Review Article

Molecular mechanisms of alveolar epithelial cell senescence and idiopathic pulmonary fibrosis: a narrative review

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Background and Objective: Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia of unknown etiology. An increasing number of studies have reported that the incidence of IPF increases with age. Simultaneously, the number of senescent cells increased in IPF. Epithelial cell senescence, an important component of epithelial cell dysfunction, plays a key role in IPF pathogenesis. This article summarizes the molecular mechanisms associated with alveolar epithelial cell senescence and recent advances in the applications of drugs targeting pulmonary epithelial cell senescence to explore novel therapeutic approaches for the treatment of pulmonary fibrosis.

Methods: All literature published in English on PubMed, Web of Science, and Google Scholar were electronically searched online using the following keyword combinations: aging, alveolar epithelial cell, cell senescence, idiopathic pulmonary fibrosis, WNT/β-catenin, phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), mammalian target of rapamycin (mTOR), and nuclear factor kappa B (NF-κB).

Key Content and Findings: We focused on signaling pathways associated with alveolar epithelial cell senescence in IPF, including WNT/β-catenin, PI3K/Akt, NF-κB, and mTOR signaling pathways. Some of these signaling pathways are involved in alveolar epithelial cell senescence by affecting cell cycle arrest and secretion of senescence-associated secretory phenotype-associated markers. We also found that changes in lipid metabolism in alveolar epithelial cells can be induced by mitochondrial dysfunction, both of which contribute to cellular senescence and development of IPF.

Conclusions: Decreasing senescent alveolar epithelial cells may be a promising strategy for the treatment of IPF. Therefore, further investigations into new treatments of IPF by applying inhibitors of relevant signaling pathways, as well as senolytic drugs, are warranted.

Keywords: Aging; alveolar epithelial cells; cell senescence; idiopathic pulmonary fibrosis (IPF); molecular pathway

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a commonly diagnosed chronic, progressive, and fibrotic interstitial pneumonia that accounts for 20–30% of interstitial lung diseases. It usually occurs in middle-aged and elderly individuals (1). The most common features observed on high-resolution computed tomography (HRCT) of the chest in patients with IPF are ground-glass opacity (GGO), reticular structures, traction bronchiectasis, and honeycomb-like structures (2). It is now generally accepted that persistent alveolar epithelial damage and repair dysregulation are the principal mechanisms leading to progressive pulmonary fibrosis. Repetitive epithelial cell injury and deficiencies in regeneration result in the release of mediators, including cytokines, chemokines, fibrogenic factors, coagulant proteins, oxidants, and regulators of apoptosis. This leads to the recruitment, proliferation, and activation of interstitial fibroblasts to form fibrotic foci (3,4). Additionally, excessive deposition of the extracellular matrix leads to destruction of lung parenchymal structures (5). Interestingly, a variety of cells, including alveolar epithelial type II cells (ATII) and fibroblasts, can drive IPF (6,7). Regardless of the driver cell types, senescence leads to a decrease in the repair capacity of damaged alveolar epithelium. As a result, fibrous tissue replaces the damaged alveolar epithelium (8).

From a histopathological point of view, IPF formation is a dynamic process involving complex interactions among epithelial cells, fibroblasts, immune cells (such as macrophages and T lymphocytes), and endothelial cells (9). Alveolar epithelial cells undergo cytoskeletal remodeling and acquire a mesenchymal phenotype through epithelial-mesenchymal transition (EMT), in which epithelial cells lose intercellular attachment, polarity, and epithelial-specific markers, leading to fibrosis (10). Some investigators have identified ATII as a major player in the synthesis of transforming growth factor-beta (TGF-β) and tumor necrosis factor-alpha (TNF-α) in lung biopsies from patients with IPF (11). In the process of organ fibrosis formation, including pulmonary fibrosis, TGF-β acts as the master switch for the induction of the EMT process (12). In particular, TGF-β mediates fibrous proliferative effects by inducing apoptosis in alveolar epithelial type I (ATI) cells (13,14). However, there is no direct evidence that TGF-β promotes IPF by inducing senescence in the alveolar epithelial cells. In the lungs of patients with IPF, the ability of ATII cells to transdifferentiate into ATI cells is diminished. Emerging evidence also suggests that triggering ATII senescence can promote IPF (6). Therefore, studying the mechanisms of cellular senescence in the lung microenvironment is crucial to understand IPF pathogenesis and progression.

Notable progress has been made by clinicians and researchers worldwide in uncovering the pathogenic mechanisms and treatment strategies for IPF. For instance, pirfenidone (PFD) is a pleiotropic pyridine compound that improves fibrosis, inflammatory responses, and oxidative stress (15). In addition, Nintedanib is an intracellular tyrosine kinase inhibitor that inhibits the progression of pulmonary fibrosis. In line with these observations, in the 2015 Official Clinical Practice Guidelines for IPF, Raghu *et al.* proposed that PFD and nintedanib may be used to treat IPF (16). Considering that PFD and nintedanib have serious adverse effects such as photosensitivity and diarrhea, discovery of novel antifibrotic drugs still deserves priority research. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-886/rc).

Methods

PubMed, Web of Science, and Google Scholar databases were searched using the following terms to identify relevant papers for this review (*Table 1*): "cell senescence AND idiopathic pulmonary fibrosis", "aging AND idiopathic pulmonary fibrosis", "alveolar epithelial cell AND cell senescence AND idiopathic pulmonary fibrosis", "alveolar epithelial cell AND cell senescence AND lung disease", "alveolar epithelial cell AND cell senescence", "alveolar epithelial cell AND idiopathic pulmonary fibrosis", "cell senescence", "WNT/β-catenin AND cell senescence AND pulmonary fibrosis", "PI3K/Akt AND cell senescence AND pulmonary fibrosis", "mTOR AND cell senescence AND pulmonary fibrosis", "NF-κB AND cell senescence AND pulmonary fibrosis", "WNT/β-catenin AND cell senescence", "PI3K/Akt AND cell senescence", "mTOR AND cell senescence", "NF-κB AND cell senescence". Owing to the lack of studies on the correlation between IPF and aging in the database before 2000, we prioritized articles published between 2000 and 2022. Clinical trials, research articles, and review articles were examined. Publications identified as associated with both IPF and aging were further examined in detail to identify previously unidentified related articles. Partial anti-aging agents

