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Review article

Cellular senescence in chronic obstructive pulmonary disease: Molecular mechanisms and therapeutic interventions

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the world's fourth highest reason for mortality, accounting for 3.5 million deaths in 2021, and about 5 % of total global deaths. Emphysema and chronic bronchitis are the two major pathologies of COPD. Tobacco smoke, dust, vapors, and fumes, outdoor air pollutants, genetic factors, ageing, infections, and asthma are the risk factors of COPD. On the other hand, senescence is permanent halt in cell cycle accompanied by phenotypic alterations due to ageing, oxidative stress like; irreparable DNA damage, telomere shortening, oncogene activation or inactivation of tumor suppressors. COPD is often considered an accelerated ageing process of the lungs, with senescent cells impairing tissue repair and regeneration, causing progressive lung function decline. Although, cellular senescence is seen as powerful defense against risk of carcinogenesis in COPD as it arrests cell proliferation irreversibly, excessive collection of senescent cells releases senescence-associated secretory phenotype (SASP) that increase oxidative stress to lungs and leads to long-term inflammation, tissue damage, and hindered lung recovery. This review will address the accelerated ageing process and cellular senescence in COPD, therapeutic approaches targeting senescence regulation in COPD; clinical research and trial studies demonstrating the use of therapies aimed at senescence in COPD along with current obstacles and potential solutions.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the world's fourth primary contributor of mortality, accounting for 3.5 million deaths in 2021, and about 5 % of total global deaths (WHO, 2024). Emphysema and chronic bronchitis are the two major pathologies of COPD. Although, primary affected area in emphysema and chronic bronchitis are different, these conditions often coexist in the same person (Kim and Criner, 2013; Roggli and Cagle, 2008). Chronic bronchitis accounts for peribronchiolar fibrosis and persistent overproduction of mucus in the

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respiratory tract, while in emphysema, alveolar wall destructive changes occur by persistent, aberrant acinus expansion, either in part or in full (Barnes, 2019; Thurlbeck, 1973).

Inflammation plays a crucial role in development, progression, and aggravation of lungs cells damage related to COPD (Wang et al., 2018). The main objective of COPD treatment strategies is to alleviate symptoms, avert complications and hinder the disease progression. Anticholinergics, glucocorticoids, β-adrenergic receptor agonists, and phosphodiesterase-4 inhibitors are the main class of drugs used in COPD treatment which helps to reduce inflammation and relax smooth muscles around airways (Parums, 2023). Surgical option includes lung volume reduction surgery (LVRS) which remove damaged portions of the lung to allow healthier tissue to expand and function better (Geddes et al., 2000). Nevertheless, conventional drug therapies including, bronchodilators, corticosteroids, steroids and antibiotics have got significant side effects while using for long term. Muscle tremor, overstimulation of the heart, and excitation of CNS (Central Nervous System) can be caused by beta-2 agonists (Frandsen, Pennington., 2013). Inhaled corticosteroids, as long-term usage can induce osteoporosis, cataract, and adrenal suppression (Barnes, 2010). Additionally, the benefits of surgery are uncertain (Geddes et al., 2000). Thus, developing target specific novel therapeutics that can treat and prevent COPD progression with optimum side effects is essential.

Cellular senescence results in irreversible cessation in cell cycle accompanied by phenotypic alterations (Campisi and D'Adda Di Fagagna, 2007; Kuilman et al., 2010). Hayflick first reported the occurrence of cellular senescence in human fibroblasts that had been serially passaged in culture, which is caused by telomere shortening (Hayflick and Moorhead, 1961). Although process of senescence is frequently related with ageing, it can be induced by irreparable DNA damage, radiation, chemotherapy, stimulation of cancer-related genes, such as Rat Sarcoma (Ras) or B-Rapidly Accelerated Fibrosarcoma (BRAF), or the suppression of tumor suppressors, such as Phosphatase and Tensin Homolog (PTEN), oxidative metabolites from cell processes or oxidants (e.g., H_2O_2), mitochondrial dysfunction or senescence induced by the senescence-associated secretory phenotype (SASP), synthesized by a principal senescent cell (Collado et al., 2007; Hernandez-Segura et al., 2018; Sharpless and Sherr, 2015; Wadhwa et al., 2022) as shown in Fig. 1. Prolonged exposure to tobacco or biomass smoke, dust, vapors, fumes, genetic factors, airborne pollutants including pollution from traffic, coal dust, silica, asbestos in the workplace, and lung infections are risk factors of COPD (Mannino and Buist, 2007; Mehta et al., 2020). COPD is often considered an accelerated ageing process of the lungs, with senescent cells impairing tissue repair and regeneration, causing progressive lung function decline. In COPD, repeated exposure to harmful agents like cigarette smoke causes inflammation and oxidative stress, resulting in cell damage and senescence (Barnes, 2017).

Due to the irreversible cessation of cell proliferation, cellular senescence is seen as powerful defense against risk of carcinogenesis in COPD (Barnes, 2017; Bodnar et al., 1998) (Bodnar et al., 1998). Overabundance of senescent cells in tissues, however, can impair regeneration abilities and provide a proinflammatory environment that is conducive to the emergence and progression of COPD. SASP generated by a primary senescent cell activate the immune response to remove senescent cells (Acosta et al., 2013; Banerjee et al., 2021; Sharpless and Sherr, 2015). The inflammatory mediators such as those released by neutrophils and macrophages further increase oxidative stress to lungs that leads to chronic inflammation, tissue damage, and hindered lung recovery along with exacerbation of COPD symptoms (Barnes, 2017; Kirkham and Barnes, 2013).

Senolytics and senomorphics are two classes of senotherapeutics. Senolytics selectively kill senescent cells. Senomorphics attenuates the pathological SASPs to cause senostasis (Childs et al., 2017). Nevertheless, there are limitations that have to be considered for therapeutic interventions targeting senescent cells Firstly, many molecular and morphological characteristics associated with senescence exist in other

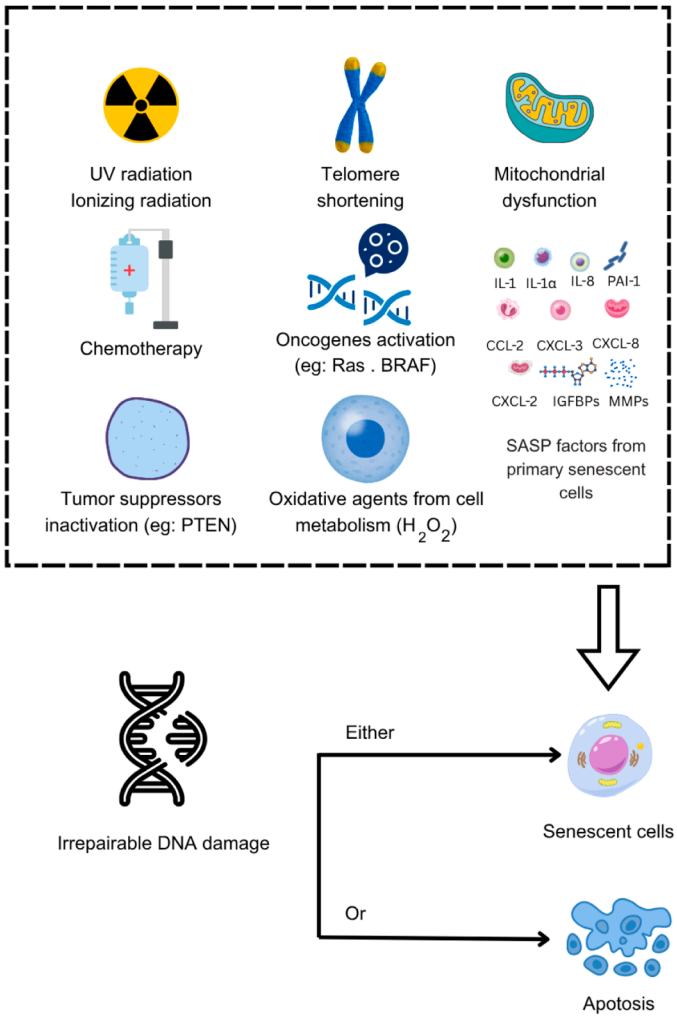


Fig. 1. Senescence can be induced by oxidative stress like; irreparable DNA damage, radiation, chemotherapy, stimulation of cancer-related genes, such as Ras or BRAF, or the inactivation suppression of tumor suppressors, such as PTEN, oxidative metabolites from cell processes or oxidants (e.g., H_2O_2), mitochondrial dysfunction and SASP factors from primary senescent cells (IL-1, IL-8, L-1α, PAI-1, CCL-2, CXCL-2, CXCL-3, CXCL-8, IGFBPs, MMPs, etc.). Figure were drawn using Canva.com.

cellular forms and situations too. Secondly, the heterogeneity in the phenotype of senescent cells and it alters over the time, likely due to the presence of different senescence pathways (Hernandez-Segura et al., 2018). The beneficial aspects of senescence make the development of senescence-related interventions in COPD challenging without causing toxic effects. However, targeting cellular senescence with drugs that eliminate or prevent senescent cells could be a potential therapeutic approach to reduce inflammation, enhance repair, and slow COPD progression (Barnes, 2017).

This review will address the following topics: the accelerated ageing process and cellular senescence in COPD, senescence-targeting therapeutic measures in COPD; clinical investigations and case analyses demonstrating the use of senescence-directed therapeutic approaches in COPD along with current obstacles and potential solutions.

2. Systemic survey of literature

The relevant scientific literature was explored for this review using two major platforms, PubMed and Scopus. Firstly, the term "cellular senescence" was searched and we found 39,500 publications from 1918 to the present. Following this, we searched for cellular senescence and

COPD and found 388 papers from 1969 to 2024. After that, we searched for accelerated ageing and COPD and found 273 publications from 1979 to present. Moreover, as we were particularly interested in the available research on senolytic and senomorphic medicines, we entered the term senolytic drug and senomorphics drug separately and received 723 articles from 2014 to 2024 and 285 results from 2018 to 2024 respectively. These results depict that while the topic cellular senescence has been studied and explored for many years, studies on senolytic and senomorphics drug for therapeutic intervention in senescence is rapidly growing interest and developing progress in recent times. Furthermore, we were particularly interested in the clinical trial study being conducted on biomarkers of cellular senescence and found 48 research publications from 1995 to 2024.

Also, we aimed to search existing research on clinical trials for senolytic drugs and senomorphics drugs, and we discovered 10 and 3 articles respectively on search tools. This indicates research on senotherapeutic drugs is still in the initial phases, especially in terms of clinical practice. More clinical studies on them are essential to establish safety, efficacy, and potential benefits of senotherapeutic agents.

3. Cellular senescence types in COPD and its characteristics

In COPD, senescence plays a key role in the disease's development. The lungs of COPD patients contain accumulated senescent cells, encompassing endothelial and alveolar epithelial cells (Amsellem et al., 2011; Rutten et al., 2016; Tsuji et al., 2006). The accumulation of senescent cells contributes to the progression of COPD by developing fibrosis of small airways and loss of alveolar cells (emphysema) (Selman et al., 2019).

COPD is considered an accelerated ageing process of the lungs, with senescent cells impairing healing and renewal of tissue, causing progressive decline in lung function which is called, "Replicative Senescence". In addition to replicative senescence, repeated exposure to harmful agents like air pollution and cigarette smoke are also known to induce senescence in COPD (Barnes, 2017).

3.1. Replicative senescence (Ageing and senescence)

In natural ageing process, proliferating cells are less capable of expanding due to halting of the cell cycle. Senescence takes place over the course of a cell's lifespan and is essential for injury recovery and organism growth (Demaria et al., 2014; Fernandes et al., 2021). In 1961, Hayflick and Moorehead investigated the permanent cessation of cellular growth, discovering that basic human cells have just about 60 cell divisions during entire life (Hayflick and Moorhead, 1961). This limitation of cell division is known as, "Hayflick limit" (biological clock). Upon each cell division, the telomeres are gradually shortened, which triggers Hayflick limit and after certain limit, cell can no longer divide which is known as replicative senescence. This type of senescence helps to prevent DNA damage and chromosomal aberrations (Courtois-Cox et al., 2008; Hayflick and Moorhead, 1961). With ageing, senescent cells accumulate in sites affected by age-associated health conditions like atherosclerosis and osteoarthritis. These cells affect the normal function of tissues, contributing to a gradual decline in their function (Calcinotto et al., 2019).

In healthy individuals also, lungs functions slowly decline over the age. Both force expiratory volume in one second (FEV)-1 and FEV2 reach their peak value around 25 years of age and slowly decrease along with the age in normal people (Bowdish, 2019). COPD is considered as an accelerated ageing process of the lungs, where collection of senescent cells impairs repair of tissues and regeneration, contributing to a steady decline in lung function (Barnes, 2017). In one meta-analysis study, the relationship between accelerated ageing, as denoted by telomere length, and COPD was studied through a meta-analysis comprising 15,846 controls and 934 COPD cases. Findings indicated that there was positive association between length of telomeres and spirometric parameters [FEV1, force vital capacity (FVC), and FEV1/FVC]. This finding suggests that in COPD patients, shorter telomeres are linked to reduced lung performance. In addition, their findings also suggests that cellular senescence is a crucial factor in the progression of COPD and that lung function can serve as an indicator of biological ageing processes (Albrecht et al., 2014). Similar findings are reported in studies by Lee et al. (2012) and Wang et al. (2022), which also noted patients with COPD had shorter telomeres in their peripheral leukocytes than those of healthy individuals. According to these studies, inflammation is an important contributor in the shortening of COPD telomeres, which can lead to an early ageing process. Moreover, another study also found that an increased likelihood of COPD and impaired lung function is associated with faster epigenetic age, both at baseline and over time (Breen et al., 2020). In a study conducted by Fernandes et al. (2021) it was demonstrated that patients with COPD exhibit telomeres shortening at an early stage of the disease, indicating a sign of accelerated cellular senescence. Also, smokers show higher telomerase activity compared to both COPD patients and healthy individuals. The results imply that smoking and COPD are known to affect telomeric maintenance and immune responses, potentially leading to cancer development. So, cellular senescence is associated with a higher risk of lung cancer in COPD (Nasim and Moua, 2020).

3.2. Other types of senescence in COPD

In COPD, senescence can induce from ageing as well as exposure to harmful factors like cigarette smoke, ionizing radiation, or cytotoxic therapies, and environmental exposures, that leads to reduction in lungs function (Bhat et al., 2015; Birch et al., 2015; Cho, 2019). In addition, irreversible cell cycle arrest may also result from oncogene activation, aneuploidy, and epigenetic modifications, metabolic dysregulation, extensive ROS (Reactive Oxygen Species) production, and mitochondrial malfunction (Fernandes et al., 2021; Kudlova et al., 2022). When glycogen phosphorylase, the catabolic enzyme, is depleted from cells then glycogen is accumulated, leading to decrease proliferation and an increase in senescence (Parrinello et al., 2003).

Oncogenic stress, which is caused by the excessive expression of certain oncogenes such as Ras or BRAF or the deletion of tumor suppressor genes (TSG) such as Phosphatase and Tensin Homolog (PTEN) in primary and tumor cells, causes senescence (Blasco et al., 1997; Counter et al., 1992). Oxidative stress, which causes DNA damage, also cause telomere attrition which accounts for the acceleration of senescence process (Richter and Zglinicki, 2007).

In the context of COPD, immunosenescence (Senescence of both adaptive and innate immune cells) also has a crucial role in the progression of the disease that increases susceptibility to cancer too (Sadighi Akha, 2018). The lungs of COPD patients are found containing macrophages and CD28null CD81 T-lymphocytes representing the senescence marker p21 (Hodge et al., 2011; Tomita et al., 2002).

3.3. Mechanism of senescence in COPD: key pathways, protein, and genes

There are mainly two mechanisms for senescence in cells; the stimulation of tumor-suppressor protein p53 during replicative senescence, and p16INK4a during stress-induced senescence (Barnes et al., 2019).

3.3.1. Senescence induced via p53 pathways

The p53 pathway induces replicative senescence. In replicative senescence, shortening of telomers occurs. Telomeres contain repeating DNA sequences of nucleotide which protects the chromosome termini from damage or merging with nearby chromosomes. In every cellular replication, 50–200 base pairs of DNA that has not undergone replication are lost at the 3′ end. The enzyme that adds nucleotides on the ends of telomeres to counteract for shortening is telomerase, or terminal transferase.

However, during accelerated rate of cell division, the activity of

telomerase is insufficient to compensate shortening of telomere by adding nucleotides on the ends of telomeres. As a result, shortening of telomers occurs which contributes to the phenomenon of ageing of cells (Calcinotto et al., 2019; Watson, 1972). In addition, telomere shortening activates DNA damage response (DDR). DDR is a signal transduction pathway in which the kinases ataxia-telangiectasia mutated (ATM) or ATM- and Rad3-related (ATR) stops progression of cell-cycle by promoting the stability of the p53 tumor suppressor protein and activating the p21 (Cazzalini et al., 2010; Fagagna et al., 2003; Fujita et al., 2009). p21 is a cell cycle inhibitor that blocks the Cyclin-dependent Kinases (CDKs), that are important for progression of cell cycle. p21 blocks CDK2/cyclin E-mediated phosphorylation of retinoblastoma protein (pRB), halting the cell cycle in the G1 phase and inhibiting the progression from G1 to S-phase results to cellular senescence (Vandenberk et al., 2011).

3.3.2. *Senescence induced via p16^{INK4A} pathways*

During stress-induced senescence also, stimulation of the cyclin-dependent kinase inhibitor occurs. In p16^{INK4A} pathways, Cyclin-dependent kinases (CDKs), that are crucial for progression across cell cycle phases, are inhibited by the protein p16^{INK4A}, acting as a tumor suppressor. p16INK4A specifically inhibits CDK4/6 / cyclin D, that prevents phosphorylation of pRb protein and keep pRb in an active state, which halts the progression in the cell cycle (Vandenberk et al., 2011).

Both of the above pathways induce the cyclin-dependent kinase inhibitor, leading to the suspension of the cell cycle (Barnes, 2019; Tchkonia et al., 2013).

3.3.3. *Senescence induced via p21CIP1 pathways*

As shown in Fig. 2, p21 is induced during replicative senescence in p53 pathways. Its induction is controlled by both p53-dependent and p53-independent mechanisms. In cellular senescence, activation of the

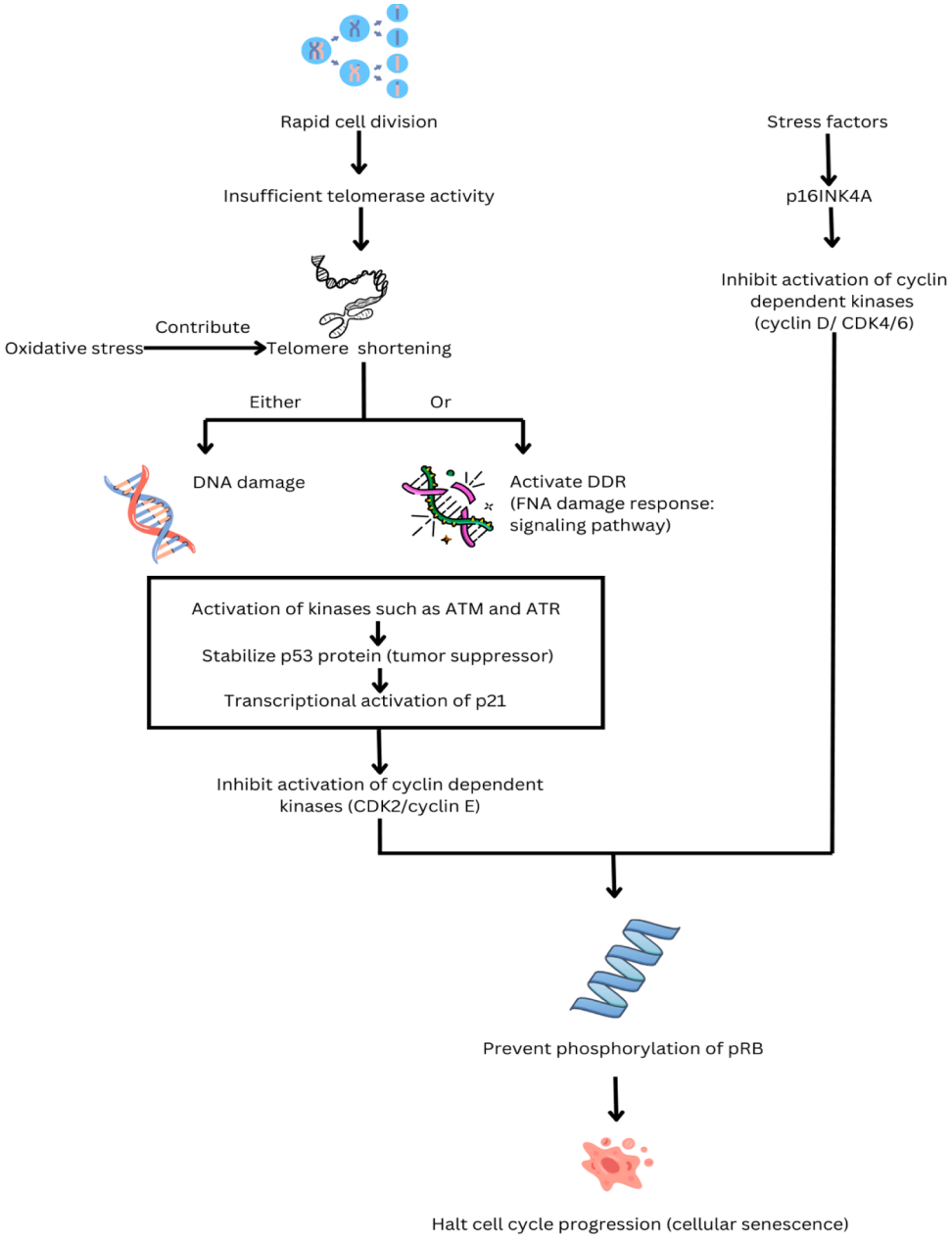


Fig. 2. p21 blocks CDK2/cyclin E-mediated phosphorylation of phosphorylate retinoblastoma protein (pRb), halting the cell cycle in the G1 phase and inhibiting the progression from G1 to S-phase. As a result, cellular senescence occurs while p16INK4A specifically inhibits CDK4/6 / cyclin D, that prevents phosphorylation of pRb protein. Figures were drawn using Canva.com.

cyclin-dependent kinase (CDK) inhibitor, p21Cip1 occurs (Chang et al., 2000). Tsuji et al. had also found elevated number of p21CIP1 in lung biopsies in emphysematous patients, suggesting cellular senescence (Tsuji et al., 2006).

4. Hallmarks of senescence in COPD and their identification

Although cell cycle arrest cannot be considered as a definitive marker, it is a major feature for identifying all types of senescence. Senescence includes various cellular processes. Various biomarkers are used to characterize senescent cells, rather than a single or specific marker (Table 1). Senescent cells are unable to express the genes that are essential for proliferation (Dimri and Campisi, 1994; Dimri et al., 1996).

Shortening of telomers: As mentioned earlier in 3.3.1, shortening of telomere indicates that cells are unable to maintain their telomeres length, supporting senescence (Fernandes et al., 2021). There is enhanced level of cell cycle inhibitors, such as p21CIP1, p16INK4a, and p27 in senescent cells, along with elevated expression of proteins involved in tumor suppression, p19ARF, p53, and PAI-1 (Aitken et al., 2021; Dulic et al., 2000; Zeng et al., 2013). In a study, conducted by Tsuji et al. (2006), as compared to asymptomatic smokers and nonsmokers, COPD patients had increased presence of endothelial and alveolar type II cells that were positive for p16INK4a and p21CIP1/-WAF1/Sdi1. Moreover, the telomeres were shorter in COPD patients than in non-COPD individuals.

In addition to that, growth factor mTORC1 is a protein complex that promotes cell growth. Low ATP levels in the cell lead to an increase in AMPK (59-AMP activated kinase), which inhibits mTOR endogenously. AMPK is the primary regulator of mTORC1 that inhibits mTORC1, and its activity is diminished in animal models of COPD, contributing to disease progression. (Cheng et al., 2017; Colman et al., 2014).

Another factor is pH, at pH 6, there is increased action of senescence-associated β-galactosidase (SA-β-gal) at in senescent cells (Calcinotto and Alimonti, 2017). As mentioned in 3.3.1, there is activation of DDR signaling pathway in cellular senescence. In senescent cells, markers like γ-H2AX (a phosphorylated form of the histone protein, H2AX) and DDR proteins such as 53BP1, NBS1, and MDC1 are commonly observed (Nakamura et al., 2010; Richter and Zglinicki, 2007). In addition to altered level of protein, lipids and enzymes, senescent cells are also represented by certain morphological changes. Senescent cells exhibit altered size featuring a smoother outline compared to normal cells, along with formation of senescence-associated heterochromatin foci formation (Narita et al., 2003).

Furthermore, a decrease in the glycogen phosphorylase enzyme in cells leads to the accumulation of glycogen, which is associated with decreased cell proliferation, and the eventual initiation of senescence. In addition, reduction in the glycogen phosphorylase leads to glycogen buildup, which inhibits cell proliferation (Parrinello et al., 2003). In the study, conducted by Delgado-Eckert et al. (2021), airway remodeling biomarkers like osteonectin, YKL-40, and matrix metalloproteinase (MMP)-3 were found being elevated in COPD patients, associated with a loss of reversible airflow, increased lung volume, decreased gas exchange efficiency.

Role of sirtuins: In cellular senescence in COPD, there is decreased expression of anti-ageing molecules, such as sirtuins (SIRT)-1 and SIRT-6 (Rajendrasozhan et al., 2008; Zhou et al., 2023). Oxidative stress can cause loss of SIRT function, which lowers the expression of PTEN (a tumor suppressor gene) to a greater extent and enhance the activation of the PI3K and mTOR pathways. miRNA-34a regulates the PI3K-mTOR signal transduction pathway which helps to lower the levels of SIRT-1 and SIRT-6 (Baker et al., 2016; Houssaini et al., 2018; Mitani et al., 2016). The pulmonary cells, epithelial tissue, and peripheral blood mononuclear cells in individuals with COPD are found with increased expression of PI3K, assessed through the phosphorylation of AKT kinase (protein kinase B). (To et al., 2010; Yanagisawa et al., 2017).

Table 1
List of hallmarks of cellular senescence.

Markers (references)	Status	Role of marker
p16INK4a, p21CIP1, p19ARF, p53, and PAI−1 (Calcinotto and Alimonti, 2017; Tsuji et al., 2006).	Increased level induces cellular senescence	Cell cycle inhibitors and tumor suppressor proteins
59-AMP activated kinase (Cheng et al., 2017; Colman et al., 2014)	Decreased level that promotes COPD progression	Major endogenous inhibitor of mTORC1 that promotes cell growth
Senescence-associated β-galactosidase (SA-β-gal) (Calcinotto and Alimonti, 2017)	Increased activity	It doesn't directly play a functional role; marker used to identify senescent cells.
γ-H2AX and DDR proteins such as 53BP1, NBS1, and MDC1 (Richter and Zglinicki, 2007)	Increased activity	inhibit cell-cycle progression
osteonectin, YKL−40, and MMP−3 (Delgado-Eckert et al., 2021)	Elevated	Airway remodeling biomarkers
sirtuins (SIRT)−1 and SIRT−6 (Baker et al., 2016; Houssaini et al., 2018; Mitani et al., 2016)	Decreased expression	Anti-ageing molecules. Decrease of this biomarker further decreases the interpretation of phosphatase, PTEN (a tumor preventing gene) and triggers the implementation of the PI3K and mTOR pathways.
miR−34a (McCubbrey et al., 2016)	Increased in macrophages	Elevated levels of miR−34 result in impaired phagocytosis and a decreased ability to uptake of apoptotic cells
miR−570 (Baker et al., 2019)	Increased expression	A rise in its expression leads to reduction in activity of sirtuin−1
miR−126 (Meister and Schmidt, 2010; Paschalaki et al., 2018)	Decreased expression	miR−126 helps in promotion of blood vessel growth so its reduction contributes to the difficulties in tissue repair and regeneration in COPD patients
miR−146a (Mohamed et al., 2019a)	Increased expression	Reduces certain anti-ageing proteins (IRAK1 and TRAF6). It also causes overproduction of **IL−1β, IL−6**, and **IL−8**
Klotho (Gao et al., 2015).	Reduced expression	An anti-ageing protein

4.1. Dysregulation of miRNAs in cellular senescence

Different types of microRNAs are found to be elevated in cellular senescence. A microRNA, miR-34a is found to increase in macrophages in COPD disease and may be accompanied by defective phagocytosis and ingestion of apoptotic cells (McCubbrey et al., 2016). Another molecule called miR-570 can downregulate the activity of sirtuin-1 (but not sirtuin-6). miR-570 is activated by certain signals in the body (p38 MAP kinase and AP-1). In individuals with COPD, the amount of miR-570 was found elevated in lungs and airways cells. Thus, by blocking miR-570 by targeting with a specific treatment can help to restore the activity of anti-ageing molecules, sirtuin-1, which reduces signs of ageing in cells, and this can be potential approach to "revitalize" ageing cells in COPD (Baker et al., 2019). Moreover, **miR-146a** is another type of microRNA that reduces certain anti-ageing proteins (IRAK1 and TRAF6). It also causes overproduction of **IL-1β, IL-6**, and **IL-8**, which play a role in the progression of diseases, including chronic lung diseases like **COPD** (Mohamed et al., 2019a). Another, miRNA, miRNA-377–3p is also elevated in COPD patients. In a study conducted by Lu et al. (2024), it was found up-regulated expression of miR-377–3p was predominantly in lung fibroblasts, result in inducing lung fibroblasts senescence (Lu

et al., 2024). It was showed that p53 and p21 were augmented by p53 and p21 was upregulated by miR-377–3p overexpression, suggesting that miR-377–3p activated DNA damage response signaling in human lung fibroblasts. Moreover, the mRNA levels of some SASP factors including IL-1β, MCP-1, MMP9 and PAI-1 were found to be increased after expression of miR-377–3p. miR-377–3p promotes lung fibroblast senescence *via* ZFP36L1 downregulation which is an RNA binding protein that counteracts the SASP.

Some types of microRNAs are also found to be lowered in cellular senescence. A microRNA, miR-126 is found lower in COPD patients. miR-126 helps in promotion of blood vessel growth so its reduction contributes to the difficulties in tissue repair and regeneration in COPD patients (Meister and Schmidt, 2010; Paschalaki et al., 2018).

Furthermore, these miRNAs can be carried by extracellular vesicles (EV), and taking up of these elements by lung cells triggers senescence, ultimately contributing the worsening of chronic lung disorders, including COPD (Barnes et al., 2019). EVs can also enter the bloodstream from the lungs, propagating senescence to other organs (Kadota et al., 2018). An anti-ageing protein, Klotho (KL) is also reduced in COPD airway epithelial cells, leading to enhanced oxidative stress, inflammation and apoptosis (Gao et al., 2015).

In addition, in senescent cells there is accumulation of lipofuscin, the formation of DNA damage foci, depletion of lamin B1, senescence-related expansion or stretching of satellite DNA regions, embryonic chondrocyte–expressed 1 (DEC1) expression and SASP secretion and decoy death receptor 2 (DCR2) (Collado et al., 2005; Georgakopoulou et al., 2012; Hernandez-Segura et al., 2018; Hewitt et al., 2012; Shimi et al., 2011; Swanson et al., 2013). Nevertheless, there is increasingly growing interest in discovering new markers of senescence (Calcinotto et al., 2019). Thus, senescent cells display a persistent growth arrest by increasing activity of cell cycle inhibitors, and alteration in the expression of proteins and cellular frameworks. In COPD, senescence is also found in cells outside the lung, such as circulating endothelial progenitor cells (Paschalaki et al., 2013).

5. Roles of senescence-associated secretory phenotype

SASP or senescence-messaging secretome (SMS) is set of molecules which are secreted by senescent cells. It contains growth factors, cytokines, immune modulators, chemokines, and proteases (Coppé et al., 2010; Hernandez-Segura et al., 2018; Kuilman and Peeper, 2009). The main elements of SASP encompasses proinflammatory cytokines (like IL-6, IL-8, and IL-1α), chemokines (such as CXCL-2, CXCL-3, CCL-2, CXCL8), and growth factors, like several insulin-like growth factor–binding proteins (IGFBPs). The molecules have the capacity to affect surrounding cells and immune responses (Acosta et al., 2008; Coppé et al., 2010, 2008; Moiseeva et al., 2009; Takaoka and Taniguchi, 2003).

As shown in Fig. 3, the formation of inflammatory mediators and additional components by senescent cells through SASP from senescent cells direct back the senescence signals to the same cells that released them which reinforce the senescence process by triggering DNA damage within those primary senescent cells. This is called autocrine mechanism

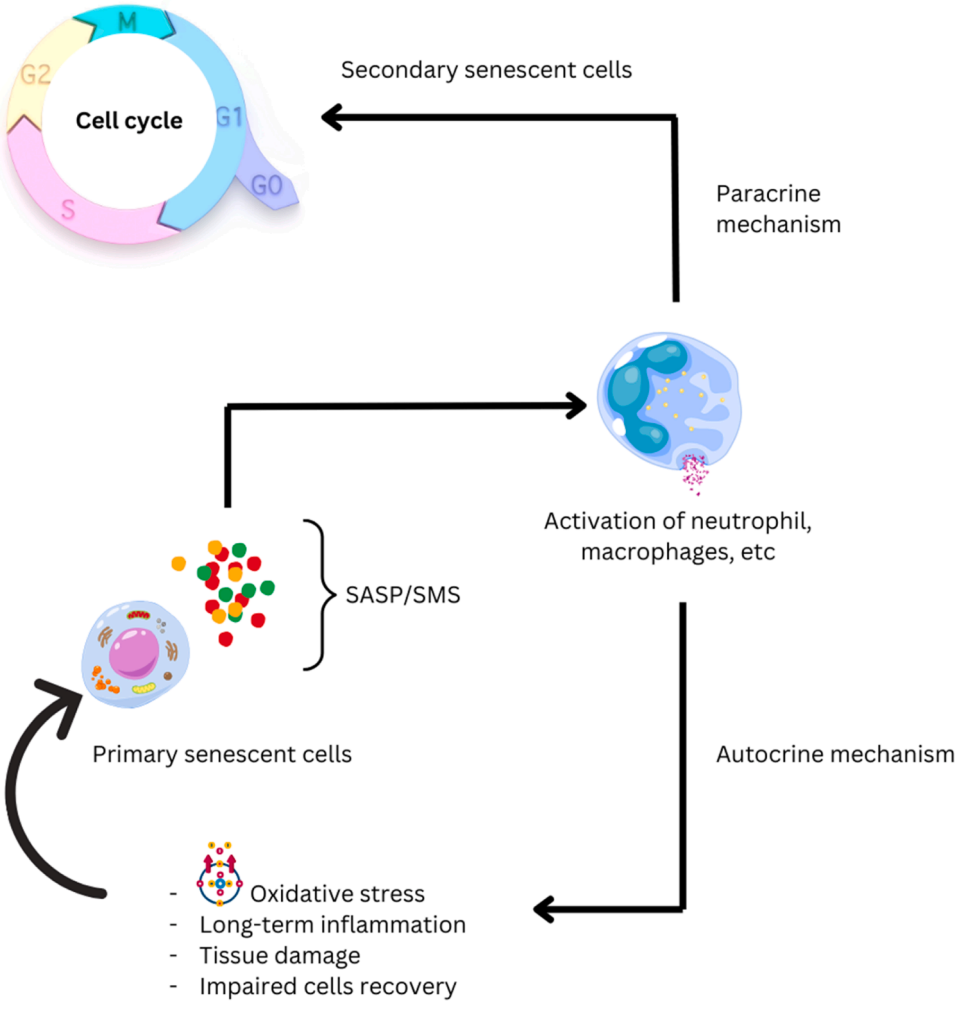


Fig. 3. Senescence can be boosted either in autocrine manner or paracrine manner by the release of SASP from senescent cells. Figures were drawn using Canva.com.

of SASP to amplify senescence or SASP release can transmit senescence to neighbouring cells via paracrine mechanisms (Calcinotto et al., 2019; Moiseeva et al., 2009; Takaoka and Taniguchi, 2003). SASP generated by a primary senescent cell activate the immune system to eliminate cells experiencing senescence (Acosta et al., 2013; Banerjee et al., 2021; Sharpless and Sherr, 2015). The activation of immune system amplifies senescence in primary senescent cells along with inducing senescence in neighbouring cells. The inflammatory mediators such as; neutrophils and macrophages are activated by SASP which further increase oxidative stress to lungs, leading to long-term inflammation, tissue damage, and impaired lung recovery accompanied by a worsening of COPD symptoms (Barnes, 2017; Kirkham and Barnes, 2013). One of the key components of SASP protein is PAI-1 (plasminogen activator inhibitor-1). It is elevated in the alveoli, sputum, and sputum macrophages, of COPD patients, indicating that cellular senescence contributes to the chronic inflammation seen in COPD (To et al., 2013).

6. Dual edge sword character of senescence

On negative side, cellular senescence adds to the pathogenesis of COPD. Senescent lung fibroblasts can stimulate myofibroblast differentiation through a paracrine signaling pathway, recommending that they release a profibrotic SASP (Schafer et al., 2017a). There is elevated level of NAPDH oxidase 4 and reduction in antioxidant response NFE2-related factor 2 expression in pulmonary senescence that causes an increase in level of ROS which induce DNA damage and senescence (Hecker et al., 2014).

A mechanism of senescence in organisms is controversial. Although, senescent cells contribute to the progression of COPD, they are crucial in different physiological functions like, tissue restructuring, and tissue repairing. Platelet-derived growth factor AA (PDGF-AA) are secreted by senescent cells in cutaneous wounds, that enhances alteration of nearby fibroblasts into myofibroblasts. This process enhance contraction of wound during the proliferative stage, aiding tissue repair and accelerating closure of wound (Demaria et al., 2014). They support fibrotic resolution by releasing MMPs and drive reprogramming of adjacent cells through an IL-6/PIM1 pathway (Calcinotto et al., 2019).

On positive side, it has been discovered that cellular senescence has antiproliferative effects on tumor cells and it helps protect cells against malignancy. However, when senescent cells accumulate over time, it leads to the dysfunction of tissues, disease related to age, and reduced lifetime for organisms (Davaapil et al., 2016; Koo et al., 2016; Muñoz-Espín and Serrano, 2014). The growth of senescent cells in tissues for shorter period of time or temporarily typically promotes beneficial functions, while sustained senescence disrupts the reestablishment of tissue homeostasis, diminishes the tissue's regenerative capacity, leading to ageing, tissue degeneration, and cancer formation (Calcinotto et al., 2019; Muñoz-Espín and Serrano, 2014). Senescence is a normal developmental mechanism in embryonic development, where it tightly controls the programmed cellular process. Which is uniquely regulated in same pattern in every embryo and cells never leave any markers of damage, this reveal that it is highly controlled cellular process not a stochastic/random response (Rhinn et al., 2019). Embryonic senescent cells are non-proliferative and exhibit characteristics similar to those of oncogene-induced senescence, such as the expression of p21, p15, and components of the senescence-associated secretory phenotype. Notably, mice lacking p21 show impairments in embryonic senescence, apical ectodermal ridge maintenance, and tissue patterning (Storer et al., 2013).

7. Therapeutic interventions targeting cellular senescence

For slowing down the COPD progression and associated mortality, use of drug therapeutics that targets senescence pathways could be potential approach, which is termed as senotherapies (Kim and Kim, 2019). For the curing ageing-related disorders involving senescence, therapeutic interventions targeting cellular senescence can be used either by preventing the senescence secretome / SASP or by reduction of senescent cells (Childs et al., