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MINI-REVIEW

Current mechanisms in the pathogenesis of lung fibrosis

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ABSTRACT

Pulmonary fibrosis is a diverse group of lung disorders defined by varying degrees of fibrosis and inflammation in the pulmonary parenchyma. While it may be caused by a known disease, e.g., autoimmune or connective tissue disorder, drugs, hypersensitivity to inhaled organic antigens, or sarcoidosis, it also occurs to be idiopathic. When we examine the pathogenesis of lung fibrosis, we see that cellular aging plays a major role. Lung fibroblasts play an active role in the regeneration process. However, despite all the information, the pathogenesis of lung fibrosis is not clearly understood. It is not yet clear how senescent cells in the lung mingle and cause fibrosis. The pathogenesis of lung fibrosis will be understood more clearly following future studies.

Keywords: Pathogenesis; Pulmonary; Idiopathic; Lung Fibrosis

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1. Introduction

Here, first lung fibrosis is briefly defined and the elements playing in the pathogenesis of this disorder are discussed one by one (**Figures 1–3**, **Table 1**).

2. Lung fibrosis

Lung fibrosis is a rare disease that occurs with fibrosis and inflammation of the lung tissues. It can be observed as idiopathic or secondary. Secondary causes include connective tissue disease, autoimmune diseases, drugs, and sarcoidosis. Idiopathic Pulmonary Fibrosis (IPF) is the most mortal lung disease with overall 2–3 year survival. Chronic and progressive fibrosis is observed in IPF with rapid loss of lung function. It is usually seen in the elderly. IPF is based on the extensive deposition of extracellular matrix (ECM) and irregular collagen with the formation of fibroblastic foci and heterogeneous fibrosis, both transiently and locally. Due to these, the loss of lung tissue occurs. The mechanism described in IPF is an abnormal response to recurrent alveolar epithelial damage when there is a genetic predisposition in aging individuals[1–3].

3. Elements playing in the pathogenesis of lung fibrosis

3.1 Cellular senescence

In cellular aging, a progressive loss of pulmonary function occurs. In studies conducted so far, it is known that cellular senes-

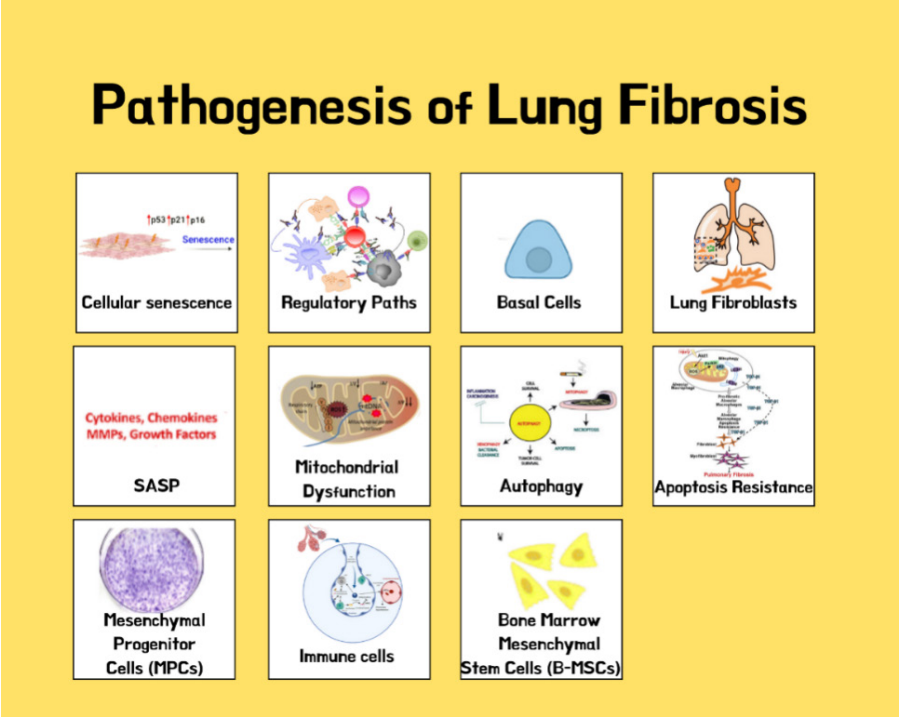

Figure 1. Elements of lung fibrosis pathogenesis.

Table 1. Tasks of the elements of the pathogenesis of lung fibrosis

Cellular senescence	It is defined as a cellular condition in which the proliferation of elderly or damaged cells is stopped and irreversible.
Regulatory paths	In the pathogenesis of lung fibrosis, many regulators are involved.
Basal cells	Airway basal and basal-like cells are involved in the process of bronchiolization observed in lung fibrosis.
Lung fibroblasts	Fibroblasts have a very important role in wound healing in response to lung damage.
SASP	SASP contributes to cell proliferation, differentiation and idiopathic pulmonary fibrosis pathology during wound repair.
Mitochondrial dysfunction	Mitochondrial dysfunction seems to have effects on cellular stress incompatible reactions, increasing sensitivity to injury and pulmonary fibrosis development.
Autophagy	During cellular aging, decreased autophagia is observed and accelerated aging is attributed to decreasing autophagy.
Apoptosis resistance	Apoptosis resistance induced by the stress of aged fibroblasts will result in the permanence of the "damaged" cells that will be suffered from apoptosis and be cleaned from the wound repair zone.
MPCs	In fibrotic lung diseases, the aging environment seems to have an advanced feeding cycle between the pathogenic behavior of MPCs and cells.
Immune cells	Aging cells physiologically activate adaptive immune systems to maintain tissue and organ homeostasis.
B-MSCs	These cells are multipotent cells that can differentiate to various cell types and therefore have an important role in reshaping and repair of tissue.