Table 1 The search strategy summary

Items	Specification
Date of search	January 1st, 2021–May 1st, 2022
Databases and other sources searched	PubMed, Web of Science, Google Scholar
Search terms used	Search terms included "cell senescence AND idiopathic pulmonary fibrosis", "aging AND idiopathic pulmonary fibrosis", "alveolar epithelial cell AND cell senescence AND idiopathic pulmonary fibrosis", "alveolar epithelial cell AND cell senescence AND lung disease", "alveolar epithelial cell AND cell senescence", "alveolar epithelial cell AND idiopathic pulmonary fibrosis", "cell senescence", "WNT/β-catenin AND cell senescence AND pulmonary fibrosis", "PI3K/Akt AND cell senescence AND pulmonary fibrosis", "mTOR AND cell senescence AND pulmonary fibrosis", "NF-κB AND cell senescence AND pulmonary fibrosis", "WNT/β-catenin AND cell senescence", "PI3K/Akt AND cell senescence", "mTOR AND cell senescence", "NF-κB AND cell senescence"
Timeframe	2000–2022
Inclusion and exclusion criteria	Inclusion criteria: lung diseases associated with aging Exclusion criteria: research with similar conclusions
Selection process	Mingjin Tu independently selected and reviewed all initial articles, with additional review by Ting Wei and Yufang Jia. Ultimate final article inclusion was determined by all authors

PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; NF-κB, nuclear factor kappa B.

and telomere protectors have been researched primarily in relation to Alzheimer's disease or other age-related disorders, whereas no studies have shown their associations with IPF; thus, they are not discussed in this narrative review.

Discussion

Cell senescence

Cellular senescence, a hallmark of the aging process, plays an important role in the pathogenesis of IPF (17). Senescent cells possess a phenotype in which cell growth stops permanently but cell death does not occur. Cellular senescence can occur at any point, from the embryonic developmental stage to the adult stage. Cellular senescence can be classified as either replicative senescence (RS) or stress-induced premature senescence (SIPS), depending on the factors that induce aging (18). Cellular senescence caused by telomere shortening is known as RS, whereas cellular senescence induced by exogenous stresses, such as oxidative stress, DNA damage, and proto-oncogene activation is called premature senescence. A common feature of senescent cells is irreversible cell cycle arrest, whereby senescent blockade is regulated by the p53-p21 and p16-retinoblastoma protein (Rb) signaling pathways (19). Senescent cells also express several cytokines, growth factors, and proteases that maintain cellular growth arrest and promote the degeneration and proliferation of neighboring cells. Given its importance, cellular senescence is involved in the development and progression of various aging-related diseases.

Aging of alveolar epithelial cells and IPF

Cellular senescence can contribute to the development of IPF through multiple mechanisms, including senescence-associated secretory phenotype (SASP) (20), telomere dysfunction (21), mitochondrial dysfunction (22), DNA damage (23), epigenetic alterations (24), inflammatory response (25), and protein homeostatic imbalance (26). Abnormal telomere shortening in IPF lungs leads to cellular senescence in the alveolar epithelial cells (27). Additionally, ATII cells in IPF lungs exhibit significant cellular senescence features such as mitochondrial malformations and dysfunction (28).

Recent studies have shown that mitochondrial dysfunction and metabolic reprogramming are distinctive features of IPF lungs (*Figure 1*). Mitochondria consume oxygen and produce reactive oxygen species (ROS), while producing the majority of cellular ATP. ROS has a fundamental signaling role and can increase the antioxidant capacity of cells through mitotic excitation processes (29). Along with cellular senescence, mitochondria accumulate abnormalities, including morphological changes (rounded

