EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Perspective

Cellular Senescence: Friend or Foe to Respiratory Viral Infections?

William J. Kelley, Rachel L. Zemans, Daniel R. Goldstein

Please cite this article as: Kelley WJ, Zemans RL, Goldstein DR. Cellular Senescence: Friend or Foe to Respiratory Viral Infections?. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02708-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Cellular Senescence: Friend or Foe to Respiratory Viral Infections?

William J. Kelley[1,2,3], Rachel L. Zemans[1,2] and Daniel R. Goldstein [1,2,3]

1:Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

2:Program in Immunology, University of Michigan, Ann Arbor, MI, USA

3:Department of Microbiology and Immunology, University of Michigan, Ann Arbor, MI USA

Email of corresponding author: drgoldst@umich.edu

Address of corresponding author:

NCRC B020-209W

2800 Plymouth Road

Ann Arbor, MI 48104, USA

Word count: 2750

Take Home

Senescence associates with fibrotic lung diseases. Emerging therapies to reduce senescence may treat chronic lung diseases, but the impact of senescence during acute respiratory viral infections is unclear and requires future investigation.

Abstract

Cellular senescence permanently arrests the replication of various cell types and contributes to age-associated diseases. In particular, cellular senescence may enhance chronic lung diseases including chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. However, the role cellular senescence plays in the pathophysiology of acute inflammatory diseases, especially viral infections, is less well-understood. There is evidence that cellular senescence prevents viral replication by increasing antiviral cytokines, but other evidence shows that senescence may enhance viral replication by downregulating antiviral signaling. Furthermore, cellular senescence leads to the secretion of inflammatory mediators, which may either promote host defense or exacerbate immune pathology during viral infections. In this perspective, we summarize how senescence contributes to physiology and disease, the role of senescence in chronic lung diseases, and how senescence impacts acute respiratory viral infections. Finally, we develop a potential framework of how senescence may contribute, both positively and negatively, to the pathophysiology of viral respiratory infections, including SARS-CoV-2.

Cellular Senescence: Definition and Evolutionary Origins

Cellular senescence describes a state of permanent replicative arrest in normally-proliferative cells. Originally discovered *in vitro* in human fibroblasts by Hayflick and colleagues, the concept of cellular senescence was met with controversy [1, 2]. Initially, some investigators were skeptical and

believed that senescence was an *in vitro* artefact. But with accumulating *in vivo* evidence including the presence of senescence in aged human skin cells [3], scientists accepted senescence as a true biological phenomenon. Senescence is now known to contribute to a variety of age-related diseases including: type 2 diabetes, obesity, atherosclerosis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and others [4–6]. With aging, our cells continually divide, shorten their telomeres, accumulate mutations and DNA damage, all of which ultimately increase the likelihood of oncogenesis [7, 8].

Under typical physiological conditions, oncogene-induced senescence may hinder the development of certain cancers including lymphoma [9] and prostate cancer [10] and improve patient response to chemotherapeutics [11]. Senescent cells may also upregulate phagocytic receptors, therefore increasing phagocytosis and immune surveillance to reduce cancer development. Additionally, senescent cells secrete extra-cellular matrix proteins and growth factors that contribute to some restorative processes including wound healing [12]. Similarly, senescent cells have been shown to reduce liver [13, 14] and pancreatic fibrosis and promote wound healing [15]. Furthermore, fibroblasts made senescent by the matricellular protein CCN1 limit fibrosis in cutaneous wounds [16]. Senescent cells may also contribute to tissue growth during embryonic development [17, 18]. In summary, senescence likely evolved to respond to the acute stress of organ development, mitigate against the acute effects of damaged cells to return tissue to homeostasis, and ultimately to reduce the development of cancer [19].

With improvements in public health in the 20th century and subsequent extensions of human life-span, senescence has emerged as a contributing factor to several *chronic* age-associated diseases. Indeed, we now recognize senescence as one of the key hallmarks of aging, as senescence occurs as we age naturally [20]. Although a key hallmark of aging, senescence is not sufficient for all aging phenotypes [20], and senescence can occur in young hosts as a result of acute stressors (see next section). However,

the importance of senescence in *acute* inflammatory conditions, especially respiratory viral infections, is less well appreciated. Here, we first briefly review how senescence contributes to chronic inflammation, particular in the context of lung diseases, and emerging therapies to treat senescence. Then, we discuss the role senescence plays in acute respiratory viral infections and implications for such a role during infection with SARS-CoV-2.

What leads to senescence and the resulting Senescence Associated Secretory Phenotype (SASP)

Senescence can arise from both repeated cellular division and cellular stressors. Replicative senescence arises from repeated cellular divisions, such as occur naturally when we age. Stress-induced senescence arises from cellular stressors such as increases in reactive oxygen species, which correlate with DNA damage [21, 22]. These can occur from irradiation, chemotherapeutic agents, chronic exposure to pollutants (cigarette smoke), exposure to pathogens, and some forms of accelerated aging syndromes, such as progeria [23–26]. Therefore, cells from both young and aged hosts can exhibit senescence. As previously mentioned, senescence is one of the key biological hallmarks of aging and contributes to aging via inflammation, tissue exhaustion and impaired stem cell renewal [20].

Importantly, stem cells can become senescent as we age. Specifically, mesenchymal stem cells isolated from older humans (>70 years of age) exhibit senescence including reduced proliferation and a chronic inflammatory secretome, which impairs hematopoietic stem and progenitor cell (HSPC) replication and increases HSPC MCP1 and IL-8 expression [27]. Consequently, senescent mesenchymal stem cells are not able to be used in stem cell therapeutics due to their inability to proliferate and their reduced expression of pro-angiogenic factors [28]. Additionally, senescent neural progenitor cells contribute to the development of multiple sclerosis [29]. Specifically, senescent neural progenitor cells inhibit oligodendrocyte differentiation and contribute to demyelination via the production of high mobility group box-1, which suppresses oligodendrocyte progenitor cell proliferation and induces pro-

inflammatory transcriptomic changes in oligodendrocyte progenitor cells [29]. Thus, senescent stem cells impair wound healing, promote the development of inflammatory diseases, and limit the use of stem cells in therapeutic applications.

In addition to the direct effects on stem cells, there are two potential pathways by which senescence may contribute to disease. First, senescent cells stop proliferating, which prevents tissue repair after injury. Second, as senescent cells accumulate, they produce, for unclear reasons, low levels of inflammatory mediators, a phenomenon which has been termed "inflammaging" particularly when evident in older people [30–33]. Senescent cells contribute to chronic inflammation via the senescence-associated secretory phenotype (SASP), the collective term for the proinflammatory chemokines and cytokines released by senescent cells [34]. The SASP is comprised of a number of proinflammatory molecules, including TNF-α, IL-1 α /β, IL-6, IL-8, CCL-2, and others [35–38]. The SASP seems to be a double-edged sword. On the one hand, long-term exposure of SASP inflammatory mediators can lead to over-recruitment of damaging immune cells, resulting in chronic inflammatory diseases and even fibrosis [5, 39]. On the other hand, in the short term, the SASP promotes wound healing that is required to respond to acute cellular damage [12, 13, 40].