*MPCs: Mesenchymal progenitor cells. **B-MSCs: Bone marrow mesenchymal stem cells.

cence plays a role in the pathogenesis of diseases together with an age-related decrease in parenchymal repair size and IPF. Cellular senescence is defined as a cellular condition in which the proliferation of senescent or damaged cells is irreversibly stopped. Senescent cells have marked phenotypic changes with decreased mitophagy, genomic instability, metabolic reprogramming, telomere erosion, increased autophagy, chromatin remodeling, and a complex proinflammatory secretome[4–7].

In the aging process, replicative senescence (RS) is observed first, which is the termination of the cell cycle after intense proliferation. However, although these cellular processes are defined in this way, they can be defined as ionizing radiation/IRIS, chromatin disruptions, DNA damage caused by strong genotoxic stress, oxidative agents/OSIS, telomere erosion, topoisomerase inhibitors and oncogene activation. These factors trigger aging programs. In this process, triggers can also use the

p53–p21 and/or p16INK4a—pRB pathways that cause cell cycle arrest[8,9].

3.2 Regulatory paths

The senescence-associated secretory phenotype (SASP) and cell cycle regulatory pathways are major molecular signaling cascades. Cells use at least one of these two ways. But considering that almost all lung cells use SASP, it shows that these cells are closely interconnected in modulating lung fibrosis through cellular senescence[10–12].

The senescence centers of cell life are mediated by classical cell signaling components such as DNA damage responses (DDR), MKK3/MMK6-p38MAPK and ARF-body, oncogenic signaling (PI3K, MYC and RAS), and TGF-β. These signaling components activate cell waste including p14, p15, p16, p17, p21 and p27 as they transport inhibitors directly and via TP53. Cell cycle inhibitors then impede cyclins (CDK1/cyclin B, CDK2/cyclin A/B/E and CDK4/6/cyclin D.) by cyclin-dependent protein kinase (CDK). This inhibition is external to the phosphorylation of Rb. Phosphorylated Rb is restricted to E2F1-3, a cell proliferative transcriptional factor, thereby knocking out normal cell transport. Some common expansions, telomere development or telomerase reverse transcriptase (TERT) mutation, and expansions of the Sin3a gene channel, p53/p21 WAF1/CIP1 in AT2 cells, cause spontaneous scanning fibrosis. Likewise, plasminogen activator inhibitor-1 (serpin 1) plays a role in AT2 senescence. Cigarette smoke causes autophagy by activating negative feedback on mTOR distributed via the Ras/PI3K signaling pathway. PTEN causes AT2 senescence. PTEN/Akt is formed by undamaged Akt residues of PTEN. Chronic chains of Wnt/β catenin chain in AT2 cells delay senescence by directly inhibiting cyclin-dependent protein kinases[10–20].

SASP occurs as a result of protein expression and secretion of senescent cells, and has also been identified in the senescent cell type in the lung. SASP contributes to cellular aging through autocrine and paracrine. CCAAT/enhancer-binding protein-β (C/EBP-β), TP53 and nuclear factor kappa-light chain enhancer (NF-κB) of activated B cells act as primary regulators of SASPs[10–13]. IL-6 regulates aging through SASPs, TNF-α and TGF-β, TP53 and NF-kB, which are prominent in fibroproliferative lung diseases[24]. Apart from these, PAI-1/TGF-β1, released from aging AT2, plays a role in alveolar macrophage activation in lung fibrosis through IL-4 and IL-13[25]. C/EBP-β also plays an important role in experimental lung fibrosis[21–26].

3.3 Basal cells

Since basal and similar cells in the airway expand abnormally in IPF, they are prominent in the pathogenesis of pulmonary fibrosis. This is consistent with the "bronchiolization" process observed in the end-stage of pulmonary fibrosis[27]. Abnormal increase in proliferation of airway basal cells such as classical murine KRT5 + TRP63 + and human KRT5 + p63 + cells, human KRT5 + KRT14 + KRT15 + KRT17 + and p63 + has been implicated in the lung repair stage[28–31].

3.4 Lung fibroblasts

Fibroblasts play a very important role in wound healing after lung injury. After epithelial damage, fibroblasts proliferate. After this stage, the ECM is activated to navigate to injury locations to rebuild the scaffold. Fibroblasts here transform into myofibroblasts that produce ECM components. As the repair process continues, myofibroblasts age and reduce ECM deposition and fibroblast activation, limiting the progression of fibrosis. As a result, cellular aging has an important role in stopping the accumulation of fibrotic tissue and facilitating the resolution of fibrosis[32–35].

Studies have shown that fibroblast aging is increased and permanent in IPF lungs. Fibroblasts from IPF lungs also exhibit insufficient autophagy, mitochondrial dysfunction, metabolic reprogramming, and reduced apoptosis. Many of the senescent fibroblasts have been associated with the pathogenesis of the disease[36–39].

3.5 SASP

Although SASP plays an important role during wound repair, it may also contribute to IPF pathology. Aged IPF fibroblasts secrete numerous proinflammatory cytokines/chemokines, reactive oxygen and profibrotic factors. These biological molecules can profoundly affect neighboring cells (paracrine action) or themselves (autocrine action). SASP promotes persistent inflammation, tissue remodeling, and profibrotic phenotypic changes of surrounding

macrophages and/or fibroblasts[36–41].