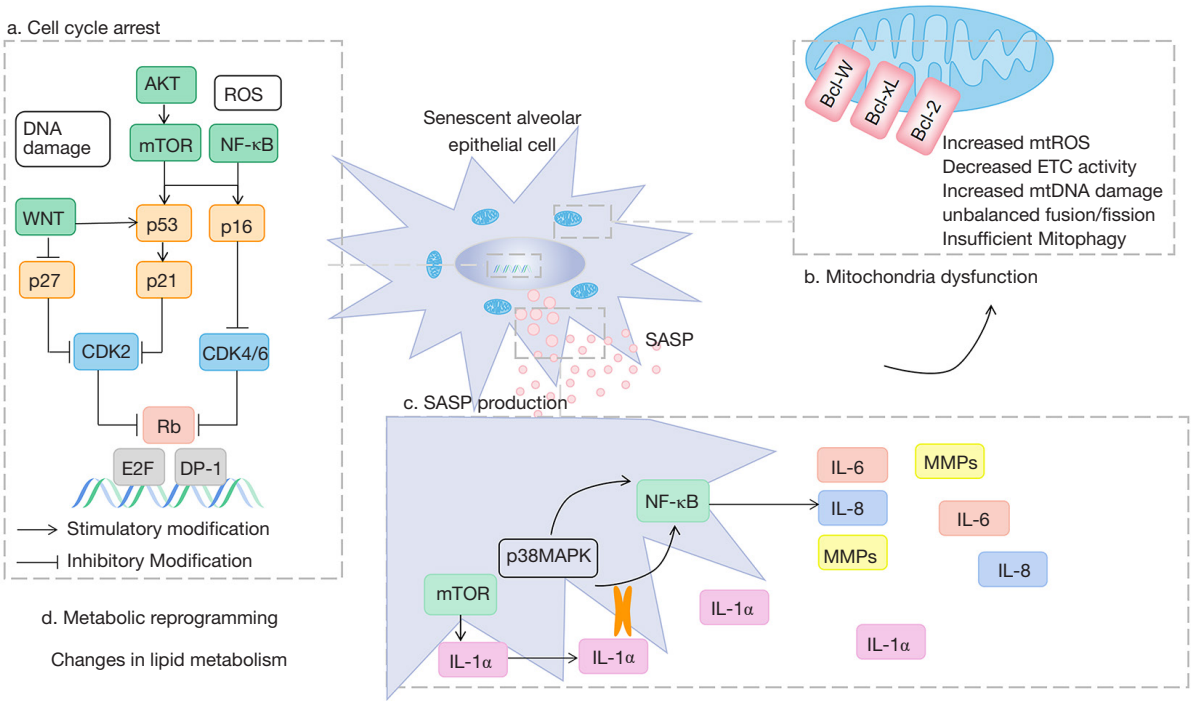

Figure 1 The main mechanism of alveolar epithelial cell senescence in idiopathic pulmonary fibrosis. DNA damage and ROS are essential causes of cycle arrest induced by WNT, PI3K/Akt, NF-κB and mTOR signaling pathways. Changes in lipid metabolism in alveolar epithelial cells can also be induced by mitochondrial dysfunction, both of which contribute to cellular senescence and IPF. NF-κB and mTOR pathways can promote IPF by promoting the secretion of senescence-associated secretory phenotype-associated markers. ROS, reactive oxygen species; IPF, idiopathic pulmonary fibrosis; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; NF-κB, nuclear factor kappa B; mTOR, mammalian target of rapamycin; mtROS, mitochondrial reactive oxygen species; ETC, electron transport chain; mtDNA, mitochondrial DNA; SASP, senescence-associated secretory phenotype; IL, interleukin; MMP, matrix metalloproteinase.

appearance, cristae, and inner membrane absence), reduced biogenesis, and decreased mitochondrial DNA copy number. Furthermore, increased mitochondrial DNA mutations, leads to a failure in respiratory chain and ATP production (30). In lung tissue of IPF patients, it has been found that ATP production is reduced and mitochondrial ROS production is increased (31). When the concentration of ROS exceeds physiological levels, it can leak into the cytosol and activate excessive inflammatory mediators such as nuclear factor kappa B (NF-κB) (32).

Mitochondrial biogenesis is controlled by the peroxisome proliferator-activated receptor γ coactivator-1alpha (PGC-1α) and PGC-1β signaling pathways. The activities of PGC-1α/β upstream activators, such as AMP-activated protein kinase (AMPK) and SIRT1, decrease as an organism age, leading to a decline in mitochondrial biogenesis (33,34).

Dysfunctional mitochondria are less efficient in oxidizing NADH to NAD+, resulting in a lower NAD+/NADH ratio, with the activation of AMPK and p53 leading to a senescent phenotype (35). Waters *et al.* demonstrated that knockdown of PGC-1α in lung fibroblasts effectively reduced the expression of cellular senescence markers in IPF fibroblasts (36). In a bleomycin-induced mouse model of senescence, senescent alveolar epithelial cells exhibited increased mTOR/PGC-1α/β activation, which is also associated with increased mitochondrial mass and upregulation of oxidative phosphorylation (37).

The lung tissue in IPF has been shown to increase metabolic activity (38). Lung samples from IPF have altered metabolite production and downregulated expression of key enzymes involved in multiple metabolic pathways, including glycolysis and key mitochondrial-related metabolic pathways, such as mitochondrial β-oxidation and the tricarboxylic acid cycle (39). Similarly, alveolar macrophages isolated from bleomycin-treated mice showed glycolytic reprogramming and increased fatty acid (FA) oxidation (40). Moreover, IPF myofibroblasts have a higher glycolytic enzyme expression and lactate content (41).

Metabolic homeostasis is the basis of physiological state maintenance in cells, tissues, and organs. Not surprisingly, various metabolic pathways are involved in structural remodeling of the lung. In particular, lipid synthesis is essential for the production of pulmonary surfactants. Single-cell RNA sequence data in alveolar epithelial cells indicated low expression of enzymes required for lipid metabolism (42). However, aging modifies lipid metabolism by modulating several important pathways including: adipose tissue lipolysis, lipoprotein, and triglyceride metabolism, as well as shifts in lipid transport proteins (43,44). During β-oxidation, FAs attach to coenzyme A for transport to the mitochondria via the carnitine shuttle. These intermediates are oxidized to produce NADH and $FADH_2$, which generates ATP in the electron transport chain. This process occurs within the mitochondrial matrix. In IPF lungs, long- and medium-chain FA (caproic, caprylic, myristic, and palmitic acids) levels were elevated, and carnitine and medium-chain acyl carnitine (caproic, caprylic, palmitoyl, and succinyl carnitine) levels were significantly reduced (39). FAs allow β-oxidation via the carnitine shuttle transport to the mitochondrial matrix. This finding suggests a mechanism for lipid accumulation and downregulation of β-oxidation in the IPF lungs. In addition to these alterations in metabolic processes, changes in organelles are associated with aging and lipid metabolism, such as mitochondrial dysfunction.

Mitochondria are the primary sites of lipid metabolism. Mitofusins, including Mitofusin1 (MFN1) and Mitofusin2 (MFN2), are GTPase proteins that coordinate outer mitochondrial membrane fusion. In bleomycin-induced mice, Mfn1 or Mfn2 deficiency disrupts lipid metabolism in AEC2 cells. Fatty acid synthase (FASN) is a key enzyme in lipid metabolism. Through AEC2 cell-specific deletion of FASN Chung *et al.* demonstrated that loss of lipid synthesis in AEC2 cells exacerbated pulmonary fibrosis in a mouse model after mitochondrial injury (45). Interestingly, alveolar macrophages expressing a dominant negative mitochondrial calcium uniporter (MCU) diverted glycolysis to fatty acid oxidation (FAO) through metabolic reprogramming, increasing MCU and mitochondrial calcium, resulting in protective effects in a mouse model of IPF (46). As alluded above, during aging, FA uptake increases, adipogenesis from the head decreases, and FA oxidation processes decrease, leading to ectopic lipid accumulation. Decreased lipid catabolism is primarily caused by mitochondrial dysfunction. All of these changes further lead to lipotoxicity in cells, exhaustion of energy in tissues, and alteration of cell signaling, accelerating the onset of IPF.

Alveolar epithelial cell senescence, cell cycle arrest, and the SASP may contribute to the development and perpetuation of fibrotic scarring. In a mouse model of bleomycin-induced pulmonary fibrosis, alveolar epithelial cells exhibited increased expression of senescence-associated markers, including β-galactosidase activity, p16, p21, pRb (47,48).

