HHS Public Access

Author manuscript

Chin Med J Pulm Crit Care Med. Author manuscript; available in PMC 2024 April 02.

Published in final edited form as:

Chin Med J Pulm Crit Care Med. 2024 March ; 2(1): 10–16. doi:10.1016/j.pccm.2024.01.001.

Emerging role of cellular senescence in normal lung development and perinatal lung injury

Phyllis A. Dennery[a,b], **Hongwei Yao**[a,*]

[a]Department of Molecular Biology, Cell Biology & Biochemistry, Division of Biology and Medicine, Brown University, Providence, RI 02912, USA

[b]Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI 02903, USA

Abstract

Cellular senescence is a status of irreversible growth arrest, which can be triggered by the p53/p21^{cip1} and p16^{INK4}/Rb pathways via intrinsic and external factors. Senescent cells are typically enlarged and flattened, and characterized by numerous molecular features. The latter consists of increased surfaceome, increased residual lysosomal activity at pH 6.0 (manifested by increased activity of senescence-associated beta-galactosidase [SA-β-gal]), senescence-associated mitochondrial dysfunction, cytoplasmic chromatin fragment, nuclear lamin b1 exclusion, telomere-associated foci, and the senescence-associated secretory phenotype. These features vary depending on the stressor leading to senescence and the type of senescence. Cellular senescence plays pivotal roles in organismal aging and in the pathogenesis of aging-related diseases. Interestingly, senescence can also both promote and inhibit wound healing processes. We recently report that senescence as a programmed process contributes to normal lung development. Lung senescence is also observed in Down Syndrome, as well as in premature infants with bronchopulmonary dysplasia and in a hyperoxia-induced rodent model of this disease. Furthermore, this senescence results in neonatal lung injury. In this review, we briefly discuss the molecular features of senescence. We then focus on the emerging role of senescence in normal lung development and in the pathogenesis of bronchopulmonary dysplasia as well as putative signaling pathways driving senescence. Finally, we discuss potential therapeutic approaches targeting senescent cells to prevent perinatal lung diseases.

Keywords

Senescence; Normal lung development; Bronchopulmonary dysplasia; Down syndrome; Senolytics

*Corresponding author at: Department of Molecular Biology, Cell Biology & Biochemistry, Division of Biology and Medicine, Brown University, 185 Meeting Street, SFH, Providence, RI 02912, USA., Hongwei_Yao@brown.edu (H. Yao).

Declaration of competing interest

Authors have declared that no conflict of interest exists.

Introduction

Cellular senescence is a term used to describe cells that cease to divide/proliferate and show enlarged morphology. Although demonstrating proliferation arrest, senescence cells are metabolically active and are prone to secrete inflammatory mediators termed senescence-associated secretory phenotype (SASP). Senescence can be triggered by intrinsic and/or external factors. Intrinsic factors consist of telomere shortening (replicative senescence), DNA damage/deficient DNA repair, oncogene activation, metabolism, and endogenous oxidative stress, whereas chemotherapeutics, pollution, hyperoxic exposure, cigarette smoke exposure, radiation, ultraviolet (UV) light, and virus infection are extrinsic factors [Fig. 1].

Senescent cells accumulate in aging tissues, which plays pivotal roles in organismal aging and in the pathogenesis of aging-related diseases, such as Alzheimer's disease, chronic lung diseases[1] and premature aging as seen in Down Syndrome. Senescence can also both promote and inhibit wound healing.[2,3] Interestingly, accumulating evidence shows that cellular senescence also contributes to the development of organs, including limbs, hindbrain roofplate, mesonephros, neural tube, endolymphatic sac, pharyngeal arches, and gut endoderm in humans, naked mole rats, and mice.[4–6] We recently reported that senescent cells are observed and peak at the saccular stage of normal lung development in mice.[7] Reducing the number of senescent cells during the saccular stage disrupts normal lung development, suggesting that senescence is a programmed process for lung development. Interestingly, neonatal hyperoxia interrupts the normal reduction in developmental senescence by causing a transient increase during the alveolar stage. This leads to alveolar and vascular simplification, characteristics of bronchopulmonary dysplasia, a chronic lung disease in premature infants.[7,8] This highlights the paradoxical importance of the timing of senescence in mediating normal lung development and also neonatal hyperoxia-induced alveolar simplification.

In this review, we briefly discuss the molecular features of senescence. We then focus on the emerging role of senescence in normal lung development and in the pathogenesis of bronchopulmonary dysplasia as well as putative signaling pathways involved in this senescence. Finally, we discuss potential therapeutic approaches targeting senescent cells to prevent this disease.

Molecular features of senescent cells

Compared to normal cells, senescent cells display unique morphological and molecular features [Fig. 1]. Morphologically, senescent cells are flattened with enlarged nuclei and low saturation density at the plateau phase of cell growth. This can be detected by image-assisted cytometry such as laser scanning cytometry.[9] Senescent cells express specific cell surface proteins termed the senescent surfaceome, such as urokinase-type plasminogen activator receptor (uPAR), dipeptidyl peptidase 4 (DDP4), and β_2 microglobulin (B2M).[10–12] This can be used for identification and subsequent targeted ablation of senescent cells.

In the cytoplasm, senescence-associated β-galactosidase (SA-β-gal) is the most commonly used biomarker for senescent cells, and this is defined as β-galactosidase activity detectable

at pH 6.0. A previous study reported that mitochondrial defects trigger a distinct senescence phenotype called mitochondrial dysfunction-associated senescence (Mi-DAS).[13] This type of senescence is induced by an increase in the ratio of nicotinamide adenine dinucleotide $(NAD)^+$/reduced nicotinamide adenine dinucleotide (NADH) and the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), which in turn activates p53. Interestingly, MiDAS is not associated with increased oxidative stress or nuclear DNA damage (53BP1 foci).[14]

Lamin B1 is a scaffolding component of the nuclear envelope. Loss of nuclear lamin b1 is a feature of senescent cells.[15, 16] In the nucleus, telomere shortening and telomere-associated foci due to DNA damage are observed in aging and aging-related diseases.[17] Mechanistically, disruption of shelterin, a protein complex that safeguards telomeres, and the resulting cyclic guanosine monophosphate (GMP)-AMP synthase activation by cytosolic chromatin fragments may trigger cellular senescence.[18, 19] Indeed, phosphorylation of the H2AX histone at C-terminal serine-139 (γ-H2AX) is the most sensitive marker of double-stranded DNA breaks, which is the second most common marker of cellular senescence after SA-β-gal.

Although their cell cycle is arrested, senescent cells are metabolically active and usually secrete a variety of SASP factors, including pro-inflammatory cytokines, chemokines, extracellular matrix-degrading proteins, and growth factors. This could generate autocrine and/or paracrine effects that contribute to physiological function and pathological alterations.

The p53/$p21^{CIP1}$ and $p16^{INK4A}$/Rb pathways are activated during induction of cellular senescence. A previous study shows that downregulation of p300 histone acetyltransferase activity induces a robust G2/M cell cycle arrest and senescence by a mechanism that is independent of the activation of p53, $p21^{CIP1}$ or $p16^{INK4A}$,[20] suggesting multiple pathways involved in cellular senescence.

There are no unique markers for senescence. Thus, a combination of the above morphological and molecular features is commonly used to identify senescent cells. It is also important to note that senescent cells do not always have all these molecular features, and that this depends on the stressor inducing senescence and the type of senescence (developmental *vs*. stress-induced).