3.6 Mitochondrial dysfunction

Mitochondria are central to signaling pathways that regulate mitophagy, ROS production, biogenesis, mitochondrial energies, maintenance and repair of mitochondrial DNA (mtDNA). Altered mitochondrial homeostasis is found in different cells in diseased and healthy aging pulmonary tissues. Mitochondrial dysfunction and cellular aging are linked to the influx. The coexistence of loss of mitochondrial homeostasis and aging is implicated in the development of lung fibrosis, maladaptive responses to cellular stress, and increased susceptibility to injury. Dysregulation of various regulatory mechanisms controlling mitochondrial function in IPF has been described in fibroblasts[39,42–47].

There is an overall reduction in mitochondrial mass and function in IPF lung fibroblasts. The resulting reduction in mitochondrial mass observed is associated with an abnormality in mitochondrial biogenesis and mitophagy. Mitochondrial biogenesis is the process of creating additional mitochondria and associated cellular energy production capacity. In addition, selective mitophagy of damaged mitochondria occurs via PINK1—Parkin signaling. PINK1 primarily functions as a mitochondrial membrane depolarization sensor, activating Parkin, which tags dysfunctional mitochondria for post-function autophagosome traffic. Damage to parkin deficiency-mediated mitophagy in IPF pulmonary tissue fibroblasts is associated with increased TGF-β—Mediated accumulation of the extracellular matrix. Defects in autophagy and mitophagy result in increased ROS production and activation of platelet-derived growth factor receptor (PDGFR)/mammalian rapamycin target (mTOR) signaling pathways that increase fibroblast-myofibroblast conversion[39,48,49].

3.7 Autophagy

Autophagy is a lysosomal self-degradation process that contributes to the maintenance of homeostatic balance in the synthesis, degradation and recycling of organelles and proteins in the cell (**Figure 2**). Studies show that autophagy plays an important role in the cellular aging process. Aging is accelerated due to decreased autophagy. In addition, the reduction of autophagy in IPF also resulted in senescence of fibroblasts. Beclin1, the master regulator of autophagy in IPF lung fibroblasts, was downregulated compared to normal lung fibroblasts. Fibroblasts in fibroblastic foci express both p62 and ubiquitin, which are also indicative of decreased autophagy[50–55].

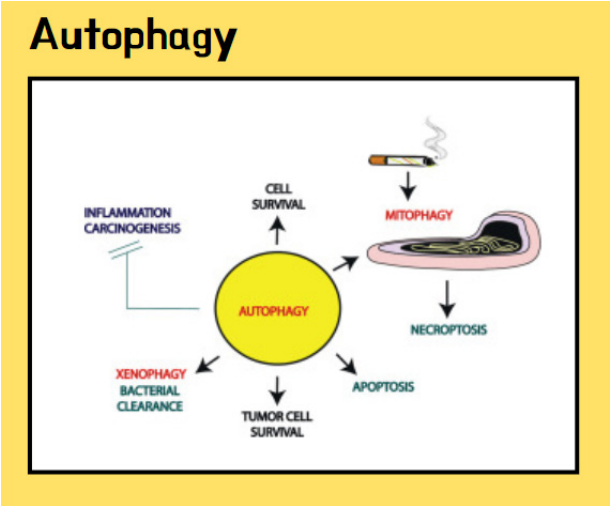

Figure 2. Autophagy stage in lung fibrosis.

Autophagy is also involved in different tasks, one of which is the regulation of activated IPF fibroblasts. Abnormalization of the PTEN/Akt/mTOR axis produces a viable IPF fibroblast phenotype on collagen by inhibiting autophagy and desensitizing IPF fibroblasts to stress from polymerized collagen. Abnormal regulation of the autophagic pathway suggests that it will play an important role in maintaining the pathological IPF fibroblast phenotype[56].

3.8 Apoptosis resistance

Fibroblasts from IPF lung cells are highly resistant to apoptosis. In many studies, it was observed that aged IPF fibroblasts showed decreased sensitivity to cytotoxic and proapoptotic signals. Fibroblasts resist cell death after senescence, resulting in the persistence of "damaged" cells that will undergo apoptosis and be cleared from the wound repair site. Also, little or no evidence of apoptosis was observed in cells expressing α-SMA in these areas; this confirms the apoptotic resistant phenotype of senescent myofibroblasts in areas with lung fibrosis[37–39,57,58].

Several mechanisms have been associated with the apoptosis-resistant phenotype of senescent fibroblasts and/or myofibroblasts in lung fibrosis (**Figure 3**). When we look at these mechanisms, the

most studied mechanism has been the differences in the levels of Bcl-2 family proteins. Apart from the decreased levels of proapoptotic proteins Bak and Bax, increased anti-apoptotic protein Bcl-2 family proteins are present in aged IPF fibroblasts. The increase in Bcl-2 family member (Bcl-W and Bcl-XL) proteins contributes to the resistance of senescent cells to apoptosis. TGF-β1 signal formed in the cell activates STAT3 and JAK2, increasing the level of Bcl-2 protein. Bax and Bcl-2 protein levels in fibroblasts appear to be STAT3 dependent, as resistance to apoptosis can be blocked by inhibiting STAT3 signaling. Some conditions are also associated with epigenetic modifications, which are DNA methylation, histone modification, changes in the expression of antiapoptotic and proapoptotic genes[55,59,60].