Importantly, the specific characteristics of the SASP may be dependent on the cell type and the mechanism of senescence induction [41]. For example, the SASP associated with fibroblasts contains significantly more SASP factors than the SASP associated with renal epithelial cells [41]. Some SASP pathways are shared between fibroblasts and epithelial cells, while some pathways are distinct to each cell type. Specifically, senescent epithelial cells upregulate pathways associated with protein translation and degradation; senescent fibroblasts upregulate pathways associated with apoptosis, ROS generation, and extracellular matrix reorganization; and both senescent fibroblasts and epithelial cells upregulated pathways associated with vesicle transport, metabolism, and detoxification [41]. Note that in this

particular study, senescence was induced *in vitro* in human cell lines. However, the investigators identified several secreted proteins in their *in vitro* models which were also found in the plasma of older subjects, suggesting that the findings of the study could be translatable *in vivo*. *In vitro* senescence is associated with the accumulation of sterile inflammatory mediators, like HMBG1, a nuclear protein that can activate inflammation [41]. Furthermore, SASP mediators such as TNF-α can induce senescence, which likely further enhances the SASP in a feed-forward loop [42]. Thus, one of the mechanisms by which senescence leads to chronic inflammation may be by the release of sterile inflammatory mediators, also known as damage associated molecular patterns. Additionally, the SASP is temporally dynamic and the dynamics change depending on the cell type [43]. Overall, senescence induces distinct cellular programs that lead to the secretion of proteins that promote chronic inflammation. Clearly, dissecting the physiological from the pathophysiological aspects of senescence will be required for the development of effective therapies targeting senescence to alleviate age-related diseases.

Senescence-Targeted Therapeutics

Recently, there has been a focus on alleviating the negative effects of cellular senescence using senescence-targeted therapeutics. Such therapeutics fall into two primary categories: SASP inhibition and senescent cell removal. SASP inhibition involves downregulating various components of the SASP, or inhibiting the inflammatory pathways that SASP factors engages, with the goal of ameliorating the deleterious effects of SASP factors. This strategy is successful in a variety of contexts. For example, Janus kinase (JAK) inhibition alleviates inflammation, both locally in the adipose tissue and systemically, and reduces frailty in aged mice [44]. Evidence that the SASP may be related to the pathogenesis of age-related diseases comes from reports that pharmacological tools to inhibit NF-κB signaling ameliorate age-related diseases. Inhibition of the mammalian target of rapamycin (mTOR) by rapamycin selectively reduces NF-κB signaling (a major inflammation signaling hub) in senescent cells through suppression of

IL-1α activity, reduces age-associated cognitive decline, improves immune function in older people, and increases the lifespan of mice [45–49]. Metformin, a commonly-used type-2 diabetes drug, also inhibits NF-κB, resulting in improved lifespan in mice, and reduced all-cause mortality and age-related disease in humans [50–53]. However, inhibiting the SASP results in off-target side effects including neutrophilia, nephrotoxicity, and changes in T cell phenotype due to the myriad of interconnected pathways involved in inflammatory signaling [45.] Specifically, inhibition of the NF-κB pathway, either by genetic deletion or small-molecule inhibition, has been shown to inhibit T cell, B cell, and lymphoid progenitor cell development [55]; induce apoptosis of thymocytes, B cells, and macrophages [56, 57]; impair lymphocyte growth and cytokine production [58]; and potentially increase susceptibility to various infections [59]. All of these strategies target inflammatory pathways that senescence may activate but do not specifically target senescent cells.

Removing senescent cells involves directly targeting senescent cells by inducing apoptosis. The first therapeutics designed to directly kill senescent cells (termed 'senolytics') targeted the BCL-2 protein family, an anti-apoptotic pathway that is involved in oncogenesis. The most widely-studied therapeutic strategy, however, is a combination therapy involving the administration of the tyrosine kinase inhibitor dasatinib (D) and the flavonoid quercetin (Q). The "D+Q" combination reduces senescent cell burden and improves health span and lifespan in aged mice, reduces vascular stiffening, improves vasomotor function, and improves pulmonary function in murine models of pulmonary fibrosis [60–64]. Indeed, preliminary clinical trials have shown evidence that D+Q treatment reduces senescent cell burden and may improve physical function in patients with pulmonary fibrosis [65, 66]. However, we still do not fully appreciate the potential off-target effects of senolytic agents such as D+Q, as well as their mechanism of action in humans, which will require elucidation before they can be used to treat age-related diseases.

Cellular Senescence in the Lung

In addition to replicative senescence induced by aging, several other factors contribute to the development of stress-induced senescence in the lung, including radiation therapy, smoking, mechanical ventilation, and chronic use of supplemental oxygen (Figure 1). [24, 67–70], which supports the concept that other processes besides natural aging lead to senescence. Increasing numbers of senescent cells correlate with increasing concentrations of SASP factors. This is supported by the finding that the cytokines IL-6 and IL-10 and neutrophil counts are elevated in the bronchoalveolar lavage fluid (BALF) of older (note: "older" is designated > 65 years of age in this review) donors, which may exhibit senescence in the lung [71]. This age-related phenotype correlates with age-related lung diseases such as COPD. Furthermore, patients with COPD exhibit increased concentrations of senescent type II alveolar epithelial cells (AECs) [72, 73] and lung fibroblasts [74], as well as elevated levels of inflammatory cytokines including IL-1β, IL-6, IL-8, IL-10, and CCL-2 [75–78]. While a causal link is difficult to prove, the low-grade inflammation caused by lung senescent cells may contribute to the development of and/or exacerbates COPD. Similar patterns of elevated inflammatory cytokine levels and senescent cells are linked to other chronic lung diseases such as asthma [79, 80]. Furthermore, the exuberant wound healing response mediated by SASP factors, combined with the inability to effectively repair tissue due to cessation of proliferation, and possibly impairments in stem cell functions, may promote fibrosis and contribute to idiopathic pulmonary fibrosis [81–84]. Thus, lung senescent cells likely contribute to the severity of many chronic lung diseases.

The potential contributions of lung cellular senescence in acute respiratory conditions remain unclear. In a murine model of acute lung injury (ALI), senescent alveolar macrophages exhibit enhanced activation and secretion of proinflammatory cytokines, resulting in enhanced disease severity [85]. Similarly, aged mice, which likely exhibit increased lung senescence, also exhibit enhanced lung permeability and increased levels of reactive oxygen species in response to an LPS challenge, which is linked to deficient Nox4 (a ROS-generating mitochondrial protein) ubiquination [86]. Additionally, older

trauma patients are significantly more likely to develop acute respiratory distress syndrome (ARDS), and older patients with ARDS exhibit a higher mortality rate [87]. However, in all of these studies the pathological role of senescence was not tested. Also, a recent study found that lung cellular senescence *protects* against lung injury induced by mechanical ventilation by preventing apoptosis [68]. Clearly, the impact of cellular senescence on acute lung conditions requires future investigation.

Cellular Senescence and Respiratory Viral Infections

The COVID-19 pandemic continues to claim thousands of lives every day and disproportionately affects older people. Given this, how cellular senescence impacts the host response to acute respiratory viral infections is particularly relevant. Older people experience increased susceptibility to respiratory viruses such as influenza, respiratory syncytial virus (RSV), SARS, and now SARS-CoV-2 [88–92]. With COVID-19, the disease that results from SARS-CoV-2 infection, older people are ~20 fold more likely to die than younger people [93]. This effect has been partially attributed to defects associated with the aging of the immune system, termed "immunosenescence", which is distinct from classical cellular senescence as defined above and reviewed elsewhere [94–96]. Briefly, immunosenescence has pleiotropic effects on the immune system including: i) a decrease in the proliferative capacity of hematopoietic stem cells; ii) dysregulation of innate immunity; iii) reduced numbers of naïve T cells with thymic involution; iv) accumulation of memory T and B cells; and v) a general decline in both T and B cell function [94, 97–99]. Specifically, both $CD4^+$ and $CD8^+$ T cells from aged hosts (e.g., rodents and humans) exhibit a reduced proliferative capacity associated with downregulation of surface costimulatory receptors, CD27 and CD28, which is accompanied by shortened telomeres. Collectively, these alterations within the immune system with aging result in an impaired ability to fight viral infections and lead to reduced vaccine efficiency [90]. In addition to natural aging, chronic viral infections (e.g., HIV and cytomegalovirus infection) also induce a phenotype of reduced T cell function

(i.e., reduced proliferation and cytokine secretion) that shares features with immunosenescence [100, 101]. Although aging of the immune system impairs host defense to acute respiratory viral infections [90], the role that cellular senescence of lung cells play in the pathophysiology of acute respiratory viral infections is not well-understood. Clearly, older people are highly susceptible to viral infections due to a myriad of effects exerted by aging on the immune system. But how much of this is contributed by cellular senescence, as defined above, remains to be elucidated. Indeed, it is not clear if cellular senescence, due to natural aging or due to an age-independent stressor, promotes or prevents acute respiratory viral infections. To the best of our knowledge, there are only a few studies on the role of cellular senescence and acute respiratory viral infections, with some showing contrasting results.

There are studies which claim that cellular senescence enhances anti-viral immunity [102], which is biologically plausible, as SASP factors, which includes chemokines (e.g., CxCL1/2) that recruit innate immune cells like neutrophils may augment host defense to viral infections [103]. Specifically, one study showed that cellular senescence inhibits vesicular stomatis virus (a RNA virus) replication in both primary murine fibroblasts with replication-induced senescence, and in a tumor cell line with chemotherapy-induced senescence [102], possibly due to SASP factors, including the release of type I interferons (IFN), important anti-viral cytokines [104]. Additionally, mice that were induced to exhibit senescence within the lung via bleomycin exposure were more resistant to vesicular stomatis virus infection *in vivo* than mice that were not exposed to bleomycin. This is compatible with *in vitro* studies that found that type I IFN, in addition to other SASP components such as IL-6 and IL-8 , induces cellular senescence [105, 106], and vice versa. Additionally, cellular fusion caused by the fusogenic measles virus induces cellular senescence, including the release of SASP factors, in fibroblasts *in vitro* [107], although the *in vivo* implications of this finding are unclear. Collectively, these studies suggest that senescence that is induced acutely by viruses may be a part of the body's antiviral immune response [108, 109]. This defense mechanism may have evolved to allow virus-infected cells to secrete SASP factors to limit viral

replication in neighboring cells and ultimately viral spread throughout the lung. Furthermore, the SASP factors, may enhance host defense by promoting immune cell recruitment to the lung. But if these SASP factors are produced exuberantly, immune pathology could ensue (Figure 2). Finally, some viruses, including human papillomavirus and hepatitis B, have evolved machinery specifically to overcome cellular senescence [110, 111], suggesting that senescence plays a role in antiviral defense in some contexts.

However, there is evidence that senescence contributes to the pathophysiology of respiratory viral infections. RSV induces DNA damage resulting in senescence in both mononuclear cells and lung epithelia in young mice [25], which enhances airway tissue remodeling (exhibited by a loss of ciliated cells and an increase in secretory cells[112]), potentially leading to permanent tissue damage and fibrosis. Furthermore, senescent cells may *promote* viral replication. For example, the influenza virus replicates more efficiently within senescent human bronchial epithelial cells than non-senescent cells [113]. Similar results are found with varicella zoster virus, a herpes virus, which replicates more efficiently in senescent human dermal fibroblasts than non-senescent cells [113]. A potential explanation for this phenomenon may be that senescence induced by these viruses *downregulates* the antiviral type I IFN program, including key signaling proteins , e.g., STING and IRF-3, upon infection *in vitro* with varicella virus [113]. This downregulation could lead to reduced secretion of antiviral IFNs, promoting viral replication. Whether this occurs *in vivo* is not known, however. Differences between this study and the contrasting one above, which found that senescence *reduces* replication of vesicular stomatis virus [102], could be due to the different viruses employed (i.e., vesicular stomatitis vs. influenza, varicella), different cell types (MCF7, A549 cell lines and primary murine embryo fibroblast cells in the vesicular stomatitis study vs. primary human bronchial epithelial cells and primary human dermal fibroblasts in the influenza/varicella study), and different approaches to induce senescence (replicative senescence and bleomycin in the vesicular stomatitis study vs. only replicative senescence in

the influenza/varicella study). Clearly, future studies are required to determine if senescence is harmful or beneficial to pathologically relevant respiratory viruses.

Cellular Senescence: Friend or Foe in Respiratory Viral Infections?

The overall impact of cellular senescence on acute respiratory viruses may depend on host resilience factors (Figure 2). For example, the SASP may have evolved to enhance host defense by increasing the recruitment of immune cells. This is likely beneficial in resilient young hosts who do not overproduce SASP factors. Indeed, initial neutrophil recruitment to the lung is critical to host defense to influenza infection [103]. But in vulnerable aged hosts, the SASP factors may be produced at pathologically high levels to promote immune pathology. Specifically, CXCL-1, CXCL-2, and IL-17, are increased in the lungs of aged mice even before viral infection, and accompany excessive neutrophil recruitment into the lung to enhance mortality during acute influenza infection [103]. In this study, senescent alveolar epithelial cells were found to produce more neutrophil chemoattractants and thus increase neutrophil chemotaxis. Similarly, aged rhesus macaques express higher levels of CCL-2, IL-6, and IL-8 in the lungs in response to influenza infection, suggesting an exaggerated innate immune response [114]. Based on these studies, inhibiting the SASP or reducing lung senescent cells might be beneficial in aged hosts infected with acute respiratory viral infections. However, formal investigation is required to determine if removing senescent cells prior to infection is sufficient, or if treatment during infection is required. Importantly, vulnerable hosts, including older people and people with comorbidities such as diabetes, are more susceptible to SARS-COV-2, which emerging studies suggest is due to the cytokine storm and excessive neutrophil effector functions within the lung [90].

We still do not know whether senescent cells in the lung ultimately increase or reduce viral replication. Respiratory viruses may “hijack” the senescent machinery within the infected cell to downregulate the IFN pathway to promote viral packaging and ultimately enhance viral replication

within the cell. It is not clear yet if this occurs *in vivo* and, if so, what underlying mechanisms are involved. In contrast, activation of the senescence machinery within a virally-infected cell may be a damage response mechanism that leads to the secretion of antiviral cytokines to limit viral replication, an issue that also requires future investigation. Alternatively, senescence may simply be a side-effect of viral infection; during and after infection, various inflammatory cytokines are upregulated, resulting in the induction of senescence in infected cells.

Conclusions

Ultimately, the impact of senescence on respiratory viral infections requires further investigation before firm conclusions can be drawn. The impact of senescence on both viral replication and mortality in respiratory viral infections such as influenza, RSV, SARS, and SARS-CoV-2 should be comprehensively studied to determine if senescence-targeted therapies, such as senolytics, might be effective, or not, at reducing the age-dependent mortality of acute respiratory viral infections. Furthermore, it remains unclear as to whether senescence associated with natural aging results in the same impact on respiratory viral infections as stress-induced senescence; thus, a direct comparison between such models of senescence is warranted. For example, do mice with bleomycin-induced lung senescence exhibit a similar phenotype and mortality response as aged mice when infected with influenza, RSV, or other respiratory viral infections?