Programmed senescence during normal lung development

Cell-specific senescence

We recently showed that lung senescence is observed at birth and decreases throughout the saccular stage in mice (Fig. 2).[7] Further investigation of lung senescence in prenatal mice will reveal dynamic changes of senescence during different stages of lung development. Interestingly, there were no significant changes in DNA damage markers (e.g., γH2AX and 53BP1) or p16 expression during lung development.[7] This suggests that these processes are not involved in lung developmental senescence. This is corroborated by the fact that p16 is not associated with developmental senescence in embryonic kidneys or

limbs.[5,6] In agreement with previous reports on senescence in other organs,[5,6] p21 mediates developmental senescence in the lung.[7] Although we identified mesenchymal cell senescence during normal lung development, further investigation on cell types or states of mesenchymal cells is warranted. The re-analysis of single cell RNA sequencing datasets from a published single-cell atlas of mouse lung development will reveal enriched signaling pathways and potential mechanisms underlying developmental senescence in the lung.[21] Although cells undergoing developmentally programmed senescence are cleared by macrophages,[6] further study is warranted to determine how macrophages are migrated into the surrounding of senescent cells.

Signaling pathways driving developmental senescence

Transforming growth factor-β (TGF-β) is able to activate the transcription of the p21 gene through Smad complexes. A previous report demonstrates that p21-mediated developmentally programmed senescence in the mesonephros and endolymphatic sac is causally induced by the TGF-β/Smad pathway.[6] This is corroborating with the findings that inhibiting TGF-β signaling decreases senescence in Xenopus laevis cement gland in axolotl, resulting in abnormal morphology in neighboring structures.[22] Once activation, Smad proteins can form a complex with forkhead box O (FOXO) proteins. Munoz-Espin et al[6] further elucidated that phosphoinositide 3-kinase (PI3K)/FOXO and TGF-β/Smad pathways are intertwined in modulating developmental senescence in the mesonephros and endolymphatic sac. Interestingly, cellular senescence in the axolotl pronephros is independent of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway.[22] This suggests specific signaling pathways responsible for developmental senescence (Fig. 2).

TGF-β/Smad pathways are temporally and spatially regulated during normal lung development, which plays pivotal roles in promoting branching morphogenesis and alveolarization. Mesenchyme-specific deletion of TGF-β receptor 2 gene causes lung malformation with prenatal pulmonary cysts in mice.[23] Further study is warranted to identify signaling pathways, including the TGF-β/Smad pathway, which mediate senescence during normal lung development.

Abnormally induced senescence in perinatal lung diseases

Down syndrome

Abnormally induced lung senescence in Down syndrome—Down syndrome is a genetic disorder caused by an extra copy of chromosome 21 (trisomy 21). Although Down syndrome is a multisystem disorder, lung disease remains a leading cause of morbidity and mortality in this condition. Pulmonary manifestations in Down syndrome include pulmonary hypoplasia, underdeveloped pulmonary vasculature, and pulmonary vascular remodeling.[24,25] Down syndrome has been described as a progeroid syndrome, characterized by accelerated maturation and aging.[26] This could be due to abnormal overexpression of genes on human chromosome 21 (HSA21) and downstream effects on non-HSA21 genes, which modulate longevity and senescence.[27–31] Trisomy 21 induces chromosomal introversion, disrupts lamina-associated domains, and alters the genome-wide chromatin accessibility,

which results in senescence in cultured neural progenitor cells.[32] Interestingly, trisomy 21 fetal lungs (at 17–20 weeks of gestation) have reduced proliferation and increased expression of p21, p16, and SASP gene expression compared to euploid fetuses,[33, 34] suggesting abnormal induction of senescence. These studies raise the possibility that senescence observed in Down syndrome may occur either through mis-timed activation of the endogenous senescence program, or through aberrant induction of senescence in various cells. Further study is warranted to investigate whether this abnormal induction of senescence contributes to pulmonary hypoplasia, underdeveloped pulmonary vasculature, and pulmonary vascular remodeling observed in Down syndrome.

Signaling pathways for lung senescence in Down syndrome—There is only one study which employed single cell RNA sequencing and analyzed differentially expressed senescence genes in various fetal organs from trisomy 21 fetuses (20–24 weeks of gestation), including the lung.[34] This study revealed that the differentially expressed genes identified in Down syndrome cells correlate with the critical gene expression alterations identified in RAS oncogene, and ionizing radiation-induced senescence. Interestingly, the differentially expressed genes identified in Down syndrome cells have a low correlation with altered gene expression in oxidative stress-induced senescence or replicative senescence. This suggests specific signaling pathways underlying senescence in Down syndrome. Further reanalysis of these differentially expressed genes is warranted to reveal specific signaling pathways for senescence in organs from patients with Down syndrome.

Bronchopulmonary dysplasia

Lung senescence in a hyperoxia-induced murine model—We and others have reported that hyperoxia causes senescence in cultured lung fibroblasts, epithelial cells, and fetal airway smooth muscle cells.[35–38] Using a neonatal hyperoxia-induced murine model of bronchopulmonary dysplasia, we demonstrate that neonatal hyperoxia at the saccular stage causes transient senescence in the lung at the alveolar stage (Fig. 3).[7] This is corroborated by a recent report showing that neonatal hyperoxia at both the saccular and alveolar stages of lung development causes lung senescence in rats.[8] This senescence is mediated by the p53/p21 pathway, and is associated with increased oxidative stress and DNA damage. Translationally, increased nuclear lamin b1 loss, a senescence biomarker, is also observed in the lungs of premature human infants requiring mechanical ventilation compared to control subjects. Immunostaining of autopsy samples showed increased triple localization of p21, γH2AX and smooth muscle actin in the airways of infants exposed to 4 days of hyperoxia compared with those who died within 1 day of birth.[35] Additionally, increased senescence indicators, including 8-hydroxy-2′-deoxyguanosine, lipofuscin, and phosphorylated p53, are observed in the lung of premature infants with bronchopulmonary dysplasia.[8] Altogether, these findings suggest that the DNA damage response participates in lung cellular senescence in neonatal hyperoxic lung injury, in contrast to developmental senescence.

Cell specificity of senescence—The lung is composed of over 40 cell types. There are no changes in co-localization of p21 with type I alveolar cell or endothelial cell biomarkers in the lung of mice exposed to hyperoxia as neonates.[7] However, neonatal hyperoxia-

exposed rats have increased co-localization of p16 in type I alveolar cells and endothelial cells in the lung,[8] suggesting senescence in these cells. The discrepancies between these studies may be due to the differences of strains (mouse *vs.* rat), hyperoxic exposure durations (at the saccular stage only in mice *vs.* at both the saccular and alveolar stages in rats), and senescent indicators (p21 *vs.* p16) . Although type II alveolar cells account for a very small percentile of senescent cells, these cells contribute to hyperoxic lung injury via paracrine SASP factors.[7 , 39] In fact, the majority (92%) of 5-dodecanoylaminofluorescein di-β-D-galactopyranoside (C_{12} FDG; a substrate of SA-β-gal) positive cells were lung macrophages. These macrophages also highly express the senescence biomarkers *B2M* (encoding β2-microglobulin)[40] and *Plaur* (encoding uPAR)[10] as well as SASP factors, further confirming that these macrophages are senescent.

Fate of senescent macrophages—Senescent macrophages usually have a deficit in phagocytosis.[41–43] Senescent macrophages can be polarized into an M2 phenotype.[42 , 44] Indeed, certain subpopulations of senescent macrophages display distinct markers of M1, M2 or mixed polarization status in mice exposed to hyperoxia as neonates.[7] Whether these macrophages are from resident, monocyte-derived alveolar macrophages, or interstitial macrophages is still unclear. Resident alveolar macrophages are master regulators of arrested alveolarization in neonatal mice exposed to hyperoxia.[45] Senescent M2 macrophages could serve to resolve inflammation and repair hyperoxic lung injury, or promote a pro-fibrotic transcriptional program after neonatal hyperoxia.

Putative signaling pathways in neonatal hyperoxia-induced senescence—There are no reports investigating signaling pathways that directly contribute to senescence in lung injury seen in bronchopulmonary dysplasia. However, certain pathways that regulate cellular senescence are altered in the lungs of premature infants with bronchopulmonary dysplasia and of rodents exposed to hyperoxia as neonates (Fig. 2). For instance, the histone deacetylase Sirtuin1, well-known for modulating aging and age-related diseases, including chronic obstructive pulmonary disease, inhibits cellular senescence.[46–48] Mechanistically, Sirtuin1 can deacetylate nuclear factor-κB (NF-κB)/p65, p53, FOXO3, FOXO4, tuberous sclerosis complex 2 (TSC2), AMPK and peroxisome proliferator-activated receptor-γ coactivator-1 α (PGC-1 α), thereby regulating inflammation, DNA damage response, autophagy, and mitochondrial dysfunction. Indeed, Sirtuin1 levels are reduced in peripheral blood mononuclear cells and leukocytes isolated from tracheal aspirates of premature infants with bronchopulmonary dysplasia compared to controls without bronchopulmonary dysplasia.[49 , 50] Additionally, inflammation, DNA damage response, and impaired autophagic activity are observed in premature infants with bronchopulmonary dysplasia and in a baboon model of this disease.[51 , 52] Another example is microRNA (miRNA)-34a, which is upregulated in the lungs of premature infants with bronchopulmonary dysplasia.[53] We recently reported that miRNA-34a contributes to hyperoxia-induced senescence in cultured lung epithelial cells.[39] Nevertheless, further study is warranted to investigate whether these signaling pathways participate in the development of alveolar and vascular simplification seen in bronchopulmonary dysplasia by modulating cellular senescence.

Strategies to target or remove senescent cells

Strategies to target senescent cells in aging and adult diseases

Previous studies have shown that reducing the senescent cell burden extends healthy lifespan and delays the onset of age-related diseases in adulthood.[54, 55] Therefore, there is growing interest in developing senotherapeutics that integrate multidisciplinary technologies from biology, chemistry, nanotechnology, and immunology.[56] Both the surfaceome and intracellular senescence-associated pathways can be exploited for diagnosis and therapy. Currently, senotherapeutic strategies, such as senolytics, senomorphics, protein degraders, nanocarriers, and immunotherapies, are in development (Table 1).

Senolytics are a class of drugs that selectively kill senescent cells via apoptosis by transiently disabling antiapoptotic pathways in these cells. Previous reports demonstrate the value of senolytics in preventing aging and its deleterious consequences.[57–64] The first senolytic drugs discovered are dasatinib, quercetin, fisetin and navitoclax. The re-accumulation of senescent cells takes weeks. Thus, senolytics can be administered intermittently. The two most studied senolytics are a dasatinib plus quercetin cocktail, and fisetin, and both therapies have entered clinical trials for the treatment of various age-related diseases. The senolytic combination of quercetin and dasatinib is well tolerated in patients with diabetic kidney disease and idiopathic pulmonary fibrosis.[65, 66] However, the results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial demonstrate that changes in forced vital capacity, forced expiratory volume in 1 second, 6-min walk distance, and fatigability do not appear to differ significantly after treatment of quercetin and dasatinib in patients with idiopathic pulmonary fibrosis.[66] Larger randomized controlled trials are warranted to confirm the safety and efficacy of quercetin and dasatinib in patients with idiopathic pulmonary fibrosis.

Previous studies have shown that a combination of dasatinib with quercetin has a toxic effect on non-senescent cells.[67, 68] Therefore, other approaches, such as galactose-based prodrugs, proteolysis-targeting chimera and nanocarriers, are currently being exploited to deliver cytotoxic drug or senolytics into senescent cells.[67, 69, 70] For instance, a recent study designed a new prodrug SSK1 based on elevated β-gal, a major senescence marker, to direct gemcitabine and kill senescent cells in a highly selective manner.[67] Functionally, this drug can attenuate low-grade local and systemic inflammation, and restore physical function in aged mice and in bleomycin-induced lung injury.[67]

Senomorphics, also known as senostatics, are compounds that decrease the detrimental effects of the SASP or suppress senescence without inducing senescent cell death. Mechanistically, senomorphics ameliorate transcription of SASP factors by inhibiting ataxia telangiectasia mutated (ATM), p38 MAPK, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), and the NF-κB and mammalian target of rapamycin (mTOR) pathways. Unfortunately, administration of senomorphics may cause off-target effects due to suppression of cytokine secretion by non-senescent cells.

Although senotherapies prevent, or reverse chronic disorders, geriatric syndromes and loss of physiological resilience in preclinical studies and clinical trials,[54, 65, 71–73] they may

also negatively affect non-senescent cells. Senescent surfaceome-based immunotherapies offer an alternative strategy to specifically target senescent cells.[64] Such immunotherapies take advantage of cell surface protein antigens and receptors preferentially upregulated on the surface membrane of senescent cells, including uPAR, B2M, and DDP4.[10, 64, 74] For instance, CAR T cells are redirected to recognize the senescent surfaceome protein uPAR and preferentially remove senescent cells in different models.[10] Antibody-drug conjugates are monoclonal antibodies attached to cytotoxic drugs that have been successfully used for cancer treatment. The first senolytic antibody-drug conjugate was designed by conjugation of a B2M immunoglobulin G1 (IgG1) monoclonal antibody with duocarmycin, an irreversible DNA alkylating agent, to remove senescent cells *in vitro*.[40] Further study is warranted to test their efficacy and toxicity.

Strategies to remove senescent cells in neonates

There are no clinical trials using senotherapies to prevent or treat neonatal diseases, including Down syndrome and bronchopulmonary dysplasia. Although quercetin alone inhibits neonatal hyperoxia-induced alveolar simplification in mice by reducing oxidative stress and inflammation in mice, there are no experimental studies using a senolytic cocktail of quercetin and dasatinib in neonatal lung injury.

Using senolytics as a tool, we demonstrated that reducing senescent cells at the saccular stage of lung development disrupts normal lung development.[7] This suggests that senescence contributes to normal lung development perhaps by reducing mesenchymal cells and allowing for better approximation of alveolar sacs and blood vessels. In contrast, reducing senescent cells using a senolytic cocktail of quercetin and dasatinib or a selective p21 inhibitor in the alveolar stage of lung development protected against neonatal hyperoxia-induced alveolar and vascular simplification in mice.[7] Similarly, clearing senescent cells by FOXO4-D-retro-inverso (DRI), a peptide antagonist designed to block the interaction of FOXO4 and p53, at the alveolar stage inhibits neonatal hyperoxia-induced lung injury in rats.[8] Therefore, the timing of senescence is important in mediating normal lung development, as well as pulmonary hypoplasia and pulmonary vascular anomalies in Down syndrome and bronchopulmonary dysplasia. Therefore, lung developmental senescence should be preserved while developing novel therapies that clear senescent cells to prevent bronchopulmonary dysplasia and its long-term consequences.