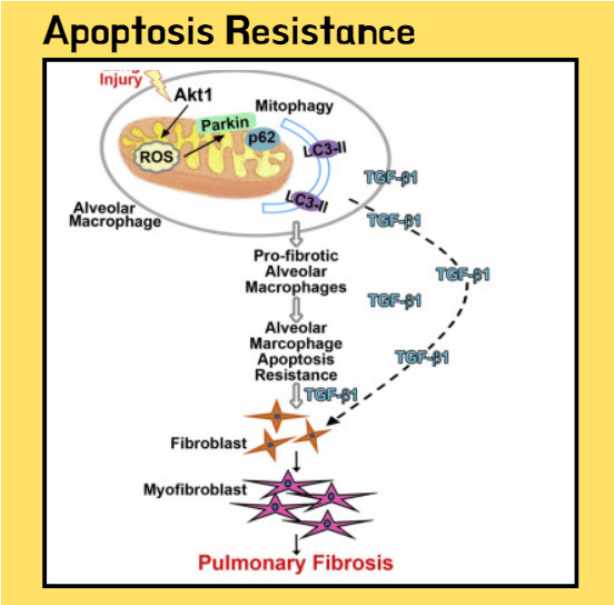

Figure 3. Apoptosis resistance stage in lung fibrosis.

When IPF pulmonary tissue fibroblasts age, they are highly resistant to TNF-associated apoptotic ligand-induced (TRAIL) and Fas ligand-induced (FasL) apoptosis. Decreased expression of caveolin-1 (Cav-1) and FasL receptor protein, together with increased AKT activity, is predicted to contribute to the apoptosis-resistant phenotype. Increasing AKT activity in the center of various signaling pathways involved in cell survival reduces autophagy and triggers the activation of the PI3K/AKT/mTOR pathway. Decreased expression of caveolin-1 in IPF fibroblasts is associated with aberrant activation of the PI3K/AKT pathway. The decrease in the level of caveolin-1 in the plasma membrane creates a micromembrane environment in which PTEN phosphatase activation decreases and PI3K/AKT activation increases. It also leads to decreased expression of caveolin-1 and Fas by decreasing PTEN activity. In this case, it leads to the inactivation of FoxO3a, the transcription activator dependent on PTEN/Akt[38,61–63].

The formation of the apoptosis-resistant and senescent myofibroblast phenotype has also been attributed to increased expression of the ROS-producing enzyme Nox4 and impaired capacity to induce Nrf2 antioxidant responses. Studies have shown that Nrf2 expression decreases in pulmonary tissues taken from people with IPF, and Nox4 expression increases in fibroblastic foci. In vivo knockdown of Nox4 and pharmacological targeting of Nox4 during the persistent phase of lung fibrosis in aged mice reduced Bcl-2 levels and restored the capacity of aged fibroblasts to undergo apoptosis, allowing fibrosis to resolve[37].

3.9 Mesenchymal progenitor cells (MPCs)

Recent studies have identified a subtype of embryonic antigen (SSEA4), expressing mesenchymal progenitor cells (MPCs) in the pulmonary tissues of patients with IPF. This type of cells has been termed the main starting cells for fibroblasts with fibrotic reticulum in IPF. Studies have differentiated the gene and protein expression profile of IPF lung mesenchymal progenitors from control lung MPCs by amplification of disease-associated genes. These cells were propagated for DNA-PKcs, senescence factors and pro-fibrotic factors. Previous studies have shown the relationship between DNA damage and repair, aging and lung fibrosis. For example, loss of clusterin can induce aging and deterioration in fibroid pulmonary tissues with loss of DNA damage response and repair pathways. It is noteworthy that the chemokines CCl28 and IL-8 increase after aging, stimulating the expansion and activation of SSEA4 + MPCs, as well as their fibrogenicity and expression of markers. Thus, the production and expansion of MPCs appear to be a feedforward loop between the aging environment and their aging and pathogenic behavior in pulmonary fibrosis diseases such as IPF[64–70].

3.10 Immune cells

The relationship between immunity and cell

aging is very strong. Because senescent cells activate their adaptive immune systems and maintain tissue and organ homeostasis. Other than that, the persistence or accumulation of senescent cells can certainly unleash their immune systems. It may also predispose the organ microenvironment to a chronic inflammatory condition that is partially seen in many age-related conditions, including in pulmonary tissues. In general, the immune system has two features in pulmonary fibrosis. These are dysfunction of the immune system called "immune aging" and spontaneous aging of immune cells. Despite controversy regarding the role of inflammation in pulmonary fibrosis, persistent chronic inflammation is undoubtedly one of the hallmarks of pulmonary fibroproliferative disorders, as many immunosuppressant drugs cannot cure IPF[22,70–77].

3.11 Bone marrow mesenchymal stem cells (B-MSCs)

Mesenchymal stromal cells (MSC) were first identified in the bone marrow, but are a human stem cell assemblage that has subsequently been demonstrated in many tissues. MSCs can differentiate into many cell types, thus they are multipotent stromal cells that have an important role in tissue remodeling and repair. In addition, B-MSCs are one of the experimental stem cell-based therapies in pulmonary fibrosis. In studies in mice, administration of B-MSCs improved pulmonary fibrosis. Therefore, senescence of these stem cells will impair the tissue repair capacity needed in IPF[78,79].

Known key cellular players in the pathogenesis of pulmonary fibrosis, namely mesenchymal cells, immune cells and epithelial cells, exhibit cellular senescence phenotypes in preclinical studies and human lung samples. It is possible that stages of aging occur in more than one cell type in the lung, as observed in different studies of intact single-cell RNA sequencing. As a result, it is unclear whether these senescent cells work in concert to trigger pulmonary fibrosis or whether a dominant cell type drives the process[80].

It is also thought that the major cause of fibrosis in systemic sclerosis is excessive deposition of extracellular matrix in multiple organs[81]. In conclusion, when we examine the pathogenesis of lung fibrosis, we see that cellular aging plays a major role. Lung fibroblasts take an active role in the regeneration process. However, despite all the information, the pathogenesis of lung fibrosis is not clearly understood. It is not yet clear how senescent cells in the lung interact and cause fibrosis. The pathogenesis of lung fibrosis will be understood more clearly after future studies.

4. Conclusion

Cellular senescence is a significant factor in the development of lung fibrosis. Research indicates that senescence processes occur in key cellular components involved in lung fibrosis during abnormal lung tissue growth. AT2 cells and lung fibroblasts are crucial for tissue repair and regeneration, with inflammation also playing a vital role. Some shared factors and signaling pathways, such as autophagy and mitophagy, are observed in both AT2 cells and lung fibroblasts. The main culprit appears to be SASP (senescence-associated secretory phenotype), which creates a vicious cycle by acting as trigger and effector molecules. Eliminating senescent cells is a logical approach to counteract the damaging effects of SASP, but it is a challenging task. The current knowledge gap lies in understanding how senescent cells interact in the lung, modify the lung's microenvironment, and contribute to persistent and progressive fibrosis. Advancements in scientific technologies like single-cell RNA sequencing, nuclear sequencing, and multi-omics approaches will provide further insights into the role of cellular senescence in lung fibrosis. Therefore, many mechanisms may play a role in lung fibrosis, as we mentioned above, the pathogenesis of the disease is still not fully understood. Research to be conducted in the near future will greatly contribute to the elucidation of the causes, follow-up and treatment of this disorder.

Conflict of interest

The authors declare no conflict of interest.

References

1. Raghu G, Remy-Jardin M, Myers JL, *et al*. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. American Journal of Respiratory and Critical Care Medicine 2018; 198(5): e44–e68. doi: 10.1164/rccm.201807-1255ST.
2. Rabeyrin M, Thivolet F, Ferretti GR, *et al*. Usual interstitial pneumonia end-stage features from

explants with radiologic and pathological correlations. Annals of Diagnostic Pathology 2015; 19(4): 269–276. doi: 10.1016/j.anndiagpath.2015.05.003.
3. Selman M, Pardo A. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. An integral model. American Journal of Respiratory and Critical Care Medicine 2014; 189(10): 1161–1172. doi: 10.1164/rccm.201312-2221PP.
4. McHugh D, Gil J. Senescence and aging: Causes, consequences, and therapeutic avenues. Journal Cell of Biology 2017; 217(1): 65–77. doi: 10.1083/jcb.201708092.
5. Loaiza N, Demaria M. Cellular senescence and tumor promotion: Is aging the key? Biochimica et Biophysica Acta (BBA)—Reviews on Cancer 2016; 1865(2): 155–167. doi: 10.1016/j.bbcan.2016.01.007.
6. Sun N, Youle RJ, Finkel T. The mitochondrial basis of aging. Molecular Cell 2016; 61(5): 654–666. doi: 10.1016/j.molcel.2016.01.028.
7. Kuilman T, Michaloglou C, Mooi WJ, Peeper DS. The essence of senescence. Genes & Development 2010; 24(22): 2463–2479. doi: 10.1101/gad.1971610.
8. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Experimental Cell Research 1961; 25: 585–621. doi: 10.1016/0014-4827(61)90192-6.
9. Robles SJ, Adami GR. Agents that cause DNA double strand breaks lead to p16INK4a enrichment and the premature senescence of normal fibroblasts. Oncogene 1998; 16: 1113–1123. doi: 10.1038/sj.onc.1201862.
10. Martínez-Zamudio RI, Robinson L, Roux PF, Bischof O. SnapShot: Cellular senescence pathways. Cell 2017; 170: 816–816.e1. doi: 10.1016/j.cell.2017.07.049.
11. Muñoz-Espín D, Serrano M. Cellular senescence: From physiology to pathology. Nature Reviews Molecular Cell Biology 2014; 15(7): 482–496. doi: 10.1038/nrm3823.
12. Salama R, Sadaie M, Hoare M, Narita M. Cellular senescence and its effector programs. Genes & Development 2014; 28(2): 99–114. doi: 10.1101/gad.235184.113.
13. Salminen A, Kauppinen A, Kaarniranta K. Emerging role of NF-κB signaling in the induction of senescence-associated secretory phenotype (SASP). Cellular Signalling 2012; 24(4): 835–845. doi: 10.1016/j.cellsig.2011.12.006.
14. Liu T, De Los Santos FG, Zhao Y, *et al*. Telomerase reverse transcriptase ameliorates lung fibrosis by protecting alveolar epithelial cells against senescence. Journal of Biology Chemistry 2019; 294(22): 8861–8871. doi: 10.1074/jbc.RA118.006615.
15. Yao C, Guan X, Carraro G, *et al*. Senescence of alveolar type 2 cells drives progressive pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine 2021; 203(6): 707–717. doi: 10.1164/rccm.202004-1274OC.
16. Jiang C, Liu G, Luckhardt T, *et al*. Serpine 1 induces alveolar type II cell senescence through activating p53-p21-Rb pathway in fibrotic lung disease. Aging Cell 2017; 16(5): 1114–1124. doi: 10.1111/acel.12643.
17. Zhang Y, Huang W, Zheng Z, *et al*. Cigarette smoke-inactivated SIRT1 promotes autophagy-dependent senescence of alveolar epithelial type 2 cells to induce pulmonary fibrosis. Free Radical Biology and Medicine 2021; 166: 116–127. doi: 10.1016/j.freeradbiomed.2021.02.013.
18. Young AR, Narita M. Connecting autophagy to senescence in pathophysiology. Current Opinion in Cell Biology 2010; 22(2): 234–240. doi: 10.1016/j.ceb.2009.12.005.
19. Qiu T, Tian Y, Gao Y, *et al*. PTEN loss regulates alveolar epithelial cell senescence in pulmonary fibrosis depending on Akt activation. Aging 2019; 11(18): 7492–7509. doi: 10.18632/aging.102262.
20. Lehmann M, Hu Q, Hu Y, *et al*. Chronic WNT/β-catenin signaling induces cellular senescence in lung epithelial cells. Cellular Signalling 2020; 70: 109588. doi: 10.1016/j.cellsig.2020.109588.
21. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: The dark side of tumor suppression. Annual Review of Pathology: Mechanisms of Disease 2010; 5: 99–118. doi: 10.1146/annurev-pathol-121808-102144.
22. Freund A, Orjalo AV, Desprez PY, Campisi J. Inflammatory networks during cellular senescence: Causes and consequences. Trends in Molecular Medicine 2010; 16(5): 238–246. doi: 10.1016/j.molmed.2010.03.003.
23. Lopes-Paciencia S, Saint-Germain E, Rowell MC, *et al*. The senescence-associated secretory phenotype and its regulation. Cytokine 2019; 117: 15–22. doi: 10.1016/j.cyto.2019.01.013.
24. Wiley CD, Brumwell AN, Davis SS, *et al*. Secretion of leukotrienes by senescent lung fibroblasts promotes pulmonary fibrosis. JCI Insight 2019; 4(24): e130056. doi: 10.1172/jci.insight.130056.
25. Rana T, Jiang C, Liu G, *et al*. PAI-1 regulation of TGF-β1-induced alveolar type II cell senescence, SASP secretion, and SASP-mediated activation of alveolar macrophages. American Journal of Res-

