and oxidative injury.	Off-on switch-like upregulation of MMP1 and lysosomal proteases like CTSB.	Drives extensive basement membrane degradation, facilitating active fibroblast invasion into the alveolar space.	Fu et al. (2026)
Ciliary-Deficient Small Airway Epithelial Cells (SAECs)	FOXJ1 (low), -IV-tubulin (low), MUC5B, MUC5AC	Conducting small bronchioles and distal terminal bronchioles in advanced stages of IPF.	Mature ciliated small airway epithelial cells undergoing phenotypic degradation and loss of multiciliogenesis.	DNA damage response (DDR) activation and stable cycle withdrawal via the TP73-MYB-FOXJ1 axis.	Enhanced secretion of pro-fibrotic cytokines, particularly TGF-1, IL-6, and MMP1.	Triggers severe impairment in mucociliary clearance (MCC), promoting alveolar mucus plugging, and drives fibroblast activation.	Wang et al. (2025)
Proximal Basal Stem Cells (Small Bronchi-Derived / Healthy State)	p63, Krt5, ITGA6, NGFR, Ki67	Proximal cartilaginous small bronchi spared from severe distal parenchymal distortion.	Healthy, resident tissue-specific adult stem cell pool maintained in a protected, homeostatic niche.	Distinctly non-senescent phenotype, preserving robust proliferative and clonogenic properties across multiple passages.	Lacks inflammatory SASP; secretes homeostatic and regenerative growth factors.	Retains complete capacity to differentiate into functional ciliated and club cells, serving as a clean therapeutic transplant reservoir.	Snyder et al. (2025)

Injured Alveolar Type II (AT2) Cells with Proteostatic Stress	SFTPC (mutant), BIP, ATF4, CHOP, p53	Alveolar niches adjacent to active fibrotic areas and collapsing septa.	Alveolar progenitor AT2 cells exposed to genomic instability, microinjuries, or genetic mutations (e.g., SFTPC/ERT).	UPR-induced endoplasmic reticulum stress (ERS) triggering stable senescence arrest via the PERK/eIF2 axis.	High-level production of TGF-1, PAI-1, IL-6, and CXCL1 chemokines.	Compromises lung surfactant production, induces apoptosis resistance, and recruits macrophages to establish a pro-inflammatory microenvironment.	Gong et al. (2026); Jones et al. (2026); Torres-Machorro et al. (2025)
SIRT3-Deficient Alveolar Progenitor Cells	SIRT3 (low), SFTPC, p21	Distal gas-exchange alveoli and active transitional zones.	Alveolar type II cells experiencing age-related metabolic and mitochondrial decay.	Mitochondrial-driven senescence due to increased mitochondrial oxidative stress and bioenergetic crash.	Elevated levels of PAI-1, TNF- α , endothelin-1, and PDGF.	Enhances adjacent myofibroblast proliferation, disrupts stem cell renewal, and accelerates spatial propagation of fibrotic niches.	Baurzhan et al. (2026); Min et al. (2026)
MUC5B-Overexpressing Metaplastic Alveolar Cells	MUC5B (rs35705950 promoter variant), KRT5	Pathological honeycomb cysts and distal airspace lesions.	AT2 cells or club cells undergoing metaplastic lineage conversion under chronic endoplasmic reticulum stress.	Stress-induced senescence driven by proteostatic collapse and accumulated mucin-protein folding stress.	High levels of mucin secretion, IL-6, and ADAM17.	Promotes severe mucus retention, plugs alveolar gas exchange surfaces, and induces a self-perpetuating fibrotic niche via mechanochemical stress.	Deng et al. (2026); Svobodová et al. (2025); Wang et al. (2025)
Damage-Associated Transitional Progenitors (DATPs / KRT8)	KRT8, CLDN4, p21	Active transition zones linking normal alveoli to dense fibrotic scars.	Alveolar epithelial progenitor cells arrested midway during differentiation into gas-exchanging AT1 cells.	Characterized by persistent DNA damage response (DDR) and p21-mediated cycle withdrawal.	Secretes TGF-1, IL-1, and IL-6.	Perpetuates alveolar collapse and tissue traction forces, establishing a positive feedback loop of mechanobiological injury.	Deng et al. (2026); Jones et al. (2026); Svobodová et al. (2025)

Table 2. Mesenchymal lineages, heterogeneity, and activation dynamics in the fibrotic lung. This table summarizes the major fibroblast and mesenchymal-derived subpopulations described in IPF, including CTHRC1+ invasive myofibroblasts, hyaluronan-producing fibroblasts, lipofibroblasts, and several senescent fibroblast phenotypes (e.g., FABP5-overexpressing, EPDR1-upregulated, GSR-depleted). Columns detail key molecular markers, spatial niche, transcriptional/epigenetic regulators, metabolic reprogramming and bioenergetics, secreted biomarkers and ECM components, and apoptosis sensitivity/proteostasis status, with supporting citations.

Mesenchymal Lineage / Phenotype	Key Molecular Markers	Spatial Niche / Tissue Localization	Primary Transcriptional & Epigenetic Regulators	Metabolic Reprogramming & Bioenergetics	Secreted Biomarkers & ECM Components	Apoptosis Sensitivity & Proteostasis	Grounding References (APA Style)
Invasive Myofibroblasts (CTHRC1+/-SMA)	CTHRC1, ACTA2 (-SMA), COL1A1, FN1	Highly concentrated in the active core of fibroblastic foci, directly underlying the aberrant epithelial cap.	TGF- β /SMAD3 axis, mechanical YAP/TAZ nuclear translocation, and MRTF-actin signaling.	Massive shift toward aerobic glycolysis (Warburg effect) with lactate accumulation driven by PFKFB3/HK2.	Disorganized fibrillar collagens (types I, III), fibronectin, and tenascin-C.	Highly resistant to apoptosis due to upregulation of Bcl-2/Bcl-xL and downregulation of caspases.	Deng et al. (2026); Jones et al. (2026); Torres-Machorro et al. (2025); Zhang et al. (2026)
Hyaluronan-Producing Fibroblasts (HAS1 ^{high} / HAS2 ^{high})	HAS1, HAS2, CD44	Subpleural region, adjacent to aberrant basaloid epithelial cells at the fibrotic front.	Highly responsive to IL-1 and IL-4/IL-13 pro-inflammatory signaling.	Shifted toward glycan and glycosaminoglycan synthesis to sustain rapid matrix hydration.	Highly fragmented, low-molecular-weight hyaluronic acid (HA) (Jones et al., 2026).	Moderate resistance; exhibits high migratory and tissue-invasive dynamics via CD44 activation.	Jones et al. (2026)

Lipofibroblasts (LIFs / Resolution-Capable State)	PLIN2, PDGFR, FABP4	Healthy/preserved alveolar niches; can transdifferentiate reversibly in young lungs.	Active Wnt-catenin and PPAR-pathways maintaining adipogenic homeostasis.	Dominated by fatty acid storage, lipid droplet accumulation, and oxidative phosphorylation.	Matrix-remodeling enzymes and alveolar-trophic factors.	Retains physiological apoptosis sensitivity; lacks pro-survival senescence markers.	Alvarado-Vasquez et al. (2024); Deng et al. (2026)
FABP5-Overexpressing Senescent Myofibroblasts	FABP5, FASN, UCP2, p21, p16	Fibrotic foci, particularly in aged mouse models and occupational silicosis.	Induced by chronic silica-derived or bleomycin-derived oxidative stress and GSK3 activation.	Relentless fatty acid synthesis coupled to UCP2-mediated mitochondrial uncoupling and ROS overproduction.	Secretes pro-fibrotic lipid-binding chaperones as an unconventional SASP factor.	Profoundly apoptosis-resistant; persistent accumulation drives paracrine -catenin signaling in neighboring stroma.	Sun et al. (2026)
EPDR1-Upregulated Pathological Fibroblasts	EPDR1, LAMP1 (normal levels), LC3B, p62, p21	Active fibrotic lesions in lung tissue, also detectable in BALF and serum.	Epigenetic remodeling and TGF-transcriptional activation.	Suppressed lysosomal acidification and compromised autophagic degradation.	Ependymin-related protein 1 (EPDR1), a novel biomarker correlating with high mortality.	Highly resistant; EPDR1 knockdown restores lysosomal function and reverses cellular senescence.	Southern & Gadre (2025)
Glutathione Reductase (GSR)-Depleted Senescent Fibroblasts	GSR (low), FN1, COL1A1, -SMA, p53, p21	Distal lung parenchyma undergoing chronic oxidative stress.	Driven by age-related glutathione depletion and cellular redox imbalance.	Compromised glutathione-redox state (low GSH/GSSG ratio), shifting cells to hyper-oxidative senescence.	High levels of type I collagen and fibronectin deposition.	Apoptosis-resistant; exhibits marked increases in -galactosidase activity and migratory capabilities.	Zhang et al. (2025)
Senescent Primary Human Lung Fibroblasts (phLFs - Stimulus-Induced)	CDKN1A (p21), CDKN2A (p16), yH2Ax, SA-gal	Remodeled alveolar interstitial spaces and fibrotic zones.	Triggered by DNA damage (bleomycin), oxidative stress (HO), or canonical TGF-1 (5 ng/ml).	Metabolic rewiring from oxidative phosphorylation to glycolysis, driven by STAT3 and glucose transporters.	Prominent release of GDF-15, IL-6, and MMP-3 into the extracellular space.	Stable cycle arrest; TGF-1 primarily drives a pro-fibrotic rather than pure senescent phenotype at physiological doses.	Min et al. (2026); Torres-Machorro et al. (2025)
Endothelial-Derived Fibroblast-like Cells (EndMT State)	CD31 (low), -SMA (high), LGALS3 (galectin-3)	Perivascular niches and severely remodeled pulmonary microvasculature.	Governed by endothelial senescence, TGF-1, and AKT/catenin/GSK3 signaling.	Glycolytic shift driven by cellular aging and chronic tissue hypoxia.	Expresses mesenchymal contractile proteins, fibronectin, and galectin-3.	High resistance to apoptosis, actively contributing to perivascular collagen deposition.	Alvarado-Vasquez et al. (2024); Deng et al. (2026)
Pericyte-Derived Myofibroblasts	ABCG2 (loss), PDGFR, PDGFR	Alveolar capillaries and interstitial boundary layers.	Stimulated by chronic microvascular leakage, PDGF-BB, and mechanical shear stress.	Metabolic transition supporting high-contraction structural stabilization.	Deposition of specialized basement membrane collagens (e.g., type IV, type VI).	Epigenetic transition drives robust survival advantages and cellular invasiveness.	Alvarado-Vasquez et al. (2024)
Inflammatory Fibroblasts (Subpopulations 1 & 3)	SERPINE1 (PAI-1), IL-6, GDF15, p21	Interstitial septa displaying high immune-cell infiltration.	Activated by extracellular granule release from senescent CD8+ T cells and alveolar macrophage crosstalk.	Dominated by pro-inflammatory cytokine translation and high protein synthesis/folding stress.	Massive levels of IL-6, PAI-1, and MMP-3.	High proteostatic stress; survives via persistent anti-apoptotic cellular defenses.	Min et al. (2026); Okereke et al. (2026); Snyder et al. (2026)

responsible for the lysosomal degradation and recycling of misfolded proteins and damaged organelles, thereby preserving intracellular proteostasis (Baurzhan et al., 2026; Min et al., 2026). Under physiological conditions, healthy autophagic flux acts as a protective barrier that suppresses premature senescence (Min et al., 2026). In IPF, however, this protective barrier is completely disabled in both the alveolar epithelium and the mesenchymal compartments (Min et al., 2026; Torres-Machorro et al., 2025).

In the lungs of patients with IPF, impaired autophagic flux is biochemically characterized by a marked reduction in the lipidated form of microtubule-associated protein 1 light chain 3B (LC3B-II) and the pathological accumulation of p62/sequestosome-1 (Min et al., 2026; Torres-Machorro et al., 2025). This autophagic impairment is driven by hyperactive nutrient-sensing signaling via the PI3K-Akt-mTOR pathway, which directly suppresses the initiation of autophagy and the formation of autophagosomes (Min et al., 2026; Torres-Machorro et al., 2025). Furthermore, novel effectors such as ependymin-related 1 (EPDR1)---a lysosome-associated transmembrane glycoprotein that is significantly up-regulated in IPF fibroblasts and biological fluids---have been shown to negatively regulate lysosomal acidification (Southern & Gadre, 2025). The resulting loss of lysosomal acidity halts autophagic degradation, causing the intracellular accumulation of damaged macromolecular aggregates, persistent cellular stress, and the activation of p21- and p16-dependent senescent pathways (Southern & Gadre, 2025).

Figure 3 summarizes this cascade schematically, tracing the sequence from upstream PTEN/Sirt1 loss and mTOR hyperactivation through disabled macroautophagy, lysosomal acidification failure, mitochondrial ROS accumulation, chronic DNA damage signaling, and, ultimately, stable p21/p16-driven senescence with SASP output.

This proteostatic collapse is directly linked to the failure of mitophagy---the selective autophagic clearance of damaged mitochondria (Min et al., 2026). Impaired mitophagy leads to the progressive accumulation of large, dysmorphic, and dysfunctional mitochondria within senescent cells (Min et al., 2026; Zhang et al., 2024). These abnormal mitochondria exhibit decreased membrane potential, impaired fatty acid oxidation, and uncoupled respiration, resulting in the massive overproduction of mitochondrial reactive oxygen species

(ROS) (Min et al., 2026; Zhang et al., 2024). This persistent oxidative stress acts as a potent DNA-damaging agent, sustaining the activation of ATM and ATR kinases, stabilizing p53, and locking the cells into an irreversible senescent state (Baurzhan et al., 2026; Li et al., 2023). Under chronic stress, senescent fibroblasts also up-regulate fatty acid binding protein 5 (FABP5), which competitively inhibits the ubiquitination and degradation of fatty acid synthase (FASN), disrupting lipid homeostasis and engaging a downstream uncoupling protein 2 (UCP2)-dependent mitochondrial axis that amplifies ROS generation and reinforces the senescent phenotype (Sun et al., 2026).

Senescent cells remain highly active metabolically and exert their pathological influence on the lung microenvironment through the robust secretion of the senescence-associated secretory phenotype (SASP) (Baurzhan et al., 2026; Torres-Machorro et al., 2025). The SASP is a complex, context-dependent cocktail of pro-inflammatory cytokines (IL-6, IL-8, IL-1), chemokines, growth factors (TGF-1, connective tissue growth factor \[CTGF\]), and extracellular matrix-remodeling metalloproteinases (such as MMP-3 and MMP-12) (Baurzhan et al., 2026; Melo-Narváez et al., 2024; Torres-Machorro et al., 2025). Additionally, metabolic chaperones like FABP5 are actively secreted as unconventional SASP factors by senescent myofibroblasts, directly activating paracrine -catenin signaling in neighboring quiescent cells (Sun et al., 2026).

The chronic secretion of these SASP factors into the interstitial space induces paracrine \"bystander\" senescence in adjacent healthy epithelial cells and fibroblasts, creating a self-reinforcing, pathogenic circuit that drives spatial fibrotic expansion (Baurzhan et al., 2026; Min et al., 2026). Furthermore, the SASP establishes a highly immunosuppressive and pro-fibrotic niche by recruiting and metabolically reprogramming SPP1/MERTK monocyte-derived alveolar macrophages, which actively cooperate with activated fibroblasts to write the physical scar at the fibroblast-focus edge (Deng et al., 2026).

2.4 Branch 4: Emergent Senotherapeutic Targets and Functional Reversal Strategies

Table 4 summarizes the translational landscape described below, spanning approved antifibrotics through early-phase senotherapeutics. The recognition of cellular

Table 3. Intercellular signaling pathways, crosstalk axes, and mechanical feedback loops sustaining fibrotic remodeling. This table details the principal ligand-receptor signaling axes that connect epithelial, mesenchymal, macrophage, and T-cell compartments in the IPF lung, including the canonical TGF-1/Smad axis, PI3K/Akt/mTOR signaling, the Sirt1/HSF1/HSPs quality-control pathway, and the mitochondrial cGAS-STING mtDNA leakage axis. Each row specifies the ligands/receptors involved, the sender-receiver cell dialogue, downstream intracellular cascades, mechanobiological feedback mechanics, effects on cellular senescence programs, and autophagy/mitophagy regulatory consequences, with supporting citations.