Additionally, the effectiveness (or lack thereof) of senescence-targeted therapies broadly, and senolytics, specifically, has yet to be assessed during respiratory viral infections. While senolytics have shown some therapeutic efficacy in preclinical models of chronic illnesses such as pulmonary fibrosis, it is unknown if these effects translate to more acute conditions, and if so, how the therapeutic regimen might be optimized. For example, it may be that prophylactic senolytic treatment is effective at reducing the total senescent cell concentration in the lungs, thereby improving disease outcomes, while post-

infection treatment may not be as effective, especially if removing senescent cells impairs wound healing and reduces inflammation resolution. Examining these outstanding questions will shed light on how senescence impacts our host defense to respiratory viruses, which will continue to disproportionately impact older people for the foreseeable future, particularly during the current COVID-19 pandemic. Thus, moving forward, significant research efforts focused on the interactions between cellular senescence and respiratory viral infections are clearly warranted.

Author contributions

All authors were involved in the design of the review. WJK wrote the first draft, which was then edited by DRG and RLZ. All authors approved the final manuscript.

Conflict of Interest

The authors report no conflicts.

Support Statement

WJK is supported by the National Institutes of Health Training Grant T32HL007622.

DRG is supported by NIH awards: R01AG028082, R01HL127687, R01AI13834, K07AG050096 and T32AG062403. RLZ is supported by NIH awards: R01HL147920, R01HL131608, R01AG028082.

Figure Legends

Figure 1—Causes of lung senescence. Many factors contribute to the induction of senescence within lung cells. Apart from natural aging, other sources of senescence include chronic exposure to pollutants and cigarette smoke, chemotherapy, ionizing radiation, respiratory viral infections, and the use of mechanical ventilators. Each of these sources may induce senescence to varying degrees, and it remains unclear whether senescence originating from different sources and in different cells contributes to pathology similarly or differently.

Figure 2—Hypothesis: Senescence may play divergent roles during acute respiratory viral infections depending on host resilience. In young hosts, senescence induced by viral infection may play a positive role by recruiting neutrophils (PMNs) and other immune cells via the senescence associated secretory phenotype (SASP), resulting in viral clearance and tissue repair. In aged or vulnerable hosts, however, senescence induced by viral infection, in addition to the senescence already present, may tip the balance towards pathology. This pathology is characterized by an exuberant immune response, including high levels of SASP including cytokines and chemokines, causing exaggerated recruitment of PMNs and other immune cells, resulting in lung tissue damage.

References

1. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp. Cell Res.* 1961; 25: 585–621.

2. Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp. Cell Res.* 1965; 37: 614–636.

3. Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, Peacocke M, Campisi J. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc. Natl. Acad. Sci. U. S. A.* 1995; 92: 9363–9367.

4. Morty RE, Prakash YS. Senescence in the lung: Is this getting old? *Am. J. Physiol. - Lung Cell. Mol. Physiol.* 2019; 316: L822–L825.

5. He S, Sharpless NE. Senescence in Health and Disease. *Cell* [Internet] Elsevier Inc.; 2017; 169: 1000–1011Available from: http://dx.doi.org/10.1016/j.cell.2017.05.015.

6. Childs BG, Durik M, Baker DJ, Van Deursen JM. Cellular senescence in aging and age-related disease: From mechanisms to therapy. *Nat. Med.* 2015; 21: 1424–1435.

7. Campisi J. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* 2013; 75: 685–705.

8. Sager R. Senescence as a mode of tumor suppression. *Environ. Health Perspect.* 1991; 93: 59–62.

9. Braig M, Lee S, Loddenkemper C, Rudolph C, Peters AHMF, Schlegelberger B, Stein H, Dörken B, Jenuwein T, Schmitt CA. Oncogene-induced senescence as an initial barrier in lymphoma development. *Nature* 2005; 436: 660–665.

10. Chen Z, Trotman LC, Shaffer D, Lin H-K, Dotan ZA, Niki M, Koutcher JA, Scher HI, Ludwig T, Gerald W, Cordon-Cardo C, Pandolfi PP. Crucial role of p53-dependent cellular senescence in

suppression of Pten-deficient tumorigenesis. *Nature* 2005; 436: 725–730.

11. Schmitt CA, Fridman JS, Yang M, Lee S, Baranov E, Hoffman RM, Lowe SW. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. *Cell* 2002; 109: 335–346.

12. Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, Laberge R-M, Vijg J, Van Steeg H, Dollé MET, Hoeijmakers JHJ, de Bruin A, Hara E, Campisi J. An Essential Role for Senescent Cells in Optimal Wound Healing through Secretion of PDGF-AA. *Dev. Cll* 2014; 31: 722–733.

13. Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, Yee H, Zender L, Lowe SW. Senescence of Activated Stellate Cells Limits Liver Fibrosis. *Cell* 2008; 134: 657–667.

14. Kim K-H, Chen C-C, Monzon RI, Lau LF. Matricellular Protein CCN1 Promotes Regression of Liver Fibrosis through Induction of Cellular Senescence in Hepatic Myofibroblasts. *Mol. Cell. Biol.* 2013; 33: 2078–2090.

15. Fitzner B, Müller S, Walther M, Fischer M, Engelmann R, Müller-Hilke B, Pützer BM, Kreutzer M, Nizze H, Jaster R. Senescence determines the fate of activated rat pancreatic stellate cells. *J. Cell. Mol. Med.* 2012; 16: 2620–2630.

16. Jun J Il, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. *Nat. Cell Biol.* 2010; 12: 676–685.

17. Muñoz-Espín D, Cañamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, Rodríguez-Baeza A, Varela-Nieto I, Ruberte J, Collado M, Serrano M. Programmed cell senescence during mammalian embryonic development. *Cell* 2013; 155: 1104.

18. Storer M, Mas A, Robert-Moreno A, Pecoraro M, Ortells MC, Di Giacomo V, Yosef R, Pilpel N, Krizhanovsky V, Sharpe J, Keyes WM. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. *Cell* [Internet] Elsevier Inc.; 2013; 155: 1119Available from: http://dx.doi.org/10.1016/j.cell.2013.10.041.

19. McHugh D, Gil J. Senescence and aging: Causes, consequences, and therapeutic avenues. *J. Cell Biol.* 2018; 217: 65–77.

20. López-otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. *Cell* 2013; 153: 1194–1217.

21. Ksiazek K, Mikula-Pietrasik J, Olijslagers S, Jörres A, Von Zglinicki T, Witowski J. Vulnerability to oxidative stress and different patterns of senescence in human peritoneal mesothelial cell strains. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 2009; 296: 374–382.

22. Weyemi U, Lagente-Chevallier O, Boufraqech M, Prenois F, Courtin F, Caillou B, Talbot M, Dardalhon M, Al Ghuzlan A, Bidart JM, Schlumberger M, Dupuy C. ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence. *Oncogene* Nature Publishing Group; 2012; 31: 1117–1129.

23. Van Deursen JM. The role of senescent cells in ageing. *Nature* 2014; 509: 439–446.

24. Nyunoya T, Monick MM, Klingelhutz A, Yarovinsky TO, Cagley JR, Hunninghake GW. Cigarette smoke induces cellular senescence. *Am. J. Respir. Cell Mol. Biol.* 2006; 35: 681–688.

25. Martínez I, García-Carpizo V, Guijarro T, García-Gomez A, Navarro D, Aranda A, Zambrano A. Induction of DNA double-strand breaks and cellular senescence by human respiratory syncytial virus. *Virulence* 2016; 7: 427–442.

26. Wheaton K, Campuzano D, Weili Ma, Michal Sheinis, Brandon Ho GWB, Benchimol S. Progerin-Induced Replication Stress Facilitates Premature Senescence in Hutchinson-Gilford Progeria Syndrome. *Mol. Cell. Biol.* 2017; 37: 1–18.

27. Gnani D, Crippa S, della Volpe L, Rossella V, Conti A, Lettera E, Rivis S, Ometti M, Fraschini G, Bernardo ME, Di Micco R. An early-senescence state in aged mesenchymal stromal cells contributes to hematopoietic stem and progenitor cell clonogenic impairment through the activation of a pro-inflammatory program. *Aging Cell* 2019; 18.

28. Liu J, Ding Y, Liu Z, Liang X. Senescence in Mesenchymal Stem Cells: Functional Alterations, Molecular Mechanisms, and Rejuvenation Strategies. *Front. Cell Dev. Biol.* 2020; 8.

29. Nicaise AM, Wagstaff LJ, Willis CM, Paisie C, Chandok H, Robson P, Fossati V, Williams A, Crocker SJ. Cellular senescence in progenitor cells contributes to diminished remyelination potential in progressive multiple sclerosis. *Proc. Natl. Acad. Sci. U. S. A.* 2019; 116: 9030–9039.

30. Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, Morishita R. Source of Chronic Inflammation in Aging. *Front. Cardiovasc. Med.* 2018; 5: 1–5.

31. Baylis D, Bartlett DB, Patel HP, Roberts HC. Understanding how we age: insights into inflammaging. *Longev. Heal.* 2013; 2: 1–8.

32. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S. Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. *Mech. Ageing Dev.* 2007; 128: 92–105.

33. Piber D, Olmstead R, Cho JHJ, Witarama T, Perez C, Dietz N, Seeman TE, Breen EC, Cole SW, Irwin MR. Inflammaging: Age and Systemic, Cellular, and Nuclear Inflammatory Biology in Older Adults.

Journals Gerontol. 2019; 74: 1716–1724.

34. Campisi J. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* 2013; 75: 685–705.

35. Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J. Clin. Invest.* 2013; 123: 966–972.

36. Freund A, Orjalo A V., Desprez PY, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. *Trends Mol. Med.* 2010; 16: 238–246.

37. Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol.* 2008; 6.

38. Kumar S, Millis AJT, Baguoni C. Expression of interleukin 1-inducible genes and production of interleukin 1 by aging human fibroblasts. *Proc. Natl. Acad. Sci. U. S. A.* 1992; 89: 4683–4687.

39. Childs BG, Durik M, Baker DJ, van Duersen JM. Cellular senescence in aging and age-related disease: from mechanisms to therapy Bennett. *Nat. Med.* 2015; 21: 1424–1435.

40. Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, Cordon-Cardo C, Lowe SW. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature* 2007; 445: 656–660.

41. Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, Holtz A, Shah S, Sharma V, Ferrucci L, Campisi J, Schilling B. A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol.* [Internet] 2020; 18: e3000599Available from: http://dx.doi.org/10.1371/journal.pbio.3000599.

42. Desdín-Micó G, Soto-Heredero G, Aranda JF, Oller J, Carrasco E, Gabandé-Rodríguez E, Blanco

EM, Alfranca A, Cussó L, Desco M, Ibañez B, Gortazar AR, Fernández-Marcos P, Navarro MN, Hernaez B, Alcamí A, Baixauli F, Mittelbrunn M. T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. *Science (80-.).* 2020; 368: 1371–1376.

43. Hernandez-Segura A, de Jong T V., Melov S, Guryev V, Campisi J, Demaria M. Unmasking Transcriptional Heterogeneity in Senescent Cells. *Curr. Biol.* [Internet] Elsevier Ltd.; 2017; 27: 2652-2660.e4Available from: http://dx.doi.org/10.1016/j.cub.2017.07.033.

44. Xu M, Tchkonia T, Ding H, Ogrodnik M, Lubbers ER, Pirtskhalava T, White TA, Johnson KO, Stout MB, Mezera V, Giorgadze N, Jensen MD, LeBrasseur NK, Kirkland JL. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. *Proc. Natl. Acad. Sci. U. S. A.* 2015; 112: E6301–E6310.

45. Wilkinson JE, Burmeister L, Brooks S V., Chan CC, Friedline S, Harrison DE, Hejtmancik JF, Nadon N, Strong R, Wood LK, Woodward MA, Miller RA. Rapamycin slows aging in mice. *Aging Cell* 2012; 11: 675–682.

46. Majumder S, Caccamo A, Medina DX, Benavides AD, Javors MA, Kraig E, Strong R, Richardson A, Oddo S. Lifelong rapamycin administration ameliorates age-dependent cognitive deficits by reducing IL-1β and enhancing NMDA signaling. *Aging Cell* 2012; 11: 326–335.

47. Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, Glass DJ, Klickstein LB. mTOR inhibition improves immune function in the elderly. *Sci. Transl. Med.* 2014; 6: 268ra179.

48. Laberge RM, Sun Y, Orjalo A V., Patil CK, Freund A, Zhou L, Curran SC, Davalos AR, Wilson-Edell KA, Liu S, Limbad C, Demaria M, Li P, Hubbard GB, Ikeno Y, Javors M, Desprez PY, Benz CC, Kapahi P, Nelson PS, Campisi J. MTOR regulates the pro-tumorigenic senescence-associated secretory

phenotype by promoting IL1A translation. *Nat. Cell Biol.* 2015; 17: 1049–1061.

49. Mannick JB, Morris M, Hockey HU, Roma G, Beibel M, Kulmatycki K, Watkins M, Shavlakadze T, Zhou W, Quinn D, Glass DJ, Klickstein LB. TORC1 inhibition enhances immune function and reduces infections in the elderly. *Sci. Transl. Med.* 2018; 10: 1–11.

50. Moiseeva O, Deschênes-Simard X, St-Germain E, Igelmann S, Huot G, Cadar AE, Bourdeau V, Pollak MN, Ferbeyre G. Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation. *Aging Cell* 2013; 12: 489–498.

51. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin M-J, Schwab M, Pollak M, Zhang Y, Yu Y, Becker KG, Bohr VA, Ingram DK, Sinclair DA, Wolf NS, Spindler SR, Bernier M, de Cabo R. Metformin improves healthspan and lifespan in mice. *Nat. Commun.* 2014; 4.

52. Campbell JM, Bellman SM, Stephenson MD, Lisy. K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis. *Ageing Res. Rev.* [Internet] Elsevier B.V.; 2017; 40: 31–44Available from: https://doi.org/10.1016/j.arr.2017.08.003.

53. Bannister CA, Holden SE, Jenkins-Jones S, Morgan CL, Halcox JP, Schernthaner G, Mukherjee J, Currie CJ. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. *Diabetes, Obes. Metab.* 2014; 16: 1165–1173.

54. Zhang Q, Lenardo MJ, Baltimore D. 30 Years of NF-κB: A Blossoming of Relevance to Human Pathobiology. *Cell* [Internet] Elsevier; 2017; 168: 37–57Available from: http://dx.doi.org/10.1016/j.cell.2016.12.012.

55. Horwitz BH, Scott ML, Cherry SR, Bronson RT, Baltimore D. Failure of lymphopoiesis after adoptive transfer of NF-κB-deficient fetal liver cells. *Immunity* 1997; 6: 765–772.

56. Nagashima K, Sasseville VG, Wen D, Bielecki A, Yang H, Simpson C, Grant E, Hepperle M, Harriman G, Jaffee B, Ocain T, Xu Y, Fraser CC. Rapid TNFR1-dependent lymphocyte depletion in vivo with a selective chemical inhibitor of IKKβ. *Blood* 2006; 107: 4266–4273.

57. Park JM, Greten FR, Wong A, Westrick RJ, Arthur JSC, Otsu K, Hoffmann A, Montminy M, Karin M. Signaling pathways and genes that inhibit pathogen-induced macrophage apoptosis - CREB and NF-κB as key regulators. *Immunity* 2005; 23: 319–329.

58. Schmidt-Supprian M, Tian J, Ji H, Terhorst C, Bhan AK, Grant EP, Pasparakis M, Casola S, Coyle AJ, Rajewsky K. IκB Kinase 2 Deficiency in T Cells Leads to Defects in Priming, B Cell Help, Germinal Center Reactions, and Homeostatic Expansion. *J. Immunol.* 2004; 173: 1612–1619.

59. Lavon I, Goldberg I, Amit S, Landsman L, Jung S, Tsuberi BZ, Barshack I, Kopolovic J, Galun E, Bujard H, Ben-Neriah Y. High susceptibility to bacterial infection, but no liver dysfunction, in mice compromised for hepatocyte NF-κB activation. *Nat. Med.* 2000; 6: 573–577.

60. Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, O'Hara SP, Larusso NF, Miller JD, Roos CM, Verzosa GC, Lebrasseur NK, Wren JD, Farr JN, Khosla S, Stout MB, Mcgowan SJ, Fuhrmann-Stroissnigg H, Gurkar AU, Zhao J, Colangelo D, Dorronsoro A, Ling YY, Barghouthy AS, Navarro DC, Sano T, et al. The Achilles' heel of senescent cells: From transcriptome to senolytic drugs. *Aging Cell* 2015; : 644–658.

61. Roos CM, Zhang B, Palmer AK, Ogrodnik MB, Pirtskhalava T, Thalji NM, Hagler M, Jurk D, Smith LA, Casaclang-Verzosa G, Zhu Y, Schafer MJ, Tchkonia T, Kirkland JL, Miller JD. Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. *Aging*

Cell 2016; 15: 973–977.

62. Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, Inman CL, Ogrodnik MB, Hachfeld CM, Fraser DG, Onken JL, Johnson KO, Verzosa GC, Langhi LGP, Weigl M, Giorgadze N, LeBrasseur NK, Miller JD, Jurk D, Singh RJ, Allison DB, Ejima K, Hubbard GB, Ikeno Y, Cubro H, Garovic VD, Hou X, Weroha SJ, Robbins PD, Niedernhofer LJ, et al. Senolytics improve physical function and increase lifespan in old age. *Nat. Med.* [Internet] Springer US; 2018; 24: 1246–1256Available from: http://dx.doi.org/10.1038/s41591-018-0092-9.

63. Lehmann M, Korfei M, Mutze K, Klee S, Skronska-Wasek W, Alsafadi HN, Ota C, Costa R, Schiller HB, Lindner M, Wagner DE, Günther A, Königshoff M. Senolytic drugs target alveolar epithelial cell function and attenuate experimental lung fibrosis ex vivo. *Eur. Respir. J.* 2017; 50.

64. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, Oberg AL, Birch J, Salmonowicz H, Zhu Y, Mazula DL, Brooks RW, Fuhrmann-Stroissnigg H, Pirtskhalava T, Prakash YS, Tchkonia T, Robbins PD, Aubry MC, Passos JF, Kirkland JL, Tschumperlin DJ, Kita H, LeBrasseur NK. Cellular senescence mediates fibrotic pulmonary disease. *Nat. Commun.* 2017; 8.

65. Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, Prata L, Masternak MM, Kritchevsky SB, Musi N, Kirkland JL. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. *EBioMedicine* [Internet] The Authors; 2019; 40: 554–563Available from: https://doi.org/10.1016/j.ebiom.2018.12.052.

66. Hickson LTJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, Herrmann SM, Jensen MD, Jia Q, Jordan KL, Kellogg TA, Khosla S, Koerber DM, Lagnado AB, Lawson DK, LeBrasseur NK, Lerman LO, McDonald KM, McKenzie TJ, Passos JF, Pignolo RJ, Pirtskhalava T, Saadiq IM, Schaefer KK, Textor SC, Victorelli SG, Volkman TL, Xue A, Wentworth MA, Wissler

Gerdes EO, 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.

67. Ahmad T, Sundar IK, Lerner CA, Gerloff J, Tormos AM, Yao H, Rahman I. Impaired mitophagy leads to cigarette smoke stress-induced cellular senescence: Implications for chronic obstructive pulmonary disease. *FASEB J.* 2015; 29: 2912–2929.

68. Blázquez-Prieto J, Huidobro C, López-Alonso I, Amado-Rodriguez L, Martín-Vicente P, López-Martínez C, Crespo I, Pantoja C, Fernández-Marcos PJ, Serrano M, Sznajder JI, Albaiceta GM. Cellular senescence limits acute lung injury induced by mechanical ventilation. *bioRxiv* 2020; .

69. Parikh P, Britt RD, Manlove LJ, Wicher SA, Roesler A, Ravix J, Teske J, Thompson MA, Sieck GC, Kirkland JL, LeBrasseur N, Tschumperlin DJ, Pabelick CM, Prakash YS. Hyperoxia-induced cellular senescence in fetal airway smooth muscle cells. *Am. J. Respir. Cell Mol. Biol.* 2019; 61: 51–60.

70. Klimova TA, Bell EL, Shroff EH, Weinberg FD, Snyder CM, Dimri GP, Schumacker PT, Budinger GRS, Chandel NS. Hyperoxia-induced premature senescence requires p53 and pRb, but not mitochondrial matrix ROS. *FASEB J.* 2009; 23: 783–794.

71. Meyer KC, Ershler W, Rosenthal NS, Lu XG, Peterson K. Immune Dysregulation in the Aging Human Lung. *Am. J. Respir. Crit. Care Med.* 1996; 153: 1072–1079.

72. Tsuji T, Aoshiba K, Nagai A. Alveolar cell senescence exacerbates pulmonary inflammation in patients with chronic obstructive pulmonary disease. *Respiration* 2010; 80: 59–70.

73. Zhou F, Onizawa S, Nagai A, Aoshiba K. Epithelial cell senescence impairs repair process and exacerbates inflammation after airway injury. *Respir. Res.* [Internet] BioMed Central Ltd; 2011; 12: 78Available from: http://respiratory-research.com/content/12/1/78.

74. Müller KC, Welker L, Paasch K, Feindt B, Erpenbeck VJ, Hohlfeld JM, Krug N, Nakashima M, Branscheid D, Magnussen H, Jörres RA, Holz O. Lung fibroblasts from patients with emphysema showmarkers of senescence in vitro. *Respir. Res.* 2006; 7: 1–10.

75. Traves SL, Culpitt S V., Russell REK, Barnes PJ, Donnelly LE. Increased levels of the chemokines GROα and MCP-1 in sputum samples from patients with COPD. *Thorax* 2002; 57: 590–595.

76. Boer WI De, Sont JK, Schadewijk A Van, Stolk J, Krieken JH Van, Hiemstra PS. Monocyte chemoattractant protein I, interleukin 8, and chronic airways inflammation in COPD. *J. Pathol.* 2000; 190: 619–626.

77. Gessner C, Scheibe R, Wötzel M, Hammerschmidt S, Kuhn H, Engelmann L, Hoheisel G, Gillissen A, Sack U, Wirtz H. Exhaled breath condensate cytokine patterns in chronic obstructive pulmonary disease. *Respir. Med.* 2005; 99: 1229–1240.

78. Aldera JK, Barkauskas CE, Limjunyawong N, Stanley SE, Kembou F, Tuder RM, Hogan BLM, Mitzner W, Armanios M. Telomere dysfunction causes alveolar stem cell failure. *Proc. Natl. Acad. Sci. U. S. A.* 2015; 112: 5099–5104.

79. Busse PJ, Birmingham JM, Calatroni A, Manzi J, Goryachokovsky A, Fontela G, Federman AD, Wisnivesky JP. Effect of aging on sputum inflammation and asthma control. *J. Allergy Clin. Immunol.* 2017; 139: 1808-1818.e6.

80. Hawkins GA, Robinson MB, Hastie AT, Li X, Li H, Moore WC, Howard TD, William W, Erzurum SC, Wenzel SE, Peters SP, Salem W. IL-6R Variation Asp358Ala Is a Potential Modifier of Lung Function in Asthma. *J. Allergy Clin. Immunol.* 2012; 130: 510–515.

81. Kuwano K, Kunitake R, Kawasaki M, Nomoto Y, Hagimoto N, Nakanishi Y, Hara N. P21Waf1/Cip1/Sdi1 and p53 Expression in Association With DNA Strand Breaks in Idiopathic

Pulmonary Fibrosis. *Am. J. Respir. Crit. Care Med.* 1996; 154: 477–483.

82. Lomas NJ, Watts KL, Akram KM, Forsyth NR, Spiteri MA. Idiopathic pulmonary fibrosis: Immunohistochemical analysis provides fresh insights into lung tissue remodelling with implications for novel prognostic markers. *Int. J. Clin. Exp. Pathol.* 2012; 5: 58–71.

83. Álvarez D, Cárdenes N, Sellarés J, Bueno M, Corey C, Hanumanthu VS, Peng Y, D'Cunha H, Sembrat J, Nouraie M, Shanker S, Caufield C, Shiva S, Armanios M, Mora AL, Rojas M. IPF lung fibroblasts have a senescent phenotype. *Am. J. Physiol. - Lung Cell. Mol. Physiol.* 2017; 313: L1164–L1173.

84. Habermann A, Gutierrez A, Bui L, Yahn S, Winters N, Calvi C, Peter L, Chung M-I, Taylor C, Jetter C, Raju L, Roberson J, Ding G, Wood L, Sucre JM, Richmond B, Serezani A, McDonnell W, Mallal S, Bacchetta M, Loyd J, Shaver C, Ware L, Bremner R, Walia R, Blackwell T, Banovich N, Kropski J. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. *Sci. Adv.* 2020; 6: eaba1972.

85. Brandenberger C, Kling KM, Vital M, Mühlfeld C. The role of pulmonary and systemic immunosenescence in acute lung injury. *Aging Dis.* 2018; 9: 553–565.

86. Palumbo S, Shin YJ, Ahmad K, Desai AA, Quijada H, Mohamed M, Knox A, Sammani S, Colson BA, Wang T, Garcia JGN, Hecker L. Dysregulated Nox4 ubiquitination contributes to redox imbalance and age-related severity of acute lung injury. *Am. J. Physiol. - Lung Cell. Mol. Physiol.* 2017; 312: L297–L308.

87. Johnston CJ, Rubenfeld GD, Hudson LD. Effect of age on the development of ARDS in trauma patients. *Chest* [Internet] The American College of Chest Physicians; 2003; 124: 653–659Available from: http://dx.doi.org/10.1378/chest.124.2.653.

88. Falsey AR, Walsh EE. Respiratory syncytial virus infection in elderly adults. *Drugs Aging* 2005; 22: 577–587.

89. Pop-Vicas A, Gravenstein S. Influenza in the elderly - A mini-review. *Gerontology* 2011; 57: 397–404.

90. Chen J, Kelley WJ, Goldstein DR. Role of Aging and the Immune Response to Respiratory Viral Infections: Potential Implications for COVID-19. *J. Immunol.* [Internet] 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32493812.

91. Baas T, Roberts A, Teal TH, Vogel L, Chen J, Tumpey TM, Katze MG, Subbarao K. Genomic Analysis Reveals Age-Dependent Innate Immune Responses to Severe Acute Respiratory Syndrome Coronavirus. *J. Virol.* 2008; 82: 9465–9476.

92. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *Jama* [Internet] 2020; 2019: 2019–2020Available from: http://www.ncbi.nlm.nih.gov/pubmed/32203977.

93. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* Elsevier Ltd; 2020; 6736: 1–9.

94. P. Chou J, B. Effros R. T Cell Replicative Senescence in Human Aging. *Curr. Pharm. Des.* 2013; 19: 1680–1698.

95. Shaw AC, Joshi S, Greenwood H, Panda A, Lord JM. Aging of the innate immune system. *Curr. Opin. Immunol.* 2010; 22: 507–513.

96. Dorrington MG, Bowdish DME. Immunosenescence and novel vaccination strategies for the elderly. *Front. Immunol.* 2013; 4: 1–10.

97. Aiello A, Farzaneh F, Candore G, Caruso C, Davinelli S, Gambino CM, Ligotti ME, Zareian N, Accardi G. Immunosenescence and Its Hallmarks: How to Oppose Aging Strategically? A Review of Potential Options for Therapeutic Intervention. *Front. Immunol.* 2019; 10: 2247.

98. Nikolich-Žugich J. The twilight of immunity: Emerging concepts in aging of the immune system review-article. *Nat. Immunol.* 2018; 19: 10–19.

99. Barbé-Tuana F, Funchal G, Schmitz CRR, Maurmann RM, Bauer ME. The interplay between immunosenescence and age-related diseases. *Semin. Immunopathol.* Seminars in Immunopathology; 2020; .

100. Appay V, Almeida JR, Sauce D, Autran B, Papagno L. Accelerated immune senescence and HIV-1 infection. *Exp. Gerontol.* 2007; 42: 432–437.

101. Voehringer D, Blaser C, Brawand P, Raulet DH, Hanke T, Pircher H. Viral Infections Induce Abundant Numbers of Senescent CD8 T Cells. *J. Immunol.* 2001; 167: 4838–4843.

102. Baz-Martínez M, Da Silva-Álvarez S, Rodríguez E, Guerra J, El Motiam A, Vidal A, Garciá-Caballero T, González-Barcia M, Sánchez L, Munõz-Fontela C, Collado M, Rivas C. Cell senescence is an antiviral defense mechanism. *Sci. Rep.* [Internet] Nature Publishing Group; 2016; 6: 1–11Available from: http://dx.doi.org/10.1038/srep37007.

103. Kulkarni U, Zemans RL, Smith CA, Wood SC, Deng JC, Goldstein DR. Excessive neutrophil levels in the lung underlie the age-associated increase in influenza mortality. *Mucosal Immunol.* [Internet] Springer US; 2019; 12: 545–554Available from: http://dx.doi.org/10.1038/s41385-018-0115-3.

104. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat. Rev. Immunol.* 2014; 14: 36–49.

105. Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, Aarden LA, Mooi WJ, Peeper DS. Oncogene-Induced Senescence Relayed by an Interleukin-Dependent Inflammatory Network. *Cell* 2008; 133: 1019–1031.

106. Ritschka B, Storer M, Mas A, Heinzmann F, Ortells MC, Morton JP, Sansom OJ, Zender L, Keyes WM. The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. *Genes Dev.* 2017; 31: 172–183.

107. Chuprin A, Gal H, Biron-Shental T, Biran A, Amiel A, Rozenblatt S, Krizhanovsky V. Cell fusion induced by ERVWE1 or measles virus causes cellular senescence. 2013; : 2356–2366.

108. Moiseeva O, Mallette FA, Mukhopadhyay UK, Moores A, Ferbeyre G. DNA Damage Signaling and p53-dependent Senescence after Prolonged B-Interferon Stimulation. *Mol. Biol. Cell* 2006; 17: 5356-1583–1592.

109. Yu Q, Katlinskaya Y V., Carbone CJ, Zhao B, Katlinski K V., Zheng H, Guha M, Li N, Chen Q, Yang T, Lengner CJ, Greenberg RA, Johnson FB, Fuchs SY. DNA damage-induced type I interferon promotes senescence and inhibits stem cell function. *Cell Rep.* 2015; 11: 785–797.

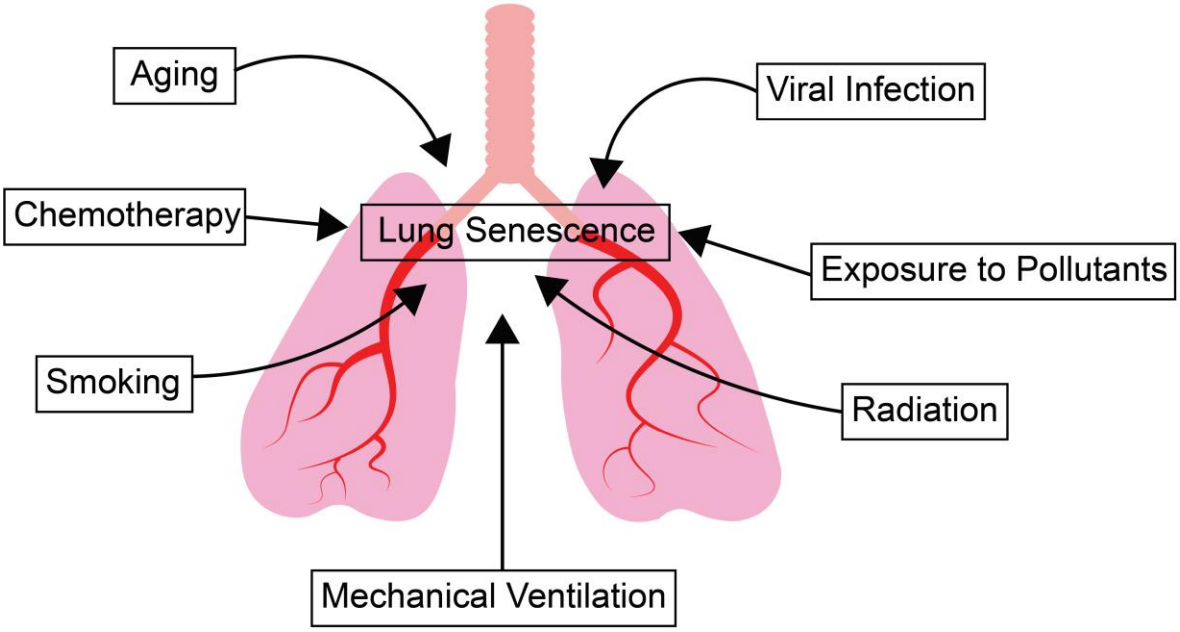
110. Oishi N, Shilagardi K, Nakamoto Y, Honda M, Kaneko S, Murakami S. Hepatitis B virus X protein overcomes oncogenic RAS-induced senescence in human immortalized cells. *Cancer Sci.* 2007; 98: 1540–1548.

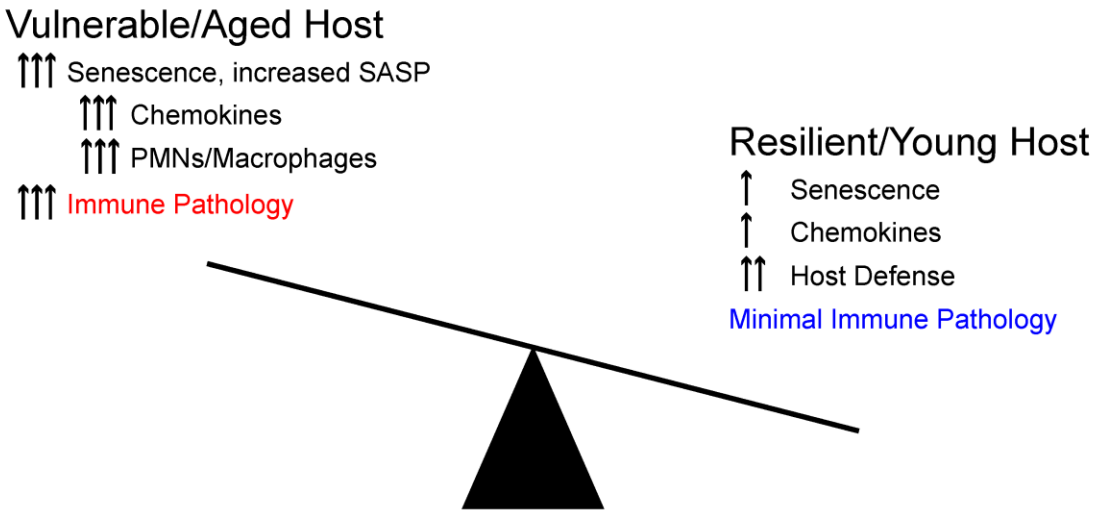
111. DiPaolo JA, Popescu NC, Alvarez L, Woodworth DC. Cellular and molecular alterations in human epithelial cells transformed by recombinant human papillomavirus. *Crit. Rev. Oncog.* 1993; 4: 337–360.

112. Persson BD, Jaffe AB, Fearns R, Danahay H. Respiratory syncytial virus can infect basal cells and alter human airway epithelial differentiation. *PLoS One* 2014; 9: 1–15.

113. Kim JA, Seong RK, Shin OS. Enhanced viral replication by cellular replicative senescence. *Immune Netw.* 2016; 16: 286–295.

114. Josset L, Engelmann F, Haberthur K, Kelly S, Park B, Kawoaka Y, Garcia-Sastre A, Katze MG, Messaoudi I. Increased Viral Loads and Exacerbated Innate Host Responses in Aged Macaques Infected with the 2009 Pandemic H1N1 Influenza A Virus. *J. Virol.* 2012; 86: 11115–11127.


Aging
Viral Infection
Chemotherapy
Lung Senescence
Exposure to Pollutants
Smoking
Radiation
Mechanical Ventilation



Lung Cellular Senescence and Respiratory Viral Infections