piratory Cell and Molecular Biology 2020; 62(3): 319–330. doi: 10.1165/rcmb.2019-0071OC.
26. Hu B, Ullenbruch MR, Jin H, *et al*. An essential role for CCAAT/enhancer binding protein β in bleomycin-induced pulmonary fibrosis. The Journal Pathology 2006; 211(4): 455–462. doi: 10.1002/path.2119.
27. Chilosi M, Carloni A, Rossi A, Poletti V. Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema. Translational Research 2013; 162(3): 156–173. doi: 10.1016/j.trsl.2013.06.004.
28. Xu Y, Mizuno T, Sridharan A, *et al*. Single-cell RNA sequencing identifies diverse roles of epithelial cells in idiopathic pulmonary fibrosis. JCI Insight 2016; 1(20): e90558. doi: 10.1172/jci.insight.90558.
29. Smirnova NF, Schamberger AC, Nayakanti S, *et al*. Detection and quantification of epithelial progenitor cell populations in human healthy and IPF lungs. Respiratory Research 2016; 17(1): 1–11. doi: 10.1186/s12931-016-0404-x.
30. Carraro G, Mulay A, Yao C, *et al*. Single-cell reconstruction of human basal cell diversity in normal and idiopathic pulmonary fibrosis lungs. American Journal of Respiratory and Critical Care Medicine 2020; 202(11): 1540–1550. doi: 10.1164/rccm.201904-0792OC.
31. De Pianto DJ, Heiden JAV, Morshead KB, *et al*. Molecular mapping of interstitial lung disease reveals a phenotypically distinct senescent basal epithelial cell population. JCI Insight 2021; 6(8): e143626. doi: 10.1172/jci.insight.143626.
32. Meyer K, Hodwin B, Ramanujam DP, *et al*. Essential role for premature senescence of myofibroblasts in myocardial fibrosis. Journal of the American College of Cardiology 2016; 67(17): 2018–2028. doi: 10.1016/j.jacc.2016.02.047.
33. Krizhanovsky V, Yon M, Dickins R, *et al*. Senescence of activated stellate cells limits liver fibrosis. Cell 2008; 134(4): 657–667. doi: 10.1016/j.cell.2008.06.049.
34. Jun JI, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. Nature Cell Biology 2010; 12(7): 676–685. doi: 10.1038/ncb2070.
35. Kendall RT, Feghali-Bostwick CA. Fibroblasts in fibrosis: Novel roles and mediators. Frontiers in Pharmacology 2014; 5: 123. doi: 10.3389/fphar.2014.00123.
36. Schafer MJ, White TA, Iijima K, *et al*. Cellular senescence mediates fibrotic pulmonary disease. Nature Communications 2017; 8: 14532. doi: 10.1038/ncomms14532.
37. Hecker L, Logsdon NJ, Kurundkar D, *et al*. Reversal of persistent fibrosis in aging by targeting Nox4-Nrf2 redox imbalance. Science Translational Medicine 2014; 6(231): 231ra47. doi: 10.1126/scitranslmed.3008182.
38. Hohmann MS, Habiel DM, Coelho AL, *et al*. Quercetin enhances ligand-induced apoptosis in senescent idiopathic pulmonary fibrosis fibroblasts and reduces lung fibrosis in vivo. American Journal of Respiratory Cell and Molecular Biology 2019; 60(1): 28–40. doi: 10.1165/rcmb.2017-0289OC.
39. Álvarez D, Cárdenes N, Sellarés J, *et al*. IPF lung fibroblasts have a senescent phenotype. American Journal of Physiology–Lung Cellular and Molecular Physiology 2017; 313(6): L1164–L1173.
40. Ramos C, Montaño M, García-Alvarez J, *et al*. Fibroblasts from idiopathic pulmonary fibrosis and normal lungs differ in growth rate, apoptosis, and tissue inhibitor of metalloproteinases expression. American Journal of Respiratory Cell and Molecular Biology 2001; 24(1): 591–598. doi: 10.1165/ajrcmb.24.5.4333.
41. Acosta JC, Banito A, Wuestefeld T, *et al*. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nature Cell Biology 2013; 15(8): 978–990. doi: 10.1038/ncb2784.
42. Zank DC, Bueno M, Mora AL, Rojas M. Idiopathic pulmonary fibrosis: Aging, mitochondrial dysfunction, and cellular bioenergetics. Frontiers in Medicine 2018; 5: 10. doi: 10.3389/fmed.2018.00010.
43. Passos JF, Nelson G, Wang C, *et al*. Feedback between p21 and reactive oxygen production is necessary for cell senescence. Molecular Systems Biology 2010; 6: 347. doi: 10.1038/msb.2010.5.
44. Wiley CD, Velarde MC, Lecot P, *et al*. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. Cell Metabolism 2016; 23(2): 303–314. doi: 10.1016/j.cmet.2015.11.011.
45. Bueno M, Lai YC, Romero Y, *et al*. PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. Journal of Clinical Investigation 2015; 125(2): 521–538. doi: 10.1172/JCI74942.
46. Mora AL, Bueno M, Rojas M. Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis. Journal of Clinical Investigation 2017; 127(2): 405–414. doi: 10.1172/JCI87440.
47. Xie N, Tan Z, Banerjee S, *et al*. Glycolytic reprogramming in myofibroblast differentiation and lung fibrosis. American Journal of Respiratory and Critical Care Medicine 2015; 192(12): 1462–1474. doi: 10.1164/rccm.201504-0780OC.
48. Caporarello N, Meridew JA, Jones DL, *et al*. PG-