Intercellular Crosstalk / Pathogenic Axis	Principal Ligands & Receptors Involved	Cell Type Dialogue (Sender Receiver)	Intracellular Downstream Cascades	Mechanobiological Feedback Mechanics	Impact on Cellular Senescence Programs	Autophagy & Mitophagy Regulatory Effects	Grounding References (APA Style)
The Canonical TGF-1/Smad Signaling Axis	TGF-1 TRII and TRI (ALK5)	Epithelial cells/Macrophages Fibroblasts & Myofibroblasts.	Smad2/Smad3 phosphorylation and nuclear translocation with Smad4 co-regulator.	Promotes high-tension stress fiber formation and -SMA upregulation, stiffness-driven integrin v monomer feedback.	Directly induces epithelial senescence via p53 and p21 pathways.	Strong inhibitor of autophagic flux; suppresses metabolic clearance to reinforce the pro-fibrotic state.	Ding et al. (2021); Deng et al. (2026); Shakeel et al. (2023); Torres-Machorro et al. (2025)
The Non-Canonical PI3K/Akt/mTOR Pathway	Growth factors (PDGF, FGF, VEGF) Tyrosine Kinase Receptors (RTKs)	Metaplastic Basal Cells Resident Fibroblasts.	Phosphorylation of PI3K, activation of Akt, and hyperactivation of mTORC1 and mTORC2 complexes.	Upregulates the translation of structural matrix proteins and triggers EMT transcription factors SNAIL1/ZEB1.	Drives replicative senescence and persistent SASP translation.	Powerful inhibitor of macroautophagy and lysosomal biogenesis; accumulates damaged organelles and p62.	Deng et al. (2026); Gao et al. (2025); Min et al. (2026); Shakeel et al. (2023)
The Sirt1/HSF1/HSPs Quality-Control Pathway	GLP-1 receptor activation (e.g., via semaglutide)	Autocrine/Paracrine loops in Alveolar Epithelial cells.	Sirt1-mediated deacetylation of HSF1 (Heat Shock Factor 1).	Mitigates cellular tension and halts stiffness-induced DNA double-strand breaks.	Potently suppresses hydrogen peroxide-induced and age-associated cellular senescence.	Rescues mitochondrial bioenergetics and protects cells from oxidative damage via chaperone expression.	Qian et al. (2026)
The PERK/eIF2/ATF4 Integrated Stress Response (ISR)	Endoplasmic reticulum (ER) stress sensors (p-PERK)	Injury-stressed AEC2 cells Interstitial Myofibroblasts.	eIF2 phosphorylation leading to the selective translation of transcription factor ATF4.	Promotes alternative splicing of matrix components under biomechanical strain.	Drives cellular senescence via activation of ATM/ATR and upregulation of p53, p21, and p16.	Linked to defective mitophagy; ISR inhibition with ISRIB reverses cellular senescence and restores proteostasis.	Baurzhan et al. (2026); Li et al. (2023)
The Osteopontin (SPP1) / CD44 Macrophage-Fibroblast Axis	SPP1 (Osteopontin) CD44 and integrin receptors	Proliferating SPP1/MERTK Macrophages CTHRC1 Myofibroblasts.	Intracellular AKT and -catenin nuclear signaling pathways.	Drives cell motility and directed migration along pathological extracellular matrix stiffness gradients.	SASP-derived SPP1 reinforces paracrine "bystander" senescence in adjacent healthy epithelium.	Suppresses basic autophagic clearance while reinforcing survival advantages and apoptosis resistance.	Deng et al. (2026)
The Interleukin-11 (IL-11) "TIME" Signaling Loop	IL-11 gp130 and IL-11RA receptor complexes	KRT5/KRT17 Metaplastic Basaloid cells AECs & Fibroblasts.	Activation of MEK/ERK ("TIME" pathway) and gp130-mediated STAT3 phosphorylation.	Upregulates matrix stiffness and myofibroblast contractility.	Amplifies the pro-inflammatory SASP profile and triggers stress-induced premature senescence.	Interferes with autophagic degradation pathways, locking AT2 cells in arrested transitional states.	Yu et al. (2025)
The FABP5/FASN Extracellular Paracrine Loop	Secreted extracellular FABP5 adjacent fibroblast membrane receptors	Senescent Myofibroblasts Quiescent resident Fibroblasts.	Intracellular -catenin signaling activation.	Amplifies tissue-wide tension and establishes a mechanical memory loop via matrix remodeling.	Induces stable cell-cycle arrest in neighboring normal fibroblasts via paracrine propagation.	Impairs mitophagy, accumulating dysfunctional and dysmorphic mitochondria.	Sun et al. (2026)

The CD8 T Cell-Derived Granzyme K Pro-Fibrotic Axis	Extracellular granzyme K (GZMK)	Senescent exhausted CD8 T cells Airway/Alveolar Epithelial cells.	Up-regulates MHC II presentation and stimulates intracellular MMP28 production.	Accelerates tissue destruction (honeycombing) and alters regional parenchymal compliance.	GZMK-exposed lung epithelial cells undergo premature senescence and express high levels of IL-8.	Compromises cellular quality control, driving the accumulation of senescent, hypofunctional CD8+ compartments.	Okereke et al. (2026)
The Integrin-FAK-YAP/TAZ Mechanotransduction Loop	Integrins v6, v1, and v3 mechanical matrix ligands	Remodeled Extracellular Matrix Epithelial Cells and Fibroblasts.	Focal Adhesion Kinase (FAK)/SRC pathway activation, halting YAP/TAZ phosphorylation to allow nuclear entry.	Central driver of mechanical memory; translates matrix rigidity into active fibrogenic gene transcription.	Sustained mechanical stress drives lung structural cells toward a chronic senescent phenotype.	Suppresses autophagy to protect activated myofibroblasts from metabolic exhaustion on stiff substrates.	Min et al. (2026); Torres-Machorro et al. (2025); Zhang et al. (2026)
The Mitochondrial cGAS-STING mtDNA Leakage Axis	Free cytosolic mitochondrial DNA (mtDNA) cGAS dimers	Stress-injured AT2 cells Surrounding Alveolar Environment.	STING oligomerization, leading to the recruitment and activation of interferon regulatory factors.	Potentiated by mechanical stretch and physical alveolar microinjury.	Triggers deep senescence arrest, driving high transcription of p21 and p16.	Mitophagy failure prevents the clearance of fractured mitochondria, spilling mtDNA and sustaining the inflammatory loop.	Gong et al. (2026); Min et al. (2026); Zhang et al. (2026)

Table 4. Translational therapeutic landscape of approved, investigational, and emerging senotherapeutic modalities in idiopathic pulmonary fibrosis. This table compares current standard-of-care antifibrotics (pirfenidone, nintedanib) with investigational pathway-directed agents (bexotegrast, nerandomilast, admilparant, inhaled treprostinil) and emerging senotherapeutics (dasatinib plus quercetin, EF24, curculigoside, ISRIB), summarizing target molecule/pathway, mechanistic class, preclinical efficacy, current clinical trial status, functional outcomes, and adverse-effect/safety considerations, with supporting citations.

Therapeutic Intervention / Drug	Target Molecule / Pathway	Class / Mechanistic Action (Senolytic, etc.)	Preclinical Efficacy Profile	Current Clinical Status / Trial ID	Functional Outcomes & Endpoints	Adverse Effects & Safety Considerations	Grounding References (APA Style)
Nintedanib (Ofev®)	VEGFR, FGFR, PDGFR tyrosine kinases, and Src family	Multitargeted tyrosine kinase inhibitor; suppresses growth factor-stimulated fibroblast contraction and motility.	Inhibits fibrocyte activity, prevents M2 macrophage polarization, and downregulates procollagen I and TGF-β.	FDA-approved for IPF and progressive pulmonary fibrosis.	Significantly reduces the annual rate of Forced Vital Capacity (FVC) decline; lowers acute exacerbation risk.	High incidence of diarrhea, nausea, vomiting, weight loss, and potential hepatotoxicity.	Baurzhan et al. (2026); Deng et al. (2026); Shakeel et al. (2023)
Pirfenidone (Esbriet®)	TGF-1, TNF-α, and downregulates HSP47	Small molecule anti-fibrotic; reduces fibroblast proliferation, TGF-β-induced Smad3 phosphorylation, and collagen deposition.	Lowers hydroxyproline accumulation, reduces fibrocytes, and displays anti-inflammatory and anti-oxidant properties.	FDA-approved for IPF.	Slows FVC decline over 52 weeks (CAPACITY/ASCEND trials) by approximately 47.9%.	Gastrointestinal dyspepsia, nausea, photosensitivity rash, headache, fatigue, and liver enzyme elevation.	Baurzhan et al. (2026); Deng et al. (2026); Shakeel et al. (2023)
Dasatinib + Quercetin (D+Q)	Src kinase, BCL-xL, and senescence survival pathways	Dual Senolytic Therapy; selectively kills senescent lung fibroblasts to reduce SASP burden.	Eliminates senescent cells, improves lung compliance, and reduces collagen burden in bleomycin models.	Completed Phase I Clinical Trial (NCT02874989).	Demonstrated safe tolerability and clinically meaningful improvements in 6-minute walk distance and physical performance.	Phase I trial highlighted gastrointestinal discomfort and a nearly threefold increase in acute exacerbation rates.	Baurzhan et al. (2026); Deng et al. (2026); Min et al. (2026); Torres-Machorro et al. (2025)

Bexotegast (PLN-74809)	Integrins v6 and v1	Dual Integrin Inhibitor; blocks the integrin-mediated activation of latent TGF- β .	Decreases COL1A1, COL3A1, and -SMA expression in human lung tissue explants and fibroblast cultures.	Phase IIb/III Adaptive Clinical Evaluation (NCT06097260).	INTEGRIS-IPF trial showed stable/improved FVC in 71% of patients and decreased N-terminal type III collagen propeptide.	Generally well-tolerated; mild diarrhea (~30%) is the most common adverse event.	Deng et al. (2026); Torres-Machorro et al. (2025); Moua et al. (2024)
Nerandomilast (BI 1015550)	Phosphodiesterase 4B (PDE4B)	Selective PDE4B Inhibitor; increases intracellular cAMP levels to suppress pro-inflammatory/pro-fibrotic cascades.	Attenuates fibroblast activation, myofibroblast differentiation, and macrophage-derived profibrotic cytokines.	Phase III FIBRONEER-IPF Clinical Trial (NCT05321069), ongoing).	Phase II trial demonstrated FVC stabilization and slowed rate of lung function decline over 12 weeks.	Gastrointestinal adverse events, primarily diarrhea and nausea (~27%), with a ~15% trial discontinuation rate.	Deng et al. (2026); Moua et al. (2024)
BMS-986278 (Admilparant)	Lysophosphatidic Acid Receptor 1 (LPAR1)	Oral LPA1 Antagonist; blocks lysophosphatidic acid-mediated fibroblast migration, vascular leak, and epithelial apoptosis.	Reduces collagen accumulation, pulmonary tissue density, and improves compliance in rodent bleomycin models.	Phase III Clinical Evaluation (NCT06003426), ongoing).	Phase II trial demonstrated a ~62% reduction in the annual rate of FVC decline; well-tolerated vs placebo.	Favorable safety profile, lacking the severe hepatobiliary toxicity seen in first-generation antagonists (e.g., BMS-986020).	Deng et al. (2026); Moua et al. (2024)
Inhaled Treprostinil	Prostacyclin Receptor / cAMP elevation	Prostacyclin Analog / Vasodilator; inhibits fibroblast migration and targets mitochondrial quality control in IPF cells.	Attenuates pulmonary remodeling and normalizes dysmorphic mitochondrial architecture.	Phase III TETON-IPF and TETON-2 Clinical Trials (NCT05255991), ongoing).	Post-hoc analysis of the INCREASE study demonstrated significantly lower FVC decline and reduced risk of cardiopulmonary hospitalization.	Local airway irritation, including persistent cough (44%), throat discomfort, and mild headaches (28%).	Deng et al. (2026); Moua et al. (2024)
Integrated Stress Response Inhibitor (ISRIB)	Eukaryotic translation initiation factor 2B (eIF2B) allosteric activation	Integrated Stress Response Inhibitor; restores cellular translation and maintains proteostasis under chronic ER stress.	Antagonizes silica-induced and bleomycin-induced AEC2 senescence, significantly reducing collagen type I, -SMA, and fibronectin.	Preclinical development / Translational Optimization.	Restores normal lung compliance, improves dynamic resistance, and eliminates senescent Krt8 transitional cells in vivo.	Rodent experiments demonstrate no significant systemic adverse events, providing a favorable safety window compared to classic anti-fibrotics.	Li et al. (2023)
EF24 (Curcumin Analogue)	Phosphatase and Tensin Homolog (PTEN) stabilization	Senomorphic and Mitophagy Enhancer; suppresses AKT/mTOR/NF- κ B signaling and restores mitochondrial membrane potential.	Reduces SA-gal, P21, and PAI-1 expression; rescues dysmorphic swollen mitochondria and halts senescent-induced fibroblast activation.	Preclinical optimization; identified as the most promising anti-aging compound among 12 candidates.	Promotes weight recovery, improves dynamic lung consolidation on micro-CT, and restores dynamic fibrosis resolution in aged TBI-mouse models.	Shows high oral bioavailability (60% in mice) and exhibits no cytotoxic or apoptotic induction in non-senescent normal cells.	Zhang et al. (2024b)
Curculigoside (CCG)	Tripartite motif-containing protein 72 (Trim72) and GSK3/SIRT1-P300 pathway	Natural Senomorphic and Antioxidant Agent; facilitates the ubiquitination and degradation of P300 to reduce acetylation of antioxidant enzymes.	Delays the natural senescence of lung fibroblasts and hydrogen peroxide-induced AEC senescence in vitro.	Preclinical evaluation in bleomycin-induced and D-galactose-induced aging models.	Restores systemic antioxidant enzyme activity (SOD1, SOD2, catalase) and robustly alleviates endoplasmic reticulum stress and tissue stiffness.	Well tolerated in rodent toxicity assays with no evidence of systemic target organ toxicity or structural weight loss.	Tang & wei (2024)

senescence as a central organizing mechanism in the pathogenesis of IPF has shifted the therapeutic focus from broad, non-selective anti-fibrotic agents toward pathway-directed molecular interventions and cellular therapies (Baurzhan et al., 2026; Deng et al., 2026). The clinical and preclinical landscape of these reversal strategies can be organized into three distinct therapeutic classes: senolytics, senomorphics, and regenerative progenitor transplantations (Baurzhan et al., 2026; Deng et al., 2026). Figure 4 organizes this therapeutic landscape into its three constituent arms — senolytics, senomorphics, and regenerative cell-based approaches

2.5. Senolytics: Selective Elimination of Senescent Cells

Senolytics are small molecules designed to selectively eliminate senescent cells by transiently disabling the pro-survival and anti-apoptotic networks (SCAPs) that protect them from their own pro-inflammatory secretome (Baurzhan et al., 2026).

- **Dasatinib + Quercetin (D+Q):** The combination of the tyrosine kinase inhibitor dasatinib and the natural flavonoid quercetin targets key pro-survival signaling pathways, including the BCL-2 family and PI3K/Akt signaling, thereby selectively inducing apoptosis in senescent cells (Baurzhan et al., 2026). In preclinical models of bleomycin-induced pulmonary fibrosis, the administration of D+Q successfully reduced the burden of senescent cells, attenuated collagen deposition, and restored lung compliance (Min et al., 2026). Crucially, a first-in-human, open-label, pilot clinical study evaluating intermittent oral administration of D+Q in 14 patients with IPF demonstrated that the treatment was well-tolerated and yielded clinically meaningful improvements in physical function—including six-minute walk distance and chair-stand times—although significant changes in forced vital capacity (FVC) were not observed over the brief treatment course (Baurzhan et al., 2026; Justice et al., 2019).

Targeting Myofibroblast Apoptosis: Emerging senolytic candidates, such as BTSA1, directly target senescent myofibroblasts by activating the pro-apoptotic protein BAX, effectively bypassing apoptosis resistance and reducing the established fibrotic burden in mouse models (Min et al., 2026).

2.6 Senomorphics: Modulating the Senescent Secretory Phenotype

Senomorphics are therapeutic agents that suppress or neutralize the SASP secretome and restore cellular quality-control systems without killing the senescent cells directly (Baurzhan et al., 2026).

Curcumin Analogue EF24: A highly bioactive monoketone derivative of curcumin, EF24 has emerged as a potent senomorphic candidate (Zhang et al., 2024). EF24 treatment significantly reduces senescence biomarkers (SA-gal, PAI-1, p21) and suppresses SASP secretion (IL-6, IL-1) in bleomycin-induced senescent AECs (Zhang et al., 2024b). Mechanistically, EF24 up-regulates and stabilizes the tumor suppressor PTEN, which subsequently suppresses the hyperactive Akt/mTOR/NF- κ B signaling cascade (Zhang et al., 2024). Furthermore, EF24 promotes mitophagy, facilitating the clearance of damaged mitochondria and reducing mitochondrial ROS production in senescent epithelial cells (Zhang et al., 2024). In vivo studies demonstrate that EF24 attenuates established fibrosis and improves survival in both acute and chronic phase mouse models of lung injury, highlighting its capacity to restore mitochondrial quality control (Zhang et al., 2024).

Semaglutide: A glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide has been shown to inhibit oxidative stress and cellular senescence in the lung (wei & Si-yuan, 2026). By suppressing the production of mitochondrial ROS and inflammatory cytokines, semaglutide limits bleomycin-induced fibrogenesis, representing a promising candidate for metabolic drug repurposing (wei & Si-yuan, 2026).

Curculigoside (CCG): A natural bioactive compound that targets cellular senescence by suppressing endoplasmic reticulum stress (ERS) and the unfolded protein response (UPR) (Tang & wei, 2024). CCG prevents crystalline silica- and bleomycin-induced senescence in AEC2s and lung fibroblasts by modulating the GSK3/ERS pathway, thereby restoring cellular redox balance (Tang & wei, 2024).

ISRIB (Integrated Stress Response Inhibitor): An engineered small-molecule inhibitor of the integrated stress response that acts by rescuing translational initiation rates (Li et al., 2023). In models of silica-induced pulmonary fibrosis and ERS-stressed AECs, ISRIB administration effectively reverses cellular senescence, restores the regenerative capacity of epithelial progenitors, and attenuates downstream

fibrosing cascades, highlighting the therapeutic potential of targeting proteostatic stress (Li et al., 2023).

2.7. Regenerative and Cell-Based Strategies

- Autologous Basal Cell (BC) Transplantation: A pioneering regenerative approach that aims to replace senescent, dysfunctional distal airway progenitors with healthy, non-senescent stem cells harvested from the patient's own proximal airways (Snyder et al., 2025). Clinical characterization reveals a striking spatial pattern of senescence along the proximal-distal axis of the IPF airway tree: while basal cells residing in the distal bronchioles demonstrate advanced functional impairment and high senescent marker expression, basal cells situated in the proximal small bronchi maintain a completely non-senescent phenotype (Snyder et al., 2025). These proximal BCs (Krt5+/p63+/ITGA6+/NGFR+) retain their self-renewal capacity, genomic stability, and multi-lineage differentiation potential (Snyder et al., 2025). In a landmark pilot clinical trial, three patients with advanced IPF received autologous proximal BCs transplanted via bronchoscopic instillation (Snyder et al., 2025). The therapy was exceptionally safe, with no severe adverse events reported, and yielded significant clinical improvements in lung volume (FVC increase), exercise capacity (6-minute walk distance), and small airway function over a 6-month follow-up period, demonstrating the translational feasibility of cellular replacement (Snyder et al., 2025).

Stem Cell Secretomes & Extracellular Vesicles: The nebulized delivery of lung stem cell-derived secretions (LSC-Sec) or mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) represents a cell-free alternative (Gao et al., 2025). These extracellular vesicles deliver a specialized cargo of anti-fibrotic microRNAs, proteins, and mitochondrial-protective factors that modulate TGF- signaling, enhance endogenous epithelial repair, and reduce the senescent secretome within the fibrotic niche (Baurzhan et al., 2026; Gao et al., 2025).

Cellular senescence is no longer viewed as a passive bystander of physiological aging, but as a central, highly integrated pathogenic network that actively coordinates the progressive, irreversible remodeling of the lung in IPF (Baurzhan et al., 2026; Deng et al., 2026). The complex crosstalk between senescent epithelial progenitors locked

in regenerative arrest, highly glycolytic and mechanosensitive fibroblasts, and SPP1 macrophages forms a self-reinforcing network that sustains the fibrotic microenvironment (Deng et al., 2026; Min et al., 2026). Traditional anti-fibrotic therapies, such as pirfenidone and nintedanib, fail to arrest or reverse this disease process because they target individual downstream pathways rather than the underlying cellular quality-control network (Baurzhan et al., 2026; Deng et al., 2026).

The emergence of senotherapeutic strategies represents a major conceptual shift in the clinical management of IPF (Baurzhan et al., 2026). By leveraging senolytics to selectively eliminate senescent cells, senomorphics (such as EF24, ISRIB, and CCG) to reprogram metabolic and proteostatic quality-control networks, and autologous basal cell transplantation to physically restore the injured epithelial stem cell niche, modern medicine is positioned to move beyond the palliative slowing of decline toward true structural and functional lung regeneration (Baurzhan et al., 2026; Snyder et al., 2025).

3. Methods

3.1 Review Design and Reporting Framework

We approached this as a narrative-synthesis review with a systematic search backbone — a hybrid that, admittedly, is not the gold-standard systematic review, but is arguably better suited to a rapidly moving mechanistic literature like this one, where the goal is conceptual synthesis rather than pooled effect estimation. Even so, we tried to hold ourselves to a standard of reproducibility that a PubMed-indexed methodology would expect, and where applicable, the search and screening workflow was structured in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting conventions, adapted for a narrative-review format (Page et al., 2021 — reporting framework only, not a primary data source for this review's biological content). No formal protocol was pre-registered, which we note as a limitation; this was a deliberate trade-off given the exploratory, mechanism-mapping nature of the review's aims, but it does mean that, strictly speaking, our search cannot claim the same protection against selective reporting as a registered systematic review would.

3.2 Eligibility Criteria

We defined our inclusion criteria before beginning the search, and applied them consistently — though, as with

any narrative synthesis, some judgment calls were unavoidable at the margins. Eligible sources were: (a) peer-reviewed original research articles (in vitro, ex vivo, animal model, or human clinical studies) addressing cellular senescence, senotherapeutics, or aging hallmarks specifically in the context of idiopathic pulmonary fibrosis or closely related fibrotic lung disease models (e.g., bleomycin-induced or silica-induced pulmonary fibrosis); (b) peer-reviewed narrative or systematic reviews addressing the same thematic scope, used for contextual synthesis rather than as primary evidence; and (c) articles published in English, with a strong preference — though not an absolute requirement — for publications from 2018 onward, reflecting the period during which single-cell transcriptomic and spatial-omic technologies substantially reshaped the field's understanding of epithelial and mesenchymal heterogeneity in IPF.

We excluded conference abstracts without full-text availability, non-peer-reviewed preprints, case reports lacking mechanistic data, and articles in which pulmonary fibrosis was a secondary or incidental finding rather than a primary focus. Articles addressing senescence in other organ systems were excluded unless they described a mechanism (e.g., a signaling axis or SASP factor) with direct, cited relevance to lung fibrosis.

3.3 Information Sources and Search Strategy

We searched PubMed/MEDLINE as the primary database, supplemented by Scopus and Google Scholar for cross-verification and citation-chasing, given that no single database indexes this literature exhaustively. Searches were conducted using combinations of Medical Subject Headings (MeSH) terms and free-text keywords, connected with Boolean operators, structured broadly as follows:

("idiopathic pulmonary fibrosis" OR "pulmonary fibrosis" OR "interstitial lung disease") AND ("cellular senescence" OR "senescent cells" OR "SASP" OR "senescence-associated secretory phenotype" OR "senolytics" OR "senomorphics" OR "aging hallmarks" OR "autophagy" OR "mitophagy" OR "aberrant basaloid" OR "alveolar type II" OR "fibroblast heterogeneity" OR "mechanotransduction")

Each core concept cluster (senescence biology, epithelial trajectories, mesenchymal/fibroblast biology, and therapeutic reversal strategies) was also searched as an individual sub-query to ensure adequate depth within each thematic branch of the review, rather than relying solely on

the combined string, which tended — as one might expect — to privilege articles that happened to use exact matching terminology.

3.4 Study Selection Process

Titles and abstracts retrieved from the search were screened for thematic relevance against the eligibility criteria above. Full texts of records passing this initial screen were then retrieved and assessed in detail. Reference lists of key included articles, particularly recent large-scale single-cell transcriptomic studies and mechanistic reviews, were manually hand-searched (a "snowball" or citation-chasing approach) to capture additional relevant primary studies not returned by the structured search string — a step we found necessary, since a meaningful proportion of the most mechanistically informative papers surfaced this way rather than through the primary query. Given the narrative-synthesis design, study selection was performed by the review author(s) without a formal dual-reviewer adjudication process; this represents a departure from systematic review methodology and is acknowledged as a limitation in Section 5.6.

3.5 Data Extraction and Synthesis

For each included study, we extracted, where reported: the cell type(s) or model system studied; the specific senescence marker(s) or pathway(s) examined; the intervention or exposure (for interventional studies); the primary outcome measures relevant to senescence, fibrosis, or lung function; and the study design (in vitro, murine model, ex vivo human tissue, or clinical trial). These data were organized thematically into four conceptual domains that structure the Literature Review section of this manuscript: (1) epithelial trajectories and regenerative failure, (2) fibroblast heterogeneity and mechanical-metabolic feedback, (3) the senescence–autophagy axis and SASP biology, and (4) senotherapeutic and regenerative reversal strategies. This thematic organization — rather than a chronological or purely alphabetical one — was chosen deliberately, since it mirrors how these pathways functionally interact within the diseased lung, and it is this functional logic, more than publication date, that we felt should drive the narrative structure.

No formal quantitative synthesis (meta-analysis) was performed, owing to the marked heterogeneity in model systems, outcome measures, and study designs across

the included literature; a pooled effect-size estimate would not be meaningful given this heterogeneity, and would arguably create a false impression of precision. Instead, findings are synthesized narratively, with an emphasis on mechanistic convergence across independent studies and explicit identification of areas where evidence remains preliminary or derived from a single model system.

3.6 Risk of Bias and Quality Considerations

Because most included studies are preclinical (in vitro or murine), we did not apply a clinical risk-of-bias tool (e.g., Cochrane RoB 2 or ROBINS-I), which are designed for randomized or observational clinical studies. Instead, we considered, on a qualitative basis, whether preclinical findings had been replicated across more than one model system or by more than one independent research group, and we have tried to flag, throughout Sections 2 and 4, where a mechanism rests on a single study rather than converging evidence. For the limited number of included clinical and pilot trial data (e.g., senolytic and cell-transplantation pilot studies), sample sizes and open-label, non-blinded designs are noted explicitly, as these substantially limit the strength of causal inference that can be drawn.

4. Molecular Trajectories, Niche Heterogeneity, and Translational Reversal in IPF

The systemic exploration of the idiopathic pulmonary fibrosis (IPF) microenvironment has shifted the scientific paradigm from a simplified model of chronic inflammation and passive collagen deposition to a highly coordinated, maladaptive cellular ecosystem (Deng et al., 2026; Min et al., 2026). By integrating single-cell transcriptomics, spatial profiling, and emerging translational models, recent research has mapped out the precise molecular trajectories that govern parenchymal remodeling, extracellular matrix (ECM) stiffness-driven feedback loops, and novel therapeutic interventions designed to reverse established scarring (Deng et al., 2026; Jones et al., 2026; Snyder et al., 2025).

4.1. Epithelial Heterogeneity, Metaplasia, and the Alveolar Regenerative Block

At the core of IPF pathogenesis lies a profound, age-associated collapse of the alveolar stem cell niche (Svobodová et al., 2025; Torres-Machorro et al., 2025). Under healthy conditions, mature alveolar type II (AEC2) progenitor cells regenerate gas-exchanging alveolar type I

(AEC1) cells (Deng et al., 2026). In the fibrotic lung, however, repetitive microinjury, telomere attrition, and endoplasmic reticulum stress (ERS) trigger cell-autonomous reprogramming, locking epithelial cells into transitional states that are unable to complete differentiation (Jones et al., 2026; Wang et al., 2025).

4.2 The Aberrant Basaloid Cell (AbBa) and Lineage Arrest

Recent single-cell and spatial transcriptomic datasets have identified the KRT5/KRT17 aberrant basaloid cell (AbBa) as a unique, highly pathologic epithelial state residing at the immediate borders of fibroblastic foci and honeycomb cysts (Adams et al., 2020; Habermann et al., 2020; Mayr et al., 2024; Svobodová et al., 2025). These cells express canonical basal markers (e.g., TP63, LAMB3, and LAMC2) and epithelial-to-mesenchymal transition (EMT) markers (e.g., CDH2, VIM, FN1, and COL1A1), whilst crucially lacking classical proximal basal markers such as KRT5 and KRT15 (Adams et al., 2020; Habermann et al., 2020; Svobodová et al., 2025). These transitional epithelial states are summarized, alongside their markers and functional consequences, in Table 1. Furthermore, AbBa cells are marked by stable, non-mitotic arrest pathways governed by the cyclin-dependent kinase inhibitors CDKN1A (p21) and CDKN2A (p16), alongside robust expression of the established clinical biomarker MMP7 and the growth differentiation factor GDF15 (Adams et al., 2020; Habermann et al., 2020). Rather than acting as productive progenitors, AbBa cells synthesize and deposit pathological anchoring proteins, such as Collagen VII (encoded by COL7A1), in their basement membrane zones, altering the physical compliance of the local niche and acting as localized secretory engines of pro-fibrotic SASP factors like TGF-1, IL-6, and IL-1 (Svobodová et al., 2025).

4.3 Alveolar Differentiation Intermediates and SAEC Dysfunction

Similarly, injured AEC2 progenitors or small airway Scgb1a1 club cells undergoing aberrant alveolar repair form Alveolar Differentiation Intermediate (ADI) cells, also known as damage-associated transitional progenitors (DATPs) (16, Jones et al., 2026; Wang et al., 2023). These transitional cells, characterized by KRT8 and CLDN4 expression, exhibit a persistent DNA damage response (DDR) and are locked in regenerative

arrest via the activation of transcription factors YAP1 and TAZ (16, Jones et al., 2026).

In the distal conducting small airways, this regenerative deficit is mirrored by a loss of multiciliogenesis and ciliary-deficient small airway epithelial cells (SAECs), driven by a downregulation of FOXJ1 and -IV-tubulin (Wang et al., 2025). These ciliary-deficient SAECs actively release TGF-1 and IL-6, promoting mucus hypersecretion (primarily MUC5B and MUC5AC), alveolar mucus plugging, and subsequent mechanical collapse (Wang et al., 2025). Meanwhile, first-line barrier club cells undergo a switch-like activation, upregulating Matrix Metalloproteinase-1 (MMP1) and the lysosomal protease Cathepsin B (CTSB) up to 21-fold upon injury, driving basement membrane degradation and licensing fibroblast invasion into the alveolar airspace (Fu et al., 2026).

4.4. Mesenchymal Lineages, Metabolic Reprogramming, and Myofibroblast Heterogeneity

The effector phase of fibrotic remodeling is driven by highly specialized, transcriptionally and metabolically reprogrammed mesenchymal lineages (Alvarado-Vasquez et al., 2024; Deng et al., 2026), whose full molecular characterization is summarized in Table 2. The classic paradigm of a homogeneous fibroblast population has been replaced by a resolved stromal atlas.

4.5 Invasive Myofibroblasts and Aerobic Glycolysis

The CTHRC1 fibroblast represents the most pathogenic, collagen-producing stromal population in the IPF lung (Tsukui et al., 2020). Residing within the active core of fibroblastic foci, these cells are driven by TGF-/SMAD3 signaling and mechanosensitive nuclear translocation of YAP/TAZ (Deng et al., 2026; Zhang et al., 2026).

To support the energetic demands of massive extracellular matrix (ECM) synthesis and deposition of fibrillar Collagens I and III, CTHRC1 fibroblasts undergo metabolic reprogramming toward aerobic glycolysis (the Warburg effect) (Alvarado-Vasquez et al., 2024; Deng et al., 2026). This metabolic shift is characterized by the upregulation of rate-limiting glycolytic enzymes, including 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) and hexokinase 2 (HK2), resulting in significant lactic acid accumulation (71, Alvarado-Vasquez et al., 2024). Lactic acid subsequently lowers extracellular pH, inducing pH-dependent activation of latent TGF-

establishing a self-sustaining glycolytic-fibrotic loop (Alvarado-Vasquez et al., 2024).

4.5.1 Hyaluronan-Synthesizing and Pathological Senescent Fibroblasts

In close spatial proximity to the subpleural, aberrant basaloid epithelium sits a distinct subset of hyaluronan-producing fibroblasts, characterized by elevated expression of HAS1 and HAS2 (Jones et al., 2026). Triggered by epithelial-derived IL-1, these fibroblasts secrete highly fragmented, low-molecular-weight hyaluronic acid (HA), which interacts with CD44 receptors to drive stromal invasiveness and cell motility (Jones et al., 2026).

In contrast, chronic tissue stress triggers stable cellular senescence in specific fibroblast subpopulations. The upregulation of Fatty Acid Binding Protein 5 (FABP5) in senescent myofibroblasts interacts with and stabilizes fatty acid synthase (FASN) from proteasomal degradation, disrupting lipid homeostasis and causing Uncoupling Protein 2 (UCP2)-dependent mitochondrial dysfunction and reactive oxygen species (ROS) overproduction (Sun et al., 2026).

Furthermore, senescent lung fibroblasts exhibit elevated levels of Ependymin-related protein 1 (EPDR1), a transmembrane glycoprotein that localizes to lysosomes (Southern & Gadre, 2025). EPDR1 acts as a negative regulator of lysosomal acidification, causing autophagic flux block---evidenced by the concurrent accumulation of p62 and LC3B---and enforcing stable cell-cycle arrest via p21 and p16 (Southern & Gadre, 2025). Similarly, age-associated depletion of Glutathione Reductase (GSR) impairs cellular antioxidant defenses, promoting ROS-mediated fibroblast migration, activation, and senescent arrest (Zhang et al., 2025).

4.6 Intercellular Signaling Dialogues, Mitochondrial DNA Leakage, and Mechanical Feedback Loops

IPF is fundamentally a disease of aberrant communication networks that bind multiple cellular compartments into a self-reinforcing, pathogenic loop (Deng et al., 2026); these crosstalk axes are catalogued systematically in Table 3.

4.6.1 The Mitochondrial cGAS-STING Axis and Innate Immunity

One of the most potent triggers of this loop is mitochondrial injury within the alveolar epithelium (Gong et

al., 2026). Exposure to environmental toxicants (such as crystalline silica) or ERS impairs mitophagy, causing the accumulation of dysmorphic, swollen mitochondria and the leakage of mitochondrial DNA (mtDNA) into the cytoplasm (Gong et al., 2026; Min et al., 2026).

This cytosolic dsDNA is recognized by cyclic guanylate adenylate synthetase (cGAS), driving STING oligomerization and downstream transcription of type I interferons and SASP factors (Gong et al., 2026). This cGAS-STING cascade establishes a deep senescent state in AT2 cells, preventing epithelial renewal and continuously driving adjacent stroma toward myofibroblast differentiation through TGF- and IL-11 secretion (Gong et al., 2026; Yu et al., 2025).

4.7 Mechanotransduction and CD8 T-Cell Crosstalk

This chemical crosstalk is further amplified by matrix stiffness-driven mechanotransduction (Zhang et al., 2026). Rigidity of the remodeled ECM stimulates structural cells via integrins (such as v6, v1, and v3), activating Focal Adhesion Kinase (FAK) and non-receptor tyrosine kinases (Src) (Deng et al., 2026; Shakeel et al., 2023). This suppresses YAP/TAZ phosphorylation, allowing its nuclear entry and transcription of profibrotic genes (Deng et al., 2026).

Sustained loading leads to chromatin remodeling, locking fibroblasts into a state of "mechanical memory" where they maintain an active, collagen-secreting phenotype even if the primary chemical stimulus is removed (Zhang et al., 2026).

This niche is further complicated by senescent, exhausted Granzyme K (GZMK)-producing CD8 T cells, which accumulate in the peripheral lung parenchyma and lymph nodes (Okereke et al., 2026). CD8 T cell-derived extracellular GZMK stimulates alveolar epithelial cells to undergo premature senescence, upregulate MHC class II presentation, and release the pro-fibrotic metalloproteinase MMP28 and IL-8, directly contributing to tissue destruction and honeycomb cyst formation (Okereke et al., 2026).

4.8. Translational Therapeutic Landscapes and Senotherapeutic Reversal Strategies

Given the failure of current standard-of-care antifibrotics (nintedanib and pirfenidone) to reverse established scars, clinical and translational focus has shifted toward targeting the underlying biology of cellular aging and proteostatic

stress (Moua et al., 2024). Table 4 summarizes this full translational landscape, from approved agents through early-phase senotherapeutics.

4.9 Integrin and Receptor Antagonist Milestones

Promising pathway-directed investigational drugs are currently in advanced clinical trials (Moua et al., 2024). The dual integrin inhibitor Bexotegast (PLN-74809), which blocks integrins v6 and v1 to prevent the localized, mechanical activation of latent TGF-, has demonstrated impressive efficacy (Deng et al., 2026; Moua et al., 2024). In the INTEGRIS-IPF trial, Bexotegast treatment achieved FVC stabilization or improvement in 71% of patients alongside excellent tolerability (Deng et al., 2026; Moua et al., 2024). Similarly, the oral phosphodiesterase 4B inhibitor Nerandomilast (BI 1015550), which elevates intracellular cAMP to suppress macrophage activation and fibroblast motility, is undergoing Phase III evaluation (FIBRONEER-IPF) after showing robust lung function stabilization (Deng et al., 2026; Moua et al., 2024). Furthermore, the oral Lysophosphatidic Acid Receptor 1 (LPAR1) antagonist BMS-986278 (Admilparant) achieved a ~62% reduction in the annual rate of FVC decline in Phase II clinical evaluation and has progressed to Phase III, demonstrating a favorable safety profile compared to first-generation antagonists (Moua et al., 2024).

4.10 Senolytics, Senomorphics, and Autologous Basal Stem Cell Transplantation

Direct targeting of the cellular senescence-autophagy axis represents a major therapeutic frontier (Min et al., 2026). The Sirt1/HSF1/HSPs quality-control pathway, activated by GLP-1 receptor agonists such as semaglutide, has been shown to reduce ROS production and cellular senescence both in vitro and in vivo (Qian et al., 2026). Specifically, semaglutide promotes the Sirt1-mediated deacetylation and activation of HSF1, enhancing downstream heat shock protein (HSP) chaperones to restore proteostasis and attenuate bleomycin-induced lung injury (Qian et al., 2026). Crucially, when mice were co-treated with semaglutide and the Sirt1 inhibitor Nicotinamide (NIC), the anti-fibrotic, antioxidant, and anti-senescence effects of semaglutide were completely abated, demonstrating that its therapeutic efficacy is Sirt1-dependent (Qian et al., 2026). Similarly, the curcumin analogue EF24 stabilizes PTEN expression, suppressing the downstream Akt/mTOR/NF-B pathway to restore mitophagy, clear damaged dysmorphic

mitochondria, and reverse persistent, age-associated fibrosis in aged mouse models (Zhang et al., 2024). In parallel, the bioactive glycoside Curculigoside (CCG) enhances the tripartite motif-containing protein 72 (Trim72)-mediated ubiquitination and degradation of P300, reducing the acetylation of superoxide dismutase (SOD1/SOD2) and catalase to alleviate endoplasmic reticulum stress and prevent stress-induced premature senescence (592, Tang & wei, 2024).

Finally, a groundbreaking clinical milestone was achieved by Snyder et al. (2025) through the isolation, expansion, and bronchoscopic transplantation of autologous, non-senescent proximal airway basal cells (Krt5/p63/ITGA6/NGFR) harvested from the fifth-generation bronchi of patients with advanced IPF and small airway dysfunction (Snyder et al., 2025).

The bronchoscopic implantation of these functional, expandable stem cells successfully reconstituted injured distal epithelia, yielding significant and sustained clinical benefits at 24 weeks post-transplant, including FVC recovery, improved small airway expiratory flow parameters, longer 6-minute walk distances, and marked reduction in CT ground-glass opacities (502, Snyder et al., 2025). This autologous stem cell approach provides the first clinical evidence that restoring functional, non-senescent progenitor populations can active-repair and reverse established pulmonary architecture distortion (Snyder et al., 2025).

5. From Descriptive Senescence Biology to a Testable Framework for Lung Regeneration

5.1 What the Evidence, Taken Together, Actually Tells Us

Pulling back from the individual mechanisms surveyed in Sections 2 and 4, a fairly consistent picture emerges — though it took a genuinely large body of single-cell and spatial-omic work to get there. Cellular senescence in IPF is not a single lesion in a single cell type; it is closer to a distributed failure mode that plays out somewhat differently in the epithelium and in the mesenchyme, yet converges on the same functional endpoint of persistent, unresolved tissue remodeling (Table 1; Table 2). Senescent AEC2 progenitors and their downstream transitional states — the KRT8 ADI population and, more strikingly, the KRT5/KRT17 aberrant basaloid cell — appear to function less as damaged bystanders and more

as active signaling hubs that recruit and sustain the fibrotic response (Deng et al., 2026; Svobodová et al., 2025). This is, we think, an important reframing. It is one thing to say senescent cells accumulate in fibrotic tissue; it is another to say they are functionally driving fibroblast activation through a defined SASP program, which is closer to what the aggregated evidence in Table 1 and Table 3 actually supports.

5.2 The Epithelium Is Not a Passive Victim

The classical model of IPF pathogenesis treated epithelial injury largely as an initiating event — a trigger that set fibroblasts in motion and then faded into the background. The evidence synthesized here complicates that story considerably. Aberrant basaloid cells persist at the fibroblastic-focus border, continuously depositing Collagen VII and secreting MMP7, GDF15, TGF-1, and IL-6 (Table 1; Svobodová et al., 2025), which suggests these epithelial-derived cells are not merely a consequence of fibrosis but an ongoing contributor to it. Similarly, the loss of ciliogenesis in small airway epithelial cells — driven by FOXJ1 downregulation — appears sufficient, on its own, to stimulate healthy fibroblasts toward a myofibroblast phenotype via conditioned medium experiments (Wang et al., 2025). That is a fairly striking finding, honestly, because it implies that epithelial dysfunction confined to the conducting airways, well outside the classic alveolar fibroblastic focus, can still propagate fibrogenic signaling. We would argue this supports treating the epithelium, across its full proximal-to-distal axis, as a therapeutic target in its own right rather than an upstream afterthought.

5.3 Metabolism and Mechanics Are Not Separate Stories One of the more conceptually satisfying threads running through the mesenchymal literature (Table 2; Table 3) is how tightly glycolytic reprogramming and biomechanical stiffening are coupled. CTHRC1 myofibroblasts shift toward aerobic glycolysis, generating lactate that acidifies the local microenvironment and activates latent TGF-1 (Alvarado-Vasquez et al., 2024) — and this happens more or less simultaneously with a mechanotransduction loop in which matrix stiffness, sensed through integrin-FAK-YAP/TAZ signaling, locks fibroblasts into a "mechanical memory" that persists even after the original stimulus is removed (Zhang et al., 2026). We suspect this dual metabolic-mechanical entrenchment is a large part of why

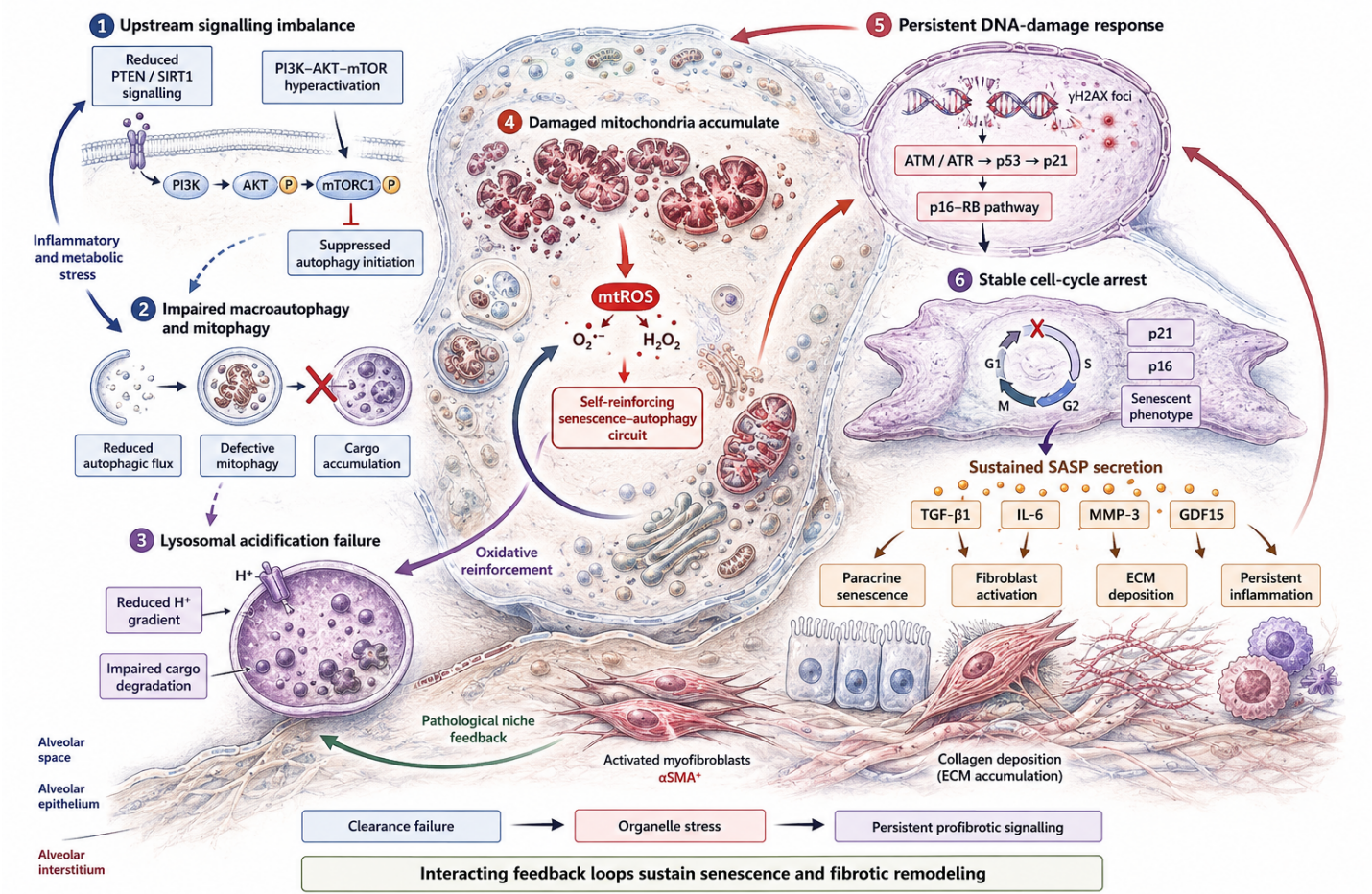


Figure 3 | The senescence–autophagy axis forms a self-reinforcing profibrotic cascade. Reduced PTEN and SIRT1 signalling, together with PI3K–AKT–mTOR hyperactivation, suppresses autophagy initiation and compromises macroautophagic and mitophagic flux. Concurrent failure of lysosomal acidification further limits cargo degradation, allowing damaged and dysfunctional mitochondria to accumulate. Excessive mitochondrial reactive oxygen species subsequently amplify oxidative stress, bioenergetic dysfunction and persistent DNA-damage signalling through the ATM/ATR–p53–p21 and p16–RB pathways. These responses stabilize cell-cycle arrest and promote the senescent phenotype. Senescent cells sustain the secretion of SASP mediators—including TGF-1, IL-6, MMP-3 and GDF15—which propagate paracrine senescence, activate fibroblasts, promote extracellular-matrix deposition and maintain inflammation. In turn, inflammatory and metabolic stress, mitochondrial oxidants and the mechanically altered fibrotic niche further impair cellular clearance and reinforce epithelial stress. The pathway therefore represents an interacting feedback system rather than a strictly unidirectional cascade.

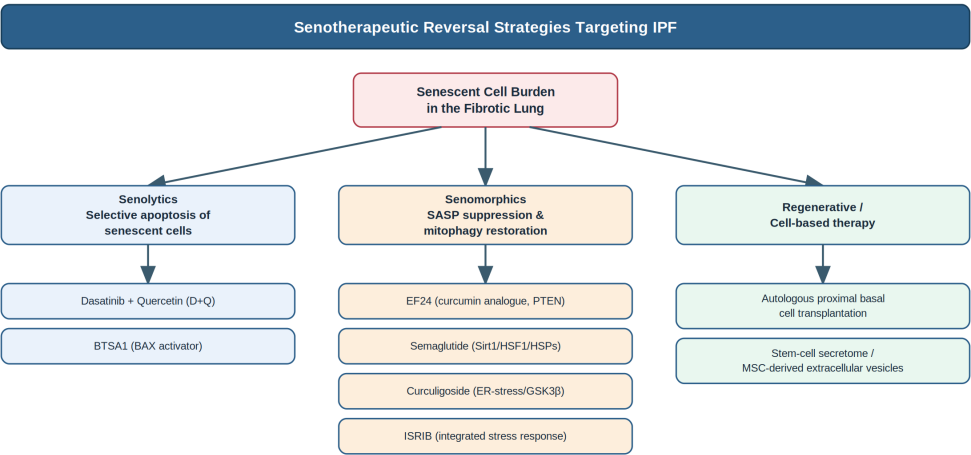


Figure 4. Senotherapeutic strategies for reversing senescence-driven fibrosis in idiopathic pulmonary fibrosis. Three mechanistically distinct arms are shown: senolytics, which selectively induce apoptosis in senescent cells; senomorphics, which suppress the pro-fibrotic secretome and restore mitophagy without killing the cell; and regenerative/cell-based approaches, which physically replace senescent progenitor populations. Representative agents or approaches are listed beneath each arm; full preclinical and clinical evidence for each is summarized in Table 4.

single-pathway antifibrotic drugs like pirfenidone and nintedanib, which do not directly address either the glycolytic shift or the epigenetic memory, can slow FVC decline without ever approaching true fibrosis reversal (Table 4). If a therapy interrupts the mechanical signal but leaves the metabolic program intact, or vice versa, the fibroblast likely has a route back to its pathogenic phenotype.

5.4 The Senescence–Autophagy Axis as a Unifying, If Imperfect, Framework

The senescence–autophagy relationship (Figure 3; Table 3) is, in our reading, the most mechanistically coherent explanatory thread in the current literature, if not necessarily the most therapeutically tractable one yet. PTEN and Sirt1 loss, mTOR hyperactivation, disabled mitophagy, mitochondrial ROS accumulation, and stable p21/p16-driven arrest form a chain that has now been demonstrated, at least in part, across several independent model systems and cell types (Li et al., 2023; Min et al., 2026; Southern & Gadre, 2025; Sun et al., 2026). That convergence across independent groups and independent injury models (silica, bleomycin, aging) gives us more confidence in this axis than in some of the more novel, single-study findings elsewhere in the literature — the EPDR1-lysosomal acidification mechanism, for instance, is compelling but currently rests on one study (Southern & Gadre, 2025), and we would want to see it replicated before treating it as established biology.

5.5 Reading the Therapeutic Landscape Honestly

Table 4 lays out a genuinely encouraging spread of interventions, spanning approved antifibrotics, late-stage investigational drugs, and early senotherapeutics — but we think it is worth being candid about how uneven the maturity of this evidence actually is. Bexotegast and nerandomilast are supported by randomized Phase II/III data (Moua et al., 2024); the D+Q senolytic combination has a small, open-label, non-blinded pilot trial behind it (Justice et al., 2019); and EF24, curculigoside, and ISRIB remain entirely preclinical (Li et al., 2023; Tang & wei, 2024; Zhang et al., 2024). It would be easy, in a review like this, to let the mechanistic elegance of the senotherapeutic story outrun the actual clinical evidence base, and we have tried to resist that pull throughout. The autologous basal cell transplantation data from Snyder et al. (2025), while limited to three patients, is arguably the most conceptually important finding in the entire

translational landscape, because it is the first direct clinical demonstration that replacing a senescent progenitor population with a non-senescent one can produce measurable functional lung recovery rather than mere stabilization — a genuinely different category of outcome than anything the approved antifibrotics have achieved.

5.6 Limitations of This Review

We should be transparent about the limits of what a narrative synthesis like this one can claim. Study selection, while guided by a structured search strategy (Section 3), was not conducted by independent dual reviewers, and no formal risk-of-bias tool was applied to the predominantly preclinical evidence base, which means some degree of selection and interpretation bias cannot be excluded. Much of the mechanistic literature summarized in Tables 1 through 3 derives from murine bleomycin or silica models and human explant/organoid systems, both of which are useful but imperfect proxies for the chronic, decades-long injury trajectory that produces IPF in actual patients — a limitation the field itself has flagged repeatedly (Torres-Machorro et al., 2025). We have also, by design, prioritized mechanistic and translational breadth over an exhaustive account of every published senescence marker, which means some legitimate findings are necessarily underrepresented here.

5.7 Where This Leaves the Field

If there is one synthesis point we would want a reader to leave with, it is this: the data increasingly support treating cellular senescence not as one pathogenic feature among many in IPF, but as a plausible organizing node that links epithelial failure, mesenchymal activation, and matrix stiffening into a single, self-sustaining circuit (Figure 1; Figure 3). That framing does not, by itself, guarantee that senotherapeutics will succeed where antifibrotics have fallen short — biology rarely rewards such tidy narratives — but it does offer a more mechanistically grounded rationale for combination strategies (e.g., pairing a senomorphic agent with autophagy restoration, or pairing pharmacologic SASP suppression with cell-based regenerative therapy) than the field has had before. The next phase of work, discussed further below, will need disease-stage-specific biomarkers, aging-relevant animal models, and cell-type-selective delivery systems before these mechanistic insights can be tested rigorously in patients.

Conclusions

Taken as a whole, this review supports reframing IPF as a senescence-organized disease rather than a purely fibrotic one — a shift with real implications for how future therapies might be designed. Rather than targeting downstream collagen deposition alone, as pirfenidone and nintedanib largely do, the mechanistic networks synthesized here point toward upstream intervention in epithelial and mesenchymal senescence itself. The convergence of independent evidence around the senescence–autophagy axis is, we think, the strongest single finding to emerge from this synthesis, while the autologous basal cell transplantation data represent the most clinically provocative. Still, we would caution against over-interpreting a literature that remains predominantly preclinical; rigorous, adequately powered clinical trials, guided by better biomarkers, are the necessary next step before senotherapeutics can meaningfully change patient outcomes.

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