Signaling pathways in alveolar epithelial cell senescence

Aging, like many other biological processes, is regulated by classical signaling pathways and transcription factors. Scientists have altered the aging process in various animal models by intervening in different biological systems and signaling pathways to delay the onset of various aging-associated diseases. Numerous crucial signaling pathways associated with aging have been identified, including the insulin/insulin-like growth factor 1 (IGF-1) (49), JAK-STAT (50), WNT/β-catenin (51), phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB/Akt) (52), mTOR (53), AMPK (54), NF-κB (55), RhoA/ROCK (56), Notch (57), and sirtuin (58) pathways. Our study revealed that several signaling pathways, including WNT, PI3K/Akt, mTOR, and NF-κB, are not only involved in the process of cellular senescence, but are also closely related to IPF (*Figure 2*).

WNT/β-catenin signaling pathway

The WNT signaling pathway has critical regulatory roles in early development, organogenesis, tissue regeneration, and other physiological processes in animal embryos.

The WNT/β-catenin signaling pathway is composed of the secreted WNT protein family, frizzled protein receptor family, casein kinase 1 (CK1), dishevelled (Dsh or Dvl), glycogen synthase kinase-3β (GSK-3β), adenomatous polyposis coli (APC), Axin, β-catenin, and the T cell factor/lymphatic enhancer factor family (TCF/LEF). In the absence of WNT, β-catenin binds to a cytoplasmic complex containing CK1α, GSK-3β, Axin, and APC proteins. In turn, this promotes the phosphorylation of β-catenin and its interaction with β-transducin repeat-containing proteins (β-TRCP). Subsequently, β-TRCP recognizes and ubiquitinates the phosphorylation of β-catenin, leading to its subsequent degradation by the proteasome (59). When the WNT/β-catenin signal is activated, WNT is secreted into the extracellular space, where it binds to the transmembrane receptor Frizzled, which in turn activates intracellular Dsh. Activated Dsh protein subsequently enhances the phosphorylation of GSK-

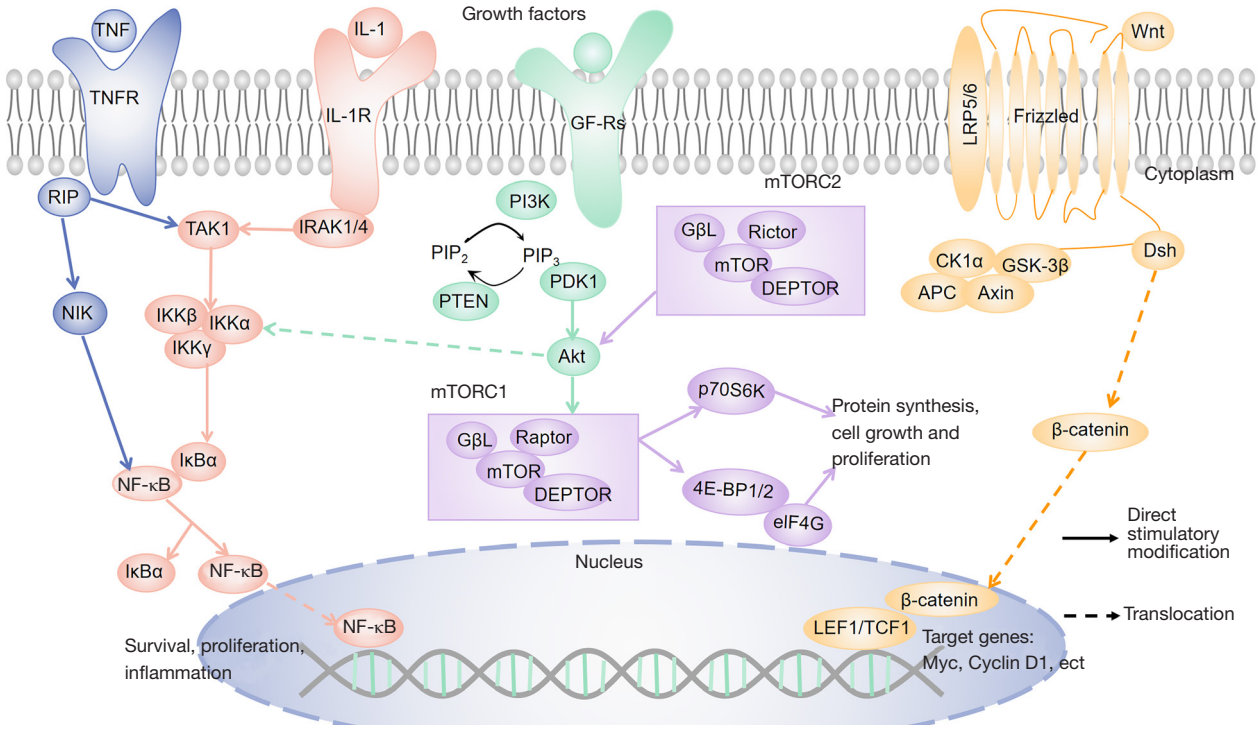

Figure 2 Signaling pathways related to senescence of alveolar epithelial cells in idiopathic pulmonary fibrosis. Each color represents a signaling pathway. Four main signaling pathways are involved in inducing the aging of alveolar epithelial cells: WNT, PI3K/Akt, NF-κB, and mTOR signaling pathways. TNF, tumor necrosis factor; IL, interleukin; LEF, lymphatic enhancer factor; TCF, T cell factor; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; NF-κB, nuclear factor kappa B; mTOR, mammalian target of rapamycin.

3β. As a result, phosphorylation of GSK-3β inhibits the formation of β-catenin degradation complex and β-catenin phosphorylation. Eventually, β-catenin accumulated in the cytoplasm. When cytoplasmic β-catenin reaches a certain concentration, it translocates to the nucleus, where it binds TCF/LEF to form a transcriptional activation complex, which further activates downstream target genes (60). Therefore, administration of the GSK3-β inhibitor CHIR99021 (CHIR) can lead to the direct accumulation of β-catenin.

Role of WNT/β-catenin signaling pathway in alveolar epithelial cell senescence

The WNT/β-catenin signaling pathway is activated when IPF is induced in rats using bleomycin. WNT components, including WNT3a, β-catenin, and pGSK-3β proteins, are increased during IPF development, and decreased GSK-3β expression has also been observed in mouse fibrotic lungs (61,62). Therefore, inhibition of the WNT/β-catenin signaling pathway leads to attenuation of IPF (63). Lehman *et al.* reported that WNT/β-catenin activity was increased in ATII cells of aged mice (16–24 months) compared to that in young mice (3 months), whereas chronic typical WNT/β-catenin activation for seven days induced cellular senescence (64).

Lehmann *et al.* have demonstrated that CHIR, an inhibitor of GSK3-β, induces the accumulation of β-catenin, thereby increasing the expression of the WNT target gene *Axin2* in mouse ATII cell line (MLE12 cells) (64). Interestingly, Damalas *et al.* showed that activated WNT/β-catenin signaling leads to p53 accumulation (65). Moreover, p21, a downstream target of p53, directly induces cellular senescence (66). Similarly, senescence of alveolar epithelial cells can be induced by increasing GSK-3β phosphorylation (67). In addition, activated β-catenin signaling triggers DNA damage response (DDR) (68). DDR induces the expression of p16 (ink4a) (69), a gene that directly induces cellular senescence (70). In summary, activated WNT/β-catenin signaling can induce cellular senescence via DDR and p53/p21 pathways.

WNT-secreted proteins are cysteine-rich glycosylated proteins that activate either the β-catenin-dependent (typical) WNT pathway (e.g., WNT3a) or the β-catenin-

independent (atypical) WNT pathway (e.g., WNT5a). Co-treatment of cells with WNT3a and WNT5a revealed that the non-standard ligand WNT5a reduces the ability of WNT3a to induce cellular senescence (64). Treatment of cells with WNT3a increases the expression of cell cycle inhibitors p16, p21, and p53, but decreased the expression of p27 (71). Moreover, p27 can block the cell cycle transition from G1 to S phase, thereby inducing cell quiescence (72). Impaired cell cycle progression, decreased DNA repair gene expression, and SASP are essential aspects of senescence (73,74). It has been demonstrated that WNT/β-catenin signaling inhibits SASP factors and prevents paracrine senescence (51). In addition, WNT7a induces cellular senescence by promoting inactivation of S-phase kinase-associated protein 2 (SKP2) in a β-catenin-independent manner. Furthermore, deficiency of WNT7a decreases the number of senescent alveolar epithelial cells (75). Like other members of the LGR family, LGR6 serves as a promoter that regulates WNT signaling (76). In addition to increased expression of LGR6 in alveolar epithelial cells of IPF tissues, higher SA-β-Gal activity and increased p16 and p21 in LGR6-expressing cells have been observed by Cortesi *et al.* (77). This suggests that LGR6 mediates the activation of the canonical WNT/β-catenin protein pathway, which ultimately leads to chronic signaling and promotes the acquisition of a senescence phenotype involved in IPF (*Figure 1*).

WNT/β-catenin as a therapeutic target in IPF: Citrus alkaline extract (CAE)

Citrus plants are an essential source of herbal medicines (78). Active ingredients from dried citrus peel have been shown to lower blood lipid levels and exert anti-tumor (79), anti-inflammatory (80), antioxidant (81), and anti-fibrosis (82) effects. CAE prepared from 75% ethanol extract is an active ingredient in the prevention of pulmonary fibrosis (83). CAE reduces pulmonary fibrosis *in vivo* and *in vitro* by suppressing fibroblast senescence (84). Moreover, CAE inhibited alveolar epithelial cell senescence through the β-catenin/p53 pathway. After 24 h of CAE treatment in Adriamycin RD (ARD)-induced A549 cells, the level of β-catenin decreased, and the expression level of its downstream target GSK-3β gradually increased; however, the expression levels of p53 and downstream factor p21 tended to decrease. In another study, the supernatant obtained after centrifuging CAE-treated A549 cells was transferred to cultures of MRC-5 cells for three days, and the protein levels of alpha smooth muscle actin (α-SMA), collagen I, and collagen II gradually decreased with increasing CAE concentrations (85). Therefore, CAE inhibited the expression of α-SMA, collagen I, and collagen II in fibroblasts, thereby alleviating pulmonary fibrosis.

PI3K/Akt signaling pathway

The PI3K/Akt signaling pathway, involving PI3K and its downstream molecule Akt, regulates various cellular functions such as proliferation, differentiation, apoptosis, and glucose transport.

Role of PI3K/Akt signaling pathway in alveolar epithelial cell senescence

Under pathological conditions, alveolar epithelial cells release IGF-1, which activates the IGF-1 receptor (IGF-1R) on the surface of adjacent normal alveolar epithelial cells, further activating intracellular downstream PI3K and Akt (86-88). Activated PI3K/Akt participates in alveolar epithelial cell senescence and IPF progression through the release of connective tissue growth factor (CTGF), TGF-β, and matrix metalloproteinases (MMPs) (89-91). Additionally, activation of PI3K/Akt can be involved in pulmonary fibrosis by regulating its downstream pathways, such as mammalian target of rapamycin (mTOR), hypoxia-inducible factor-1a (HIF-1a), and forkhead box (FOX) family.

Phosphatase and tensin homolog (PTEN) is a tumor suppressor with bispecific phosphatase activity (92). PTEN is hypothesized to function primarily via the PI3K/Akt pathway. PTEN encodes a protein with lipid phosphatase activity that dephosphorylates PIP3 [phosphatidylinositol (3,4,5)-trisphosphate] to form PIP2 [phosphatidylinositol (4,5)-bisphosphate], thereby blocking the growth factor-signaling pathway regulated by PI3K/Akt (93,94). Fibroblasts in IPF fibrotic lesions express low levels of PTEN and high levels of Akt (95). Downregulation of PTEN can accelerate the premature senescence of alveolar epithelial cells by activating the PI3K/Akt/mTOR pathway (96). In line with these observations, PTEN inhibitors activate the PI3K/Akt pathway and induce IPF in animal models (97). Nonetheless, the application of PI3K and PTEN inhibitors in the treatment of IPF in humans requires further investigation.

Three members of the Akt kinase family exist: AKT1, AKT2, and AKT3. AKT1 and AKT2 are widely expressed in many tissues and cell types, whereas AKT3 is predominantly expressed in the brain tissue. Each isoform of Akt has distinct but overlapping functions in proliferation, apoptosis, protein synthesis, and cell cycle

regulation (98). Activated Akt activates or inhibits its downstream target proteins, Bad, caspase-9, NF-κB, GSK-3, p21, and p27, which in turn regulate cell proliferation, differentiation, apoptosis, and senescence. Knocking down AKT2 expression in A549 cells significantly reduced the rate of bleomycin-stimulated alveolar epithelial cell senescence. Similarly, Akt pathway inhibitors (LY294002 and MK2206) dramatically reduced the expression of senescence-associated marker p21 and attenuated SA-β-Gal activity in bleomycin-stimulated alveolar epithelial cells (99). Moreover, it reduced the expression levels of α-SMA, fibronectin, collagen I, and collagen II by lowering the phosphorylation levels of Akt in Bleomycin (BLM)-stimulated mice (100). Thus, Akt inhibition effectively diminishes alveolar epithelial cell senescence and subsequently alleviates IPF.

PI3K/Akt as a therapeutic target in IPF: quercetin

Quercetin, a member of the flavonoid family, is a dietary antioxidant widely found in vegetables, fruits, tea, and wines (101). Quercetin exerts its antioxidant and anti-inflammatory effects by eliminating oxidants. Quercetin has been shown to reduce oxidative stress and inflammatory markers in IPF (102,103). Boots *et al.* showed that quercetin exerts antifibrotic and anti-inflammatory effects in bleomycin-induced lung injury in mice (104). Quercetin functions by regulating the activity of protein kinases including PI3K (105) and Akt (106). Hohmann *et al.* reported that quercetin attenuates bleomycin-induced pulmonary fibrosis by restoring senescent fibroblast sensitivity to pro-apoptotic stimuli through the activation of Akt in aged mice (107). Moreover, a recent study showed that the combination of quercetin in combination with the SRC/ABL protein kinase inhibitor dasatinib ameliorates lung function by reducing the expression of various aging markers to reverse bleomycin-induced IPF in aged mice (108). The beneficial effects of quercetin and dasatinib in eliminating cellular senescence during IPF were also demonstrated by Lehmann *et al.*, who reported that quercetin and dasatinib depleted senescent cells by inducing apoptosis and reducing the SASP in a bleomycin-induced alveolar epithelial cell fibrosis model (109). In addition, in an *in vivo* open-label trial in humans, the combination of quercetin and dasatinib alleviated physical dysfunction in IPF patients as measured using several tests, such as six-minute walking distance, four-meter gait speed, and five repeated chair-stand times (110). In summary, targeting the PI3K/Akt signaling pathway may similarly deplete senescent alveolar epithelial cells in IPF; however, the exact mechanism requires further investigation.

mTOR signaling pathway

mTOR is a central regulator of cellular metabolism, growth, proliferation, and cell survival. mTOR consists of two complex subunits: mTORC1 and mTORC2. The mTORC1 complex is a ternary complex composed of mTOR, Raptor (mTOR regulator related protein), and GβL (G-protein-β subunit-like protein), whereas the mTORC2 complex is composed of mTOR, GβL, and Rictor (111). mTORC1 directly regulates protein synthesis, participates in lipid and nucleotide metabolism, and negatively regulates catabolic processes (112). mTORC2 mainly regulates cell proliferation, survival, cytoskeletal remodeling, and cell migration (113).

Role of mTOR signaling pathway in alveolar epithelial cell senescence

Downregulation of mTOR counteracts the signs of aging, including nutrient dysregulation, mitochondrial dysfunction, loss of proteostasis, cellular senescence, and stem cell failure (114). mTOR can be elicited by removing PTEN or Akt to induce mTOR activation in normal mice or senescent human cells (115,116).

Cellular senescence is a characteristic feature of IPF. Both lung fibroblasts and alveolar epithelial cells show evidence of SASPs acquired from the lungs of patients with IPF (108,117). SASP is characterized by the secretion of a series of pro-inflammatory cytokines, chemokines, matrix remodeling proteases, and growth factors [including TGF-β1, interleukin (IL)-6, and MMP-12]. The secretion of these cytokines is regulated by mTORC1 signaling in senescent cells (118).

Moreover, mitochondrial dysfunction in the alveolar epithelial cells of IPF lungs has been recognized as an important contributor to cellular senescence. The mitochondrial biogenesis pathway downstream of the mTOR/PGC-1α/β axis was significantly upregulated in senescent lung epithelial cells. Using rapamycin, an inhibitor of mTORC1, bleomycin-induced cellular senescence was reduced by restoring mitochondrial homeostasis in lung epithelial cells (37).

Short-term rapamycin exposure blocks the activity of mTORC1, but not mTORC2, whereas long-term exposure inhibits the activity of both complexes (119). mTOR kinase, a major component of mTORC1 and mTORC2, directly binds p53 and increases its stability by phosphorylating p53 at serine 15. It then induces cellular senescence through accumulation of the cell cycle inhibitor p21 (120).

Therefore, mTOR kinase may be a promising target for the treatment of pulmonary fibrosis, as it acts by targeting the mTOR pathway to inhibit cellular senescence.

The mTORC1 inhibitor rapamycin slightly increases p53-mediated Akt Ser473 phosphorylation, whereas the mTORC1/mTORC2 inhibitor Torin1 inhibits Akt Ser473 phosphorylation (121). Moreover, silencing Rictor suppresses phosphorylation of the AKT1 Ser473 site, myofibroblast differentiation, CDKN1A and CDKN2A expression, and SA-GLB1/β-gal activity (122). This suggests that mTORC2 controls the expression of senescence markers and myofibroblast differentiation. In contrast, Raptor silencing does not inhibit AKT1 phosphorylation or ACTA2 overexpression, nor does it reduce CDKN1A and CDKN2A levels. However, silencing Raptor resulted in inhibition of SA-GLB1/β-gal activity. mTORC1 and mTORC2 regulate senescence through different downstream signaling pathways.

mTOR as a therapeutic target in IPF: Rapamycin

Rapamycin, an mTOR-mediated inhibitor of mammalian targets, is a potent antiproliferative agent that was originally introduced to the clinic to prevent transplant rejection (123). Rapamycin is known for its wide-ranging biological effects, including prolonging lifespan and inhibition or reversal of cellular senescence *in vitro* (124,125). In addition, rapamycin has demonstrated potent antifibrotic effects in animal models of liver (126), kidney (127), and lung fibrosis (128). In a mouse model of bleomycin-induced lung fibrosis, rapamycin attenuated IPF by inhibiting E-cadherin downregulation and fibronectin upregulation (129). Further studies have shown that the combination of rapamycin and PFD exerts antifibrotic effects on primary fibroblasts and human alveolar epithelial cells (130). Rapamycin decreases the secretion of SASP-related cytokines and alleviates ATII cell senescence by suppressing mTORC1 to an overall decrease in IPF (131). Furthermore, Herranz *et al.* found that rapamycin reduces SASP secretion from senescent cells (132). Rapamycin may also delay senescence by inhibiting mTOR to improve the mitochondrial function (133). Inhibition of the mTOR pathway by rapamycin has profound effects on aging-associated phenotypes. Therefore, rapamycin is a promising therapeutic agent for aging-related IPF.

NF-κB signaling pathway

The NF-κB family includes five transcription factors: NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), Rel B, and c-Rel (134). NF-κB proteins bind to the κB site as dimers, affecting target gene transcription (135). Activation of the NF-κB signaling pathway is achieved through phosphorylation of NF-κB.

When cells are subjected to various extracellular and intracellular stimuli, the IKK complex is activated to phosphorylate the IκB protein and induce its ubiquitination. Proteasomes degrade ubiquitinated IκB proteins, leading to the release of a heterodimer composed of p65 and p50. p65 and p50 are then activated via post-translational modifications (phosphorylation, acetylation, and glycosylation). Activated p65 and p50 then migrate into the nucleus to bind specific DNA sequences and promote the transcription of target genes (136). Thus, NF-κB proteins and the IKK complex play central roles in regulating the NF-κB pathway.

Role of NF-κB signaling pathway in alveolar epithelial cell senescence

The NF-κB signaling pathway is considered a key regulator of the SASP (137). Hyperactivation of NF-κB has been observed in various mouse models of premature and normal aging, including Sirt6$^{-/-}$, Ercc1$^{-/\Delta}$, and Zmpste24$^{-/-}$ mice with premature aging (138-140). The inhibition or knockdown of several components that regulate NF-κB signaling, such as p65, has been shown to inhibit SASP (141).

Phosphorylation of NF-κB, IKKα/β, and IκBα was increased in IPF lung tissues. However, PTEN levels were decreased. Knockdown of the *PTEN* gene in A549 cells led to activation of the NF-κB pathway and significant upregulation of senescence-related markers such as p21, p16, and SASP. This confirmed that PTEN deletion accelerates alveolar epithelial cell senescence by activating the NF-κB pathway (142). Iannetti *et al.* demonstrated that NF-κB2/RelB regulates Rb activity to regulate EZH2 expression, thereby controlling the stability of p21WAF1 and p53 in primary human fibroblasts (143). In addition, CCAAT/enhancer binding protein (C/EBP) homolog (CHOP) activates the downstream NF-κB pathway by promoting ROS production, leading to ER stress-induced alveolar epithelial cell senescence and IPF (144). These findings suggest that sustained activation of NF-κB is not only associated with cellular senescence but also promotes the aging process (145).

NF-κB as a therapeutic target in IPF: Fisetin (FIS)

FIS is a novel dietary agent present in a range of plants, fruits, and vegetables. FIS improves pulmonary inflammation by downregulating the p-STAT-1 and NF-κB signaling pathways via heme oxygenase-1 (146). It can effectively alleviate pulmonary oxidative stress induced

by strong oxidants (147). Moreover, it can reduce the number of senescent mesenchymal stem cells/progenitor cells, immune cells, and endothelial cells (148). Recently, researchers found that FIS can effectively mitigate the aging of alveolar epithelial cells by inhibiting NF-κB. It was shown to improve the SASP of senescent alveolar epithelial cells, thereby reducing the transdifferentiation of fibroblasts into myofibroblasts and collagen deposition in fibroblasts (149). Previous studies have reported that administration of FIS can prevent liver fibrosis in mice by inhibiting *COL1*, *MMP2*, *MMP3*, and *MMP9* gene expression as well as collagen accumulation (150). Furthermore, FIS can significantly inhibit fibrosis-related gene expression and prevent or mitigate myocardial fibrosis by inactivating the TGF-β1/SMADS/ERK1/2 signaling pathway (151). Notably, no side effects of FIS have been reported. Therefore, FIS may be an effective treatment option for IPF patients.

The development of IPF relation to alveolar epithelial cellular senescence

Alveolar epithelial cell senescence plays a central role in IPF development. Alveolar epithelial cell senescence can occur through the WNT/β-catenin, PI3K/Akt, mTOR, and NF-κB signaling pathways, all of which are involved in the occurrence and development of IPF. It is important to determine the role of inhibitors of various signaling pathways in the regulation of fibrosis. This can be achieved by studying the function of various signaling pathways in alveolar epithelial cell senescence, thus improving our understanding of the cellular and molecular mechanisms that regulate alveolar epithelial cell senescence and lung injury repair.

As summarized in this review, it is now generally accepted that damage to alveolar epithelial cells and the interaction between alveolar epithelial cells and fibroblasts are fundamental to the pathogenesis of IPF. For instance, senescence of alveolar epithelial cells can impair the function of ATII cells (152). Yao *et al.* demonstrated that senescence of ATII cells is sufficient to drive progressive IPF (6). Rapamycin, CAE, and FIS alleviated IPF by reducing alveolar epithelial cell senescence. Quercetin can alleviate IPF by reducing the number of senescent alveolar epithelial cells and fibroblasts. In addition, several drugs that target cellular senescence in IPF are shown in *Tables 2,3*. These drugs show broad potential in the prevention and treatment of IPF.

Conclusions

In recent years, PFD and nintedanib have been most commonly used in the clinical treatment of IPF, but their efficacy still needs to be improved, so the search for new effective drugs against IPF is still a hot topic in domestic and international research. We have summarized the molecular mechanisms associated with alveolar epithelial cell senescence and IPF to identify new therapeutic options. Recent advances in drugs targeting pulmonary epithelial cell senescence are listed in *Tables 2,3*. These drugs can be explored for their ability to target alveolar epithelial cell senescence-related pathways to reduce senescence because

Table 2 List of potential cell senescence inhibitor targeting signaling pathways

Target	Compound	Function	Ref
WNT	HBEC EVs	Reduces WNT3A, WNT5A, and WNT10B expression	(153)
	ZNF24	Inhibits cylinD1, c-MYC, cJUN, fra-1, WISP1, and MMIP7	(154)
	Klotho	Inhibits WNT1- and WNT9a-induced mitochondrial injury	(155,156)
	Ginsenoside Rg1	Inhibits TCF, LEF, p-GSK-3β, and c-MYC but activates GSK-3β	(157,158)
	Betulinic acid	Increases the phospho-β-catenin ratio (S33/S37/T41 and S45), inhibits the phosphorylation of DVL2 and LRP, and decreases the levels of Wnt3a and LRP6	(159)
	PRI-724	Reduces CBP protein and increases p300 protein binding to β-catenin in the nucleus of lung fibroblasts	(160)
	Dickkopf 1	A more specific WNT inhibitor and the mitochondria-targeted antioxidant mitoquinone	(161,162)
	Baicalein	Weaken the phosphorylation of GSK3β (S9) and alleviate the senescence of alveolar epithelial cells	(67)

Table 2 (*continued*)

Table 2 (*continued*)

Target	Compound	Function	Ref
Akt/mTOR	SHQA	Inhibits the phosphorylation of Akt, mTOR, and downstream targets of mTOR, such as p-S6K	(163)
	Resveratrol	Suppresses ROS generation and increases the activity of the PI3K/Akt pathway	(164,165)
NF-κB	ICA	Decreases the protein levels of p50 and p65	(166)
	SR12343	Inhibits NF-κB activation by disrupting the association between IKKβ and NEMO	(55)
	metformin	Increases production of collagen I–III and decreases activation of NF-κB(p65) activity under the high glucose conditions	(167)
	Avenanthramide C	Suppress SASP production by activating AMPK and inhibiting p38/NF-κB signaling pathway	(168)
	SIRT1 activators	Inhibits NF-κB activation by deacetylating the RelA/p65 component of NF-κB complex	(58,169)

Akt, protein kinase B; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; HBEC EVs, human bronchial epithelial cell-derived EVs; ZNF24, Zinc finger transcription factor 24; SHQA, sargahydroquinoic acid; ICA, icariin; TCF, transcription factor T cytokine; LEF, lymphatic enhancer factor; LRP, lipoprotein receptor-related protein; CBP, CREB binding protein; ROS, reactive oxygen species; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; NF-κB, nuclear factor kappa B; IKK, IkappaB kinase; NEMO, NF-kappaB essential modulator; SASP, senescence-associated secretory phenotype; AMPK, AMP-activated protein kinase.

Table 3 List of potential senolytic drugs in idiopathic pulmonary fibrosis

Agent	Pharmacological class	Effective target	Applicable area	Ref
Dasatinib	Tyrosine kinase inhibitors	It has a significant high affinity for BCR/ABL kinases, inhibits many kinases, including Src family kinases	Alveolar epithelial cells	(109)
Roxithromycin	Macrolide antibiotic	It inhibits NOX4-mediated ROS	Fibroblasts	(170)
Liproxstatin-1	Radical-trapping antioxidant	It reduces the levels of ROS and MDA	Alveolar epithelial cells	(25)
PTUPB	COX-2/sEH dual inhibitor	It regulates COX-2/CYP-mediated ARA metabolic imbalance	Alveolar epithelial cells	(171)
STA-21	STAT3 inhibitor	It inhibits STAT3 activity, attenuates IL-6 production, reduces p21 levels and restores normal mitochondrial function	Fibroblasts	(172)
Spermidine	naturally occurring polyamine	It reduces endoplasmic reticulum stress-mediated apoptosis and activates autophagy in primary lung fibroblasts and in vivo	Alveolar epithelial cells and fibroblasts	(173)
TM5275	PAI-1 inhibitor	It blocks TGF-β1-induced p16 expression and the secretion of SASP	Alveolar epithelial cells	(90)
IL-18BP	IL-18 binding protein	It inhibits lung fibroblast senescence by neutralizing IL-18 and promoting Klotho expression	Fibroblasts	(174)
Navitoclax (ABT263)	BCL-2 family inhibitors	It targets both the antiapoptotic proteins BCL-xL and BCL-2	Alveolar epithelial cells	(175)
A1331852 and A1155463	BCL-xL inhibitors	They bind to BCL-xL with high selectivity for closely related proteins such as BCL-2, BCL-W and MCL-1	Fibroblasts	(176)
CPT1C	A key regulator of senescence	It reverses cellular senescence through the regulation of lipid metabolism and mitochondrial function	Fibroblasts	(177)

IL, interleukin; CPT1C, carnitine palmitoyltransferase 1C; COX-2, cyclooxygenase-2; sEH, soluble epoxide hydrolase; PAI-1, plasminogen activator inhibitor 1; ROS, reactive oxygen species; NOX4, Nicotinamide adenine dinucleotide phosphate oxidase 4; ROS, reactive oxygen species; MDA, methane dicarboxylic aldehyde; CYP, cytochrome P450; ARA, arachidonic acid; TGF, transforming growth factor; SASP, senescence-associated secretory phenotype; BCL-xL, B-cell lymphoma-extra-l; BCL-2, B-cell lymphoma 2; MCL-1, myeloid cell leukemia-1.

lowering senescent alveolar epithelial cells may prove to be a promising strategy for IPF treatment.

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Footnote

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