C1α repression in IPF fibroblasts drives a pathologic metabolic, secretory and fibrogenic state. Thorax 2019; 74(8): 749–760. doi: 10.1136/thoraxjnl-2019-213064.

49. Kobayashi K, Araya J, Minagawa S, *et al*. Involvement of PARK2-mediated mitophagy in idiopathic pulmonary fibrosis pathogenesis. Journal of Immunology 2016; 197(2): 504–516. doi: 10.4049/jimmunol.1600265.
50. Sosulski ML, Gongora R, Danchuk S, *et al*. Deregulation of selective autophagy during aging and pulmonary fibrosis: The role of TGFβ1. Aging Cell 2015; 14(5): 774–783. doi: 10.1111/acel.12357.
51. Rajawat YS, Hilioti Z, Bossis I. Aging: Central role for autophagy and the lysosomal degradative system. Ageing Research Reviews 2009; 8(30): 199–213. doi: 10.1016/j.arr.2009.05.001.
52. Kuwano K, Araya J, Hara H, *et al*. Cellular senescence and autophagy in the pathogenesis of chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). Respiratory Investigation 2016; 54(6): 397–406. doi: 10.1016/j.resinv.2016.03.010.
53. Araya J, Kojima J, Takasaka N, *et al*. Insufficient autophagy in idiopathic pulmonary fibrosis. American Journal of Physiology–Lung Cellular and Molecular Physiology 2013; 304(1): L56–L69. doi: 10.1152/ajplung.00213.2012.
54. Patel AS, Lin L, Geyer A, *et al*. Autophagy in idiopathic pulmonary fibrosis. PLoS ONE 2012; 7(7): e41394. doi: 10.1371/journal.pone.0041394.
55. Ricci A, Cherubini E, Scozzi D, *et al*. Decreased expression of autophagic beclin 1 protein in idiopathic pulmonary fibrosis fibroblasts. Journal of Cellular Physiology 2013; 228(7): 1516–1524. doi: 10.1002/jcp.24307.
56. Nho RS, Hergert P. IPF fibroblasts are desensitized to type I collagen matrix-induced cell death by suppressing low autophagy via aberrant Akt/mTOR kinases. PLoS ONE 2014; 9(4): e94616. doi: 10.1371/journal.pone.0094616.
57. Cha SI, Groshong SD, Frankel SK, *et al*. Compartmentalized expression of c-FLIP in lung tissues of patients with idiopathic pulmonary fibrosis. American Journal of Respiratory Cell and Molecular Biology 2010; 42(2): 140–148. doi: 10.1165/rcmb.2008-0419OC.
58. Yanai H, Shteinberg A, Porat Z, *et al*. Cellular senescence-like features of lung fibroblasts derived from idiopathic pulmonary fibrosis patients. Aging 2015; 7(9): 664–672. doi: 10.18632/aging.100807.
59. Yosef R, Pilpel N, Tokarsky-Amiel R, *et al*. Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. Nature Communications 2016; 7: 11190. doi: 10.1038/ncomms11190.
60. Milara J, Hernandez G, Ballester B, *et al*. The JAK2 pathway is activated in idiopathic pulmonary fibrosis. Respiratory Research 2018; 19(1): 24. doi: 10.1186/s12931-018-0728-9.
61. Xia H, Khalil W, Kahm J, *et al*. Pathologic caveolin-1 regulation of PTEN in idiopathic pulmonary fibrosis. The American Journal of Pathology 2010; 176(6): 2626–2637. doi: 10.2353/ajpath.2010.091117.
62. Nho RS, Peterson M, Hergert P, Henke CA. FoxO3a (forkhead box O3a) deficiency protects idiopathic pulmonary fibrosis (IPF) fibroblasts from type I polymerized collagen matrix-induced apoptosis via caveolin-1 (cav-1) and fas. PLoS ONE 2013; 8(4): e61017. doi: 10.1371/journal.pone.0061017.
63. Romero Y, Bueno M, Ramirez R, *et al*. MTORC1 activation decreases autophagy in aging and idiopathic pulmonary fibrosis and contributes to apoptosis resistance in IPF fibroblasts. Aging Cell 2016; 15(6): 1103–1112. doi: 10.1111/acel.12514.
64. Xia, H, Bodempudi V, Benyumov A, *et al*. Identification of a cell-of-origin for fibroblasts comprising the fibrotic reticulum in idiopathic pulmonary fibrosis. The American Journal of Pathology 2014; 184(5): 1369–1383. doi: 10.1016/j.ajpath.2014.01.012.
65. Habiel DM, Hohmann MS, Espindola MS, *et al*. DNA-PKcs modulates progenitor cell proliferation and fibroblast senescence in idiopathic pulmonary fibrosis. BMC Pulmonary Medicine 2019; 19(1): 1–16. doi: 10.1186/s12890-019-0922-7.
66. Yang L, Xia H, Smith KA, *et al*. A CD44/Brg1 nuclear complex confers mesenchymal progenitor cells with enhanced fibrogenicity in idiopathic pulmonary fibrosis. JCI Insight 2021; 6(9): e144652. doi: 10.1172/jci.insight.144652.
67. Kumar V, Fleming T, Terjung S, *et al*. Homeostatic nuclear RAGE-ATM interaction is essential for efficient DNA repair. Nucleic Acids Research 2017; 45(18): 10595–10613. doi: 10.1093/nar/gkx705.
68. Habiel DM, Camelo A, Espindola M, *et al*. Divergent roles for clusterin in lung injury and repair. Scientific Reports 2017; 7(1): 15444. doi: 10.1038/s41598-017-15670-5.
69. Yang L, Herrera J, Gilbertsen A, *et al*. IL-8 mediates idiopathic pulmonary fibrosis mesenchymal progenitor cell fibrogenicity. American Journal of Physiology–Lung Cellular and Molecular Physiology 2018; 314(1): L127–L136. doi: 10.1152/ajplung.00200.2017.
70. Hohmann MS, Habiel DM, Espindola MS, *et*

al. Antibody-mediated depletion of CCR10 + EphA3 + cells ameliorates fibrosis in IPF. JCI Insight 2021; 6(11): e141061. doi: 10.1172/jci.insight.141061.

71. Vicente R, Mausset-Bonnefont AL, Jorgensen C, *et al*. Cellular senescence impact on immune cell fate and function. Aging Cell 2016; 15(3): 400–406. doi: 10.1111/acel.12455.
72. Murray MA, Chotirmall SH. The impact of immunosenescence on pulmonary disease. Mediators of Inflammation 2015; 2015: 692546. doi: 10.1155/2015/692546.
73. Shenderov K, Collins SL, Powell JD, Horton MR. Immune dysregulation as a driver of idiopathic pulmonary fibrosis. Journal of Clinical Investigation 2021; 131(2): e143226. doi: 10.1172/JCI143226.
74. Faner R, Rojas M, MacNee W, Agustí A. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine 2012; 186(4): 306–313. doi: 10.1164/rccm.201202-0282PP.
75. Linton PJ, Thoman ML. Immunosenescence in monocytes, macrophages, and dendritic cells: Lessons learned from the lung and heart. Immunology Letters 2014; 162(1): 290–297. doi: 10.1016/j.imlet.2014.06.017.
76. Aiello A, Farzaneh F, Candore G, *et al*. Immunosenescence and its hallmarks: How to oppose aging strategically? A review of potential options for therapeutic intervention. Frontiers in Immunology 2019; 10: 2247. doi: 10.3389/fimmu.2019.02247.
77. Desai O, Winkler J, Minasyan M, Herzog EL. The role of immune and inflammatory cells in idiopathic pulmonary fibrosis. Frontiers in Medicine 2018; 5: 43. doi: 10.3389/fmed.2018.00043.
78. Li X, An G, Wang Y, *et al*. Targeted migration of bone marrow mesenchymal stem cells inhibits silica-induced pulmonary fibrosis in rats. Stem Cell Research & Therapy 2018; 9(1): 335. doi: 10.1186/s13287-018-1083-y.
79. Cárdenes N, Álvarez D, Sellarés J, *et al*. Senescence of bone marrow-derived mesenchymal stem cells from patients with idiopathic pulmonary fibrosis. Stem Cell Research & Therapy 2018; 9(1): 257. doi: 10.1186/s13287-018-0970-6.
80. Parimon T, Hohmann MS, Yao C. Cellular senescence: Pathogenic mechanisms in lung fibrosis. International Journal of Molecular Sciences 2021; 22(12): 6214. doi: 10.3390/ijms22126214.
81. Jinnin M. Molecular pathogenesis of fibrosis in systemic sclerosis. Trends in Immunotherapy 2022; 6(1): 32–40. doi: 10.24294/ti.v6.i1.1453.