Previous studies show that lung uPAR levels are increased in neonatal mice exposed to hyperoxia, whereas genetic deletion of uPAR protects against hyperoxic lung injury.[75, 76] uPAR can be shed from the cell surface as a soluble protein. Indeed, elevated soluble uPAR levels are biomarkers of bronchopulmonary dysplasia in premature infants.[77, 78] We reported that senescent lung macrophages highly express uPAR in mice exposed to hyperoxia, compared to air exposed controls.[7] Thus, clearing $uPAR^{+}$ senescent macrophages using uPAR antibody conjugates may be a potential approach to prevent lung injury in bronchopulmonary dysplasia.

Conclusions and perspectives

In summary, senescent cells not only play important roles in the pathogenesis of chronic lung diseases in neonates including bronchopulmonary dysplasia, but also contribute to normal lung development. Therefore, for the treatment of bronchopulmonary dysplasia, it may be critical to maintain normal developmental senescence (during the saccular phase) while reducing senescent cells resulting from injury (Fig. 2). Intermittent administration of a combination of dasatinib and quercetin in patients with idiopathic pulmonary fibrosis is generally well-tolerated.[66] Questions remain regarding safety profiling, tolerability, and side effects of senotherapies in premature infants with bronchopulmonary dysplasia and associated comorbidities.

Rodents exposed to hyperoxia in the first days of life are the most commonly used model to study human bronchopulmonary dysplasia.[79–81] However, this model cannot recapitulate all of the characteristics of bronchopulmonary dysplasia. Large animal models such as the preterm lamb can mimic the clinical setting of preterm birth and respiratory failure that requires prolonged ventilatory support for days or weeks with oxygen-rich gas.[82] Furthermore, as with humans at term gestation, the lungs of term sheep are at the beginning of the alveolar stage. Thus, further study using larger animals, such as preterm lambs, is warranted to investigate the role of senescence during lung development and injury.

A previous study of mouse forelimb formation showed that a subset of senescent cells lost their senescence hallmarks, re-entered the cell cycle and resumed proliferation.[83] According to the definition of senescence, it is unclear whether these cells are really senescent if they resume proliferation. Further studies using lineage tracing experiments would elucidate the fate of senescent cells during normal lung development and in the lung after neonatal hyperoxia.

Senescent cells are highly heterogeneous as to cell type and tissue distribution. Cutting-edge technologies, such as single-cell RNA sequencing and spatial transcriptomics, will help us understand the regional heterogeneity of senescent cells during lung development and injury.

Accumulating evidence suggests early origins of adult chronic lung diseases, such as chronic obstructive pulmonary disease and asthma.[84–87] Indeed, bronchopulmonary dysplasia increases the risk of developing chronic obstructive pulmonary disease, asthma, and pulmonary hypertension in later life.[88–92] Further studies are warranted to investigate whether neonatal lung senescence in bronchopulmonary dysplasia contributes to the development of these pulmonary diseases in adulthood.

Funding

This work was supported by an NIH R01 R01HL166327, an Institutional Development Award (IDeA) from the NIGMS of NIH under grant No. P20GM103652 , the Rhode Island Foundation grant No. 14699_20231340 (HY), and the Warren Alpert Foundation of Brown University (PAD).

References

1. Rhinn M, Ritschka B, Keyes WM. Cellular senescence in development, regeneration and disease. Development. 2019;146:dev151837. doi: 10.1242/dev.151837. [PubMed: 31575608]
2. Demaria M, Ohtani N, Youssef SA, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell. 2014;31:722–733. doi: 10.1016/j.devcel.2014.11.012. [PubMed: 25499914]
3. Berlanga-Acosta JA, Guillén-Nieto GE, Rodríguez-Rodríguez N, et al. Cellular senescence as the pathogenic hub of diabetes-related wound chronicity. Front Endocrinol. 2020;11:573032. doi: 10.3389/fendo.2020.573032.
4. Zhao Y, Tyshkovskiy A, Muñoz-Espín D, et al. Naked mole rats can undergo developmental, oncogene-induced and DNA damage-induced cellular senescence. Proc Natl Acad Sci U S A. 2018;115:1801–1806. doi: 10.1073/pnas.1721160115. [PubMed: 29432174]
5. Storer M, Mas A, Robert-Moreno A, et al. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell. 2013;155:1119–1130. doi: 10.1016/j.cell.2013.10.041. [PubMed: 24238961]
6. Muñoz-Espín D, Cañamero M, Maraver A, et al. Programmed cell senescence during mammalian embryonic development. Cell. 2013;155:1104–1118. doi: 10.1016/j.cell.2013.10.019. [PubMed: 24238962]
7. Yao H, Wallace J, Peterson AL, et al. Timing and cell specificity of senescence drives postnatal lung development and injury. Nat Commun. 2023;14:273. doi: 10.1038/s41467-023-35985-4. [PubMed: 36650158]
8. Jing X, Jia S, Teng M, et al. Cellular senescence contributes to the progression of hyperoxic bronchopulmonary dysplasia. Am J Respir Cell Mol Biol. 2023;70:94–109. doi: 10.1165/rcmb.2023-0038OC.
9. Zhao H, Darzynkiewicz Z. Biomarkers of cell senescence assessed by imaging cytometry. Methods Mol Biol. 2013;965:83–92. doi: 10.1007/978-1-62703-239-1_5. [PubMed: 23296652]
10. Amor C, Feucht J, Leibold J, et al. Senolytic CAR T cells reverse senescence-associated pathologies. Nature. 2020;583:127–132. doi:10.1038/s41586-020-2403-9. [PubMed: 32555459]
11. Kim KM, Noh JH, Bodogai M, et al. Identification of senescent cell surface targetable protein DPP4. Genes Dev. 2017;31:1529–1534. doi: 10.1101/gad.302570.117. [PubMed: 28877934]
12. Althubiti M, Lezina L, Carrera S, et al. Characterization of novel markers of senescence and their prognostic potential in cancer. Cell Death Dis. 2014;5:e1528. doi: 10.1038/cddis.2014.489.
13. Wiley CD, Velarde MC, Lecot P, et al. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. Cell Metab. 2016;23:303–314. doi: 10.1016/j.cmet.2015.11.011. [PubMed: 26686024]
14. Moiseeva O, Bourdeau V, Roux A, Deschênes-Simard X, Ferbeyre G. Mitochondrial dysfunction contributes to oncogene-induced senescence. Mol Cell Biol. 2009;29:4495–4507. doi: 10.1128/MCB.01868-08. [PubMed: 19528227]
15. Freund A, Laberge RM, Demaria M, Campisi J. Lamin B1 loss is a senescence-associated biomarker. Mol Biol Cell. 2012;23:2066–2075. doi: 10.1091/mbc.E11-10-0884. [PubMed: 22496421]
16. Shimi T, Butin-Israeli V, Adam SA, et al. The role of nuclear lamin B1 in cell proliferation and senescence. Genes Dev. 2011;25:2579–2593. doi: 10.1101/gad.179515.111. [PubMed: 22155925]
17. Hewitt G, Jurk D, Marques FD, et al. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. Nat Commun. 2012;3:708. doi: 10.1038/ncomms1708. [PubMed: 22426229]
18. Abdisalaam S, Bhattacharya S, Mukherjee S, et al. Dysfunctional telomeres trigger cellular senescence mediated by cyclic GMP-AMP synthase. J Biol Chem. 2020;295:11144–11160. doi: 10.1074/jbc.RA120.012962. [PubMed: 32540968]
19. Mir SM, Samavarchi Tehrani S, Goodarzi G, et al. Shelterin complex at telomeres: implications in ageing. Clin Interv Aging. 2020;15:827–839. doi: 10.2147/CIA.S256425. [PubMed: 32581523]

20. Prieur A, Besnard E, Babled A, Lemaitre JM. p53 and p16(INK4A) independent induction of senescence by chromatin-dependent alteration of S-phase progression. Nat Commun. 2011;2:473. doi: 10.1038/ncomms1473. [PubMed: 21915115]
21. Negretti NM, Plosa EJ, Benjamin JT, et al. A single-cell atlas of mouse lung development. Development. 2021;148:dev199512. doi: 10.1242/dev.199512. [PubMed: 34927678]
22. Davaapil H, Brockes JP, Yun MH. Conserved and novel functions of programmed cellular senescence during vertebrate development. Development. 2017;144:106–114. doi: 10.1242/dev.138222. [PubMed: 27888193]
23. Miao Q, Chen H, Luo Y, et al. Abrogation of mesenchyme-specific TGF-β signaling results in lung malformation with prenatal pulmonary cysts in mice. Am J Physiol Lung Cell Mol Physiol. 2021;320:L1158–L1168. doi: 10.1152/ajplung.00299.2020. [PubMed: 33881909]
24. Bush D, Abman SH, Galambos C. Prominent intrapulmonary bronchopulmonary anastomoses and abnormal lung development in infants and children with Down syndrome. J Pediatr. 2017;180:156–162. e1. doi: 10.1016/j.jpeds.2016.08.063. [PubMed: 27666181]
25. Galambos C, Minic AD, Bush D, et al. Increased lung expression of anti-angiogenic factors in Down syndrome: potential role in abnormal lung vascular growth and the risk for pulmonary hypertension. PLoS One. 2016;11:e0159005. doi: 10.1371/journal.pone.0159005. [PubMed: 27487163]
26. Patterson D, Cabelof DC. Down syndrome as a model of DNA polymerase beta haploinsufficiency and accelerated aging. Mech Ageing Dev. 2012;133:133–137. doi: 10.1016/j.mad.2011.10.001. [PubMed: 22019846]
27. Anderson G, Mackay N, Gilroy K, et al. RUNX-mediated growth arrest and senescence are attenuated by diverse mechanisms in cells expressing RUNX1 fusion oncoproteins. J Cell Biochem. 2018;119:2750–2762. doi: 10.1002/jcb.26443. [PubMed: 29052866]
28. Walton CC, Begelman D, Nguyen W, Andersen JK. Senescence as an amyloid cascade: the amyloid senescence hypothesis. Front Cell Neurosci. 2020;14:129. doi:10.3389/fncel.2020.00129. [PubMed: 32508595]
29. Bruintjes JJ, Henning RH, Douwenga W, van der Zee EA. Hippocampal cystathionine beta synthase in young and aged mice. Neurosci Lett. 2014;563:135–139. doi: 10.1016/j.neulet.2014.01.049. [PubMed: 24491430]
30. Ge F, Pan Q, Qin Y, et al. Single-cell analysis identify transcription factor BACH1 as a master regulator gene in vascular cells during aging. Front Cell Dev Biol. 2021;9:786496. doi: 10.3389/fcell.2021.786496. [PubMed: 35004685]
31. Litovchick L, Florens LA, Swanson SK, Washburn MP, DeCaprio JA. DYRK1A protein kinase promotes quiescence and senescence through DREAM complex assembly. Genes Dev. 2011;25:801–813. doi: 10.1101/gad.2034211. [PubMed: 21498570]
32. Meharena HS, Marco A, Dileep V, et al. Down-syndrome-induced senescence disrupts the nuclear architecture of neural progenitors. Cell Stem Cell. 2022;29:116–130. e7. doi: 10.1016/j.stem.2021.12.002. [PubMed: 34995493]
33. Danopoulos S, Bhattacharya S, Deutsch G, et al. Prenatal histological, cellular, and molecular anomalies in trisomy 21 lung. J Pathol. 2021;255:41–51. doi: 10.1002/path.5735. [PubMed: 34050678]
34. Chen Y, Xiao Y, Zhang Y, et al. Single-cell landscape analysis reveals systematic senescence in mammalian Down syndrome. Clin Transl Med. 2023;13:e1310. doi: 10.1002/ctm2.1310. [PubMed: 37461266]
35. Parikh P, Britt RD Jr, Manlove LJ, et al. Hyperoxia-induced cellular senescence in fetal airway smooth muscle cells. Am J Respir Cell Mol Biol. 2019;61:51–60. doi: 10.1165/rcmb.2018-0176OC. [PubMed: 30508396]
36. Scaffa AM, Peterson AL, Carr JF, Garcia D, Yao H, Dennery PA. Hyperoxia causes senescence and increases glycolysis in cultured lung epithelial cells. Physiol Rep. 2021;9:e14839. doi: 10.14814/phy2.14839. [PubMed: 34042288]
37. You K, Parikh P, Khandalavala K, et al. Moderate hyperoxia induces senescence in developing human lung fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2019;317:L525–L536. doi: 10.1152/ajplung.00067.2019. [PubMed: 31411059]

38. Klimova TA, Bell EL, Shroff EH, et al. Hyperoxia-induced premature senescence requires p53 and pRb, but not mitochondrial matrix ROS. FASEB J. 2009;23:783–794. doi: 10.1096/fj.08-114256. [PubMed: 18948382]
39. Maeda H, Yao H, Go H, Huntington KE, De Paepe ME, Dennery PA. Involvement of miRNA-34a regulated Krüppel-like factor 4 expression in hyperoxia-induced senescence in lung epithelial cells. Respir Res. 2022;23:340. doi: 10.1186/s12931-022-02263-8. [PubMed: 36496404]
40. Poblocka M, Bassey AL, Smith VM, et al. Targeted clearance of senescent cells using an antibody-drug conjugate against a specific membrane marker. Sci Rep. 2021;11:20358. doi: 10.1038/s41598-021-99852-2. [PubMed: 34645909]
41. Holt DJ, Grainger DW. Senescence and quiescence induced compromised function in cultured macrophages. Biomaterials. 2012;33:7497–7507. doi: 10.1016/j.biomaterials.2012.06.099. [PubMed: 22809642]
42. Rabhi N, Desevin K, Belkina AC, et al. Obesity-induced senescent macrophages activate a fibrotic transcriptional program in adipocyte progenitors. Life Sci Alliance. 2022;5:e202101286. doi: 10.26508/lsa.202101286. [PubMed: 35181634]
43. Rawji KS, Mishra MK, Michaels NJ, Rivest S, Stys PK, Yong VW. Immunosenescence of microglia and macrophages: impact on the ageing central nervous system. Brain. 2016;139:653–661. doi: 10.1093/brain/awv395. [PubMed: 26912633]
44. Hall BM, Balan V, Gleiberman AS, et al. p16(Ink4a) and senescence-associated β-galactosidase can be induced in macrophages as part of a reversible response to physiological stimuli. Aging. 2017;9:1867–1884. doi:10.18632/aging.101268. [PubMed: 28768895]
45. Kalymbetova TV, Selvakumar B, Rodríguez-Castillo JA, et al. Resident alveolar macrophages are master regulators of arrested alveolarization in experimental bronchopulmonary dysplasia. J Pathol. 2018;245:153–159. doi: 10.1002/path.5076. [PubMed: 29574785]
46. Yanagisawa S, Papaioannou AI, Papaporfyriou A, et al. Decreased serum sirtuin-1 in COPD. Chest. 2017;152:343–352. doi: 10.1016/j.chest.2017.05.004. [PubMed: 28506610]
47. Rajendrasozhan S, Yang SR, Kinnula VL, Rahman I. SIRT1, an antiinflammatory and antiaging protein, is decreased in lungs of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177:861–870. doi: 10.1164/rccm.200708-1269OC. [PubMed: 18174544]
48. Yao H, Chung S, Hwang JW, et al. SIRT1 protects against emphysema via FOXO3-mediated reduction of premature senescence in mice. J Clin Invest. 2012;122:2032–2045. doi: 10.1172/JCI60132. [PubMed: 22546858]
49. Mody K, Saslow JG, Kathiravan S, et al. Sirtuin1 in tracheal aspirate leukocytes: possible role in the development of bronchopulmonary dysplasia in premature infants. J Matern Fetal Neonatal Med. 2012;25:1483–1487. doi: 10.3109/14767058.2011.645925. [PubMed: 22272724]
50. Yang X, Dong WB, Lei XP, Li QP, Zhang LY, Zhang LP. Resveratrol suppresses hyperoxia-induced nucleocytoplasmic shuttling of SIRT1 and ROS production in PBMC from preterm infants in vitro. J Matern Fetal Neonatal Med. 2018;31:1142–1150. doi: 10.1080/14767058.2017.1311310. [PubMed: 28420272]
51. Bhattacharya S, Go D, Krenitsky DL, et al. Genome-wide transcriptional profiling reveals connective tissue mast cell accumulation in bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2012;186:349–358. doi: 10.1164/rccm.201203-0406OC. [PubMed: 22723293]
52. Zhang L, Soni S, Hekimoglu E, Berkelhamer S, Çataltepe S. Impaired autophagic activity contributes to the pathogenesis of bronchopulmonary dysplasia. Evidence from murine and baboon models. Am J Respir Cell Mol Biol. 2020;63:338–348. doi: 10.1165/rcmb.2019-0445OC. [PubMed: 32374619]
53. Syed M, Das P, Pawar A, et al. Hyperoxia causes miR-34a-mediated injury via angiopoietin-1 in neonatal lungs. Nat Commun. 2017;8:1173. doi: 10.1038/s41467-017-01349-y. [PubMed: 29079808]
54. Robbins PD, Jurk D, Khosla S, et al. Senolytic drugs: reducing senescent cell viability to extend health span. Annu Rev Pharmacol Toxicol. 2021;61:779–803. doi: 10.1146/annurev-pharmtox-050120-105018. [PubMed: 32997601]

55. Xu Q, Fu Q, Li Z, et al. The flavonoid procyanidin C1 has senotherapeutic activity and increases lifespan in mice. Nat Metab. 2021;3:1706–1726. doi: 10.1038/s42255-021-00491-8. [PubMed: 34873338]
56. Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. FEBS J. 2023;290:1362–1383. doi: 10.1111/febs.16350. [PubMed: 35015337]
57. Kirkland JL, Tchkonia T. Cellular senescence: a translational perspective. EBioMedicine. 2017;21:21–28. doi: 10.1016/j.ebiom.2017.04.013. [PubMed: 28416161]
58. Fuhrmann-Stroissnigg H, Niedernhofer LJ, Robbins PD. Hsp90 inhibitors as senolytic drugs to extend healthy aging. Cell Cycle. 2018;17:1048–1055. doi: 10.1080/15384101.2018.1475828. [PubMed: 29886783]
59. Hwang HV, Tran DT, Rebuffatti MN, Li CS, Knowlton AA. Investigation of quercetin and hyperoside as senolytics in adult human endothelial cells. PLoS One. 2018;13:e0190374. doi: 10.1371/journal.pone.0190374. [PubMed: 29315311]
60. Lehmann M, Korfei M, Mutze K, et al. Senolytic drugs target alveolar epithelial cell function and attenuate experimental lung fibrosis ex vivo. Eur Respir J. 2017;50:1602367. doi: 10.1183/13993003.02367-2016. [PubMed: 28775044]
61. Schafer MJ, White TA, Iijima K, et al. Cellular senescence mediates fibrotic pulmonary disease. Nat Commun. 2017;8:14532. doi:10.1038/ncomms14532. [PubMed: 28230051]
62. Wang Y, Chang J, Liu X, et al. Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. Aging (Albany NY). 2016;8:2915–2926. doi:10.18632/aging.101100. [PubMed: 27913811]
63. Zhu Y, Doornebal EJ, Pirtskhalava T, et al. New agents that target senescent cells: the flavone, fisetin, and the BCL-X_L inhibitors, A1331852 and A1155463. Aging (Albany NY). 2017;9:955–963. doi: 10.18632/aging.101202. [PubMed: 28273655]
64. Zhang L, Pitcher LE, Yousefzadeh MJ, Niedernhofer LJ, Robbins PD, Zhu Y. Cellular senescence: a key therapeutic target in aging and diseases. J Clin Invest. 2022;132:e158450. doi: 10.1172/JCI158450. [PubMed: 35912854]
65. Hickson LJ, Langhi Prata L, Bobart SA, et al. Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine. 2019;47:446–456. doi: 10.1016/j.ebiom.2019.08.069. [PubMed: 31542391]
66. Nambiar A, Kellogg D 3rd, Justice J, et al. Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. EBioMedicine. 2023;90:104481. doi:10.1016/j.ebiom.2023.104481. [PubMed: 36857968]
67. Cai Y, Zhou H, Zhu Y, et al. Elimination of senescent cells by β-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice. Cell Res. 2020;30:574–589. doi: 10.1038/s41422-020-0314-9. [PubMed: 32341413]
68. Baar MP, Brandt R, Putavet DA, et al. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell. 2017;169:132–147. e16. doi: 10.1016/j.cell.2017.02.031. [PubMed: 28340339]
69. He Y, Zhang X, Chang J, et al. Using proteolysis-targeting chimera technology to reduce navitoclax platelet toxicity and improve its senolytic activity. Nat Commun. 2020;11:1996. doi: 10.1038/s41467-020-15838-0. [PubMed: 32332723]
70. Muñoz-Espín D, Rovira M, Galiana I, et al. A versatile drug delivery system targeting senescent cells. EMBO Mol Med. 2018;10:e9355. doi: 10.15252/emmm.201809355. [PubMed: 30012580]
71. Kirkland JL, Tchkonia T, Zhu Y, Niedernhofer LJ, Robbins PD. The clinical potential of senolytic drugs. J Am Geriatr Soc. 2017;65:2297–2301. doi: 10.1111/jgs.14969. [PubMed: 28869295]
72. Justice JN, Nambiar AM, Tchkonia T, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine. 2019;40:554–563. doi: 10.1016/j.ebiom.2018.12.052. [PubMed: 30616998]
73. Xu M, Pirtskhalava T, Farr JN, et al. Senolytics improve physical function and increase lifespan in old age. Nat Med. 2018;24:1246–1256. doi: 10.1038/s41591-018-0092-9. [PubMed: 29988130]

74. Hoare M, Ito Y, Kang TW, et al. NOTCH1 mediates a switch between two distinct secretomes during senescence. Nat Cell Biol. 2016;18:979–992. doi: 10.1038/ncb3397. [PubMed: 27525720]
75. ter Horst SA, Walther FJ, Poorthuis BJ, Hiemstra PS, Wagenaar GT. Inhaled nitric oxide attenuates pulmonary inflammation and fibrin deposition and prolongs survival in neonatal hyperoxic lung injury. Am J Physiol Lung Cell Mol Physiol. 2007;293:L35–L44. doi: 10.1152/ajplung.00381.2006. [PubMed: 17384081]
76. van Zoelen MA, Florquin S, de Beer R, et al. Urokinase plasminogen activator receptordeficient mice demonstrate reduced hyperoxia-induced lung injury. Am J Pathol. 2009;174:2182–2189. doi: 10.2353/ajpath.2009.080914. [PubMed: 19435793]
77. Tunc T, Cekmez F, Yildirim S, et al. Predictive value of soluble urokinase plasminogen activator receptor, soluble ST2, and IL-33 in bronchopulmonary dysplasia. Pediatr Res. 2014;75:788–792. doi: 10.1038/pr.2014.28. [PubMed: 24603291]
78. Rivera L, Siddaiah R, Oji-Mmuo C, Silveyra GR, Silveyra P. Biomarkers for bronchopulmonary dysplasia in the preterm infant. Front Pediatr. 2016;4:33. doi: 10.3389/fped.2016.00033. [PubMed: 27065351]
79. Silva DM, Nardiello C, Pozarska A, Morty RE. Recent advances in the mechanisms of lung alveolarization and the pathogenesis of bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2015;309:L1239–L1272. doi: 10.1152/ajplung.00268.2015. [PubMed: 26361876]
80. Warner BB, Stuart LA, Papes RA, Wispé JR. Functional and pathological effects of prolonged hyperoxia in neonatal mice. Am J Physiol. 1998;275:L110–L117. doi: 10.1152/ajplung.1998.275.1.L110. [PubMed: 9688942]
81. Yee M, Vitiello PF, Roper JM, et al. Type II epithelial cells are critical target for hyperoxia-mediated impairment of postnatal lung development. Am J Physiol Lung Cell Mol Physiol. 2006;291:L1101–L1111. doi: 10.1152/ajplung.00126.2006. [PubMed: 16861382]
82. Albertine KH. Utility of large-animal models of BPD: chronically ventilated preterm lambs. Am J Physiol Lung Cell Mol Physiol. 2015;308:L983–L1001. doi: 10.1152/ajplung.00178.2014. [PubMed: 25770179]
83. Li Y, Zhao H, Huang X, et al. Author Correction: Embryonic senescent cells re-enter cell cycle and contribute to tissues after birth. Cell Res. 2018;28:871. doi: 10.1038/s41422-018-0063-1. [PubMed: 29959400]
84. Carraro S, Scheltema N, Bont L, Baraldi E. Early-life origins of chronic respiratory diseases: understanding and promoting healthy ageing. Eur Respir J. 2014;44:1682–1696. doi: 10.1183/09031936.00084114. [PubMed: 25323240]
85. Ubags N, Alejandre Alcazar MA, Kallapur SG, et al. Early origins of lung disease: towards an interdisciplinary approach. Eur Respir Rev. 2020;29:200191. doi: 10.1183/16000617.0191-2020. [PubMed: 33004528]
86. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med. 2016;375:871–878. doi: 10.1056/NEJMra1603287. [PubMed: 27579637]
87. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. Proc Am Thorac Soc. 2009;6:272–277. doi: 10.1513/pats.200808-092RM. [PubMed: 19387029]
88. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015;385:899–909. doi: 10.1016/S0140-6736(14)60446-3. [PubMed: 25123778]
89. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med. 2016;374:1842–1852. doi: 10.1056/NEJMoa1513737. [PubMed: 27168434]
90. Goss KN, Beshish AG, Barton GP, et al. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med. 2018;198:1549–1558. doi: 10.1164/rccm.201710-2016OC. [PubMed: 29944842]
91. Cassady SJ, Lasso-Pirot A, Deepak J. Phenotypes of bronchopulmonary dysplasia in adults. Chest. 2020;158:2074–2081. doi: 10.1016/j.chest.2020.05.553. [PubMed: 32473946]
92. Laurie SS, Elliott JE, Beasley KM, et al. Exaggerated increase in pulmonary artery pressure during exercise in adults born preterm. Am J Respir Crit Care Med. 2018;197:821–823. doi: 10.1164/rccm.201704-0740LE. [PubMed: 28885857]

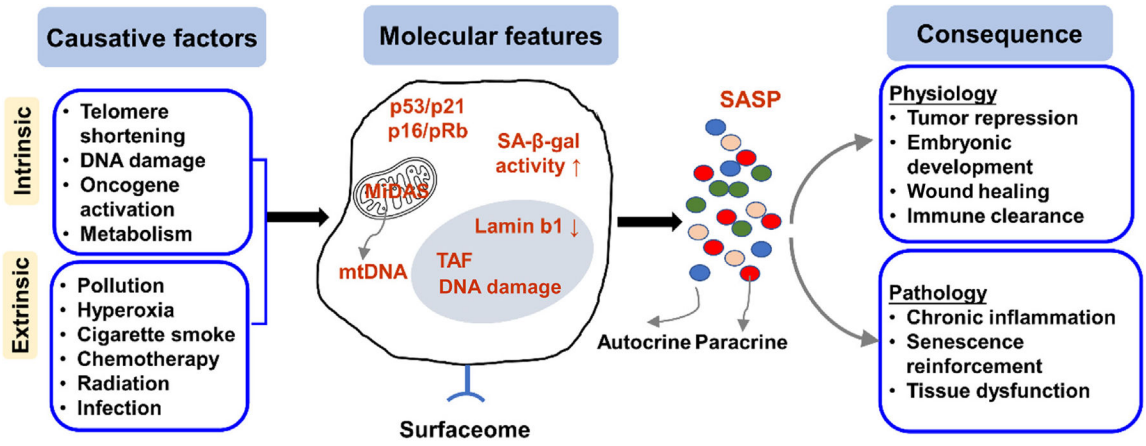

Fig. 1.

Molecular features of senescent cells and their roles in contributing to both physiological function and pathological changes. Adapted from Zhang et al.[64] Cellular senescence can be induced by intrinsic and extrinsic factors, and is characterized by numerous molecular features. Senescent cells generate SAPS factors which play pivotal roles in physiological function, pathological alteration, and tissue dysfunction. MiDAS: mitochondrial dysfunction-associated senescence; mtDNA: mitochondrial DNA; SA-β-gal: senescence-associated beta-galactosidase; SASP: senescence-associated secretory phenotype; TAF: telomere-associated DNA damage foci.

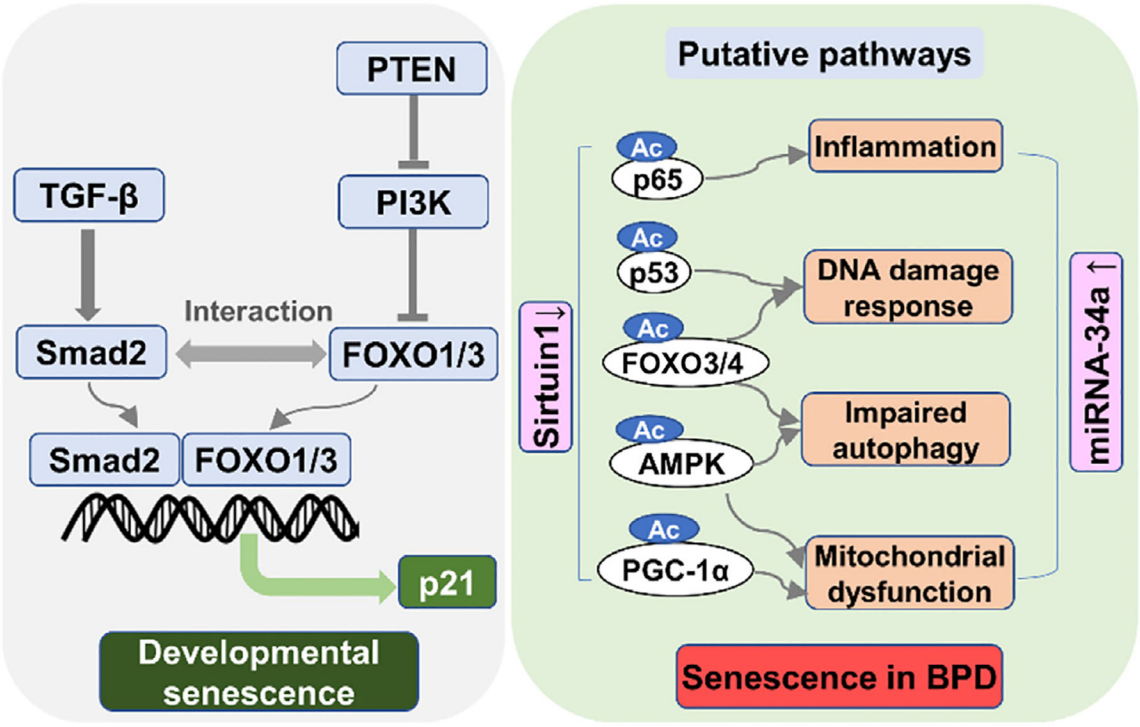

Fig. 2.

Putative signal pathways of senescence in normal lung development and bronchopulmonary dysplasia. Although there is no report regarding signal path-ways of developmental senescence in the lung, TGF-β/Smad and PI3K/FOXO1/3 signal pathways participate in senescence during the development of other organs (left panel). There are no reports studying signal pathways involved senescence in BPD. However, certain signal pathways regulated by Sirtuin1 and miRNA-34a are altered in the lung of premature infants with BPD and of neonatal hyperoxia-induced animal models (right panel). These pathways have been shown to cause senescence by upregulating inflammatory response, DNA damage response, impaired autophagy and mitochondrial dysfunction. AMPK: adenosine monophosphate-activated protein kinase; BPD: bronchopulmonary dysplasia; FOXO: forkhead box O; miRNA-34a: microRNA 34a; PGC-1 α: peroxisome proliferator-activated receptor-γ coactivator-1 α; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; TGF-β: transforming growth factor-β.

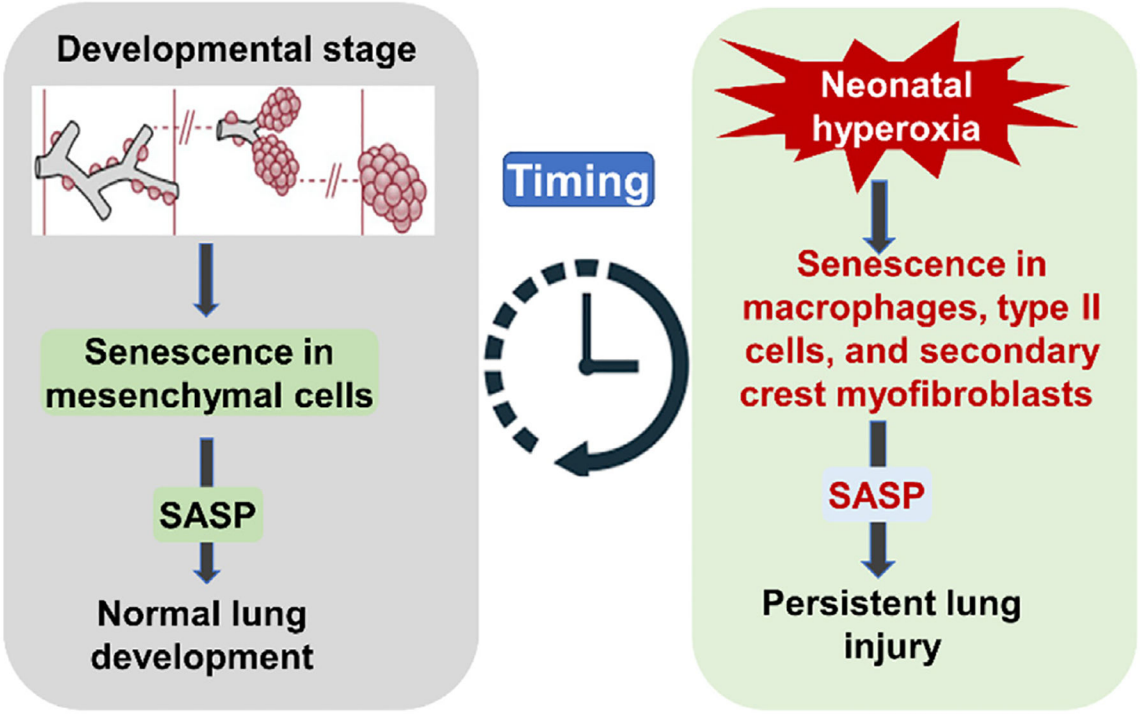

Fig. 3.

Impact of timing on senescence in lung development and neonatal lung injury. Senescence is observed in mesenchymal cells and peaks at the saccular stage, which contributes to normal lung development. Neonatal hyperoxia causes transient senescence in macrophages, type II alveolar cells and secondary crest myofibroblasts at the alveolar stage, which leads to alveolar and vascular injury. It is critical to develop novel therapies that clear senescent cells during an optimal therapeutic window to prevent bronchopulmonary dysplasia and its long-term consequences while preserving normal lung development.

Table 1

Strategies to target senescent cells.

Senotherapeutics	Examples	Targets
Senolytics	A cocktail of quercetin and dasatinib, ABT-263, fisetin	Cause apoptosis of senescent cells by decreasing anti-apoptotic proteins
Pro-drugs	SSK1, JHB75B, Nav-Gal	Direct gemcitabine to senescent cells and kill them
Senomorphics	NBD peptide, JAK inhibitor (ruxolitinib), KU-60019	Inhibit SASP factor gene transcription by targeting ATM, p38 MAPK, JAK/STAT, NF-κB and mTOR pathways
Immunotherapies	CAR T cells, antibody-drug conjugates	Target senescent cells based on expression of senescent surfaceome

ATM: ataxia telangiectasia mutated; CAR: chimeric antigen receptor; JAK: Janus kinase; JHB75B: a galactose-modified duocarmycin variations (prodrug A); MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; Nav-Gal: galacto-conjugation of navitoclax; NBD peptide: NF-κB essential modulator (NEMO) binding domain (NBD) peptide; NF-κB: nuclear factor-κB; SASP: senescence-associated secretory phenotype; SSK1: Senescence-specific killing compound 1; STAT: signal transducer and activator of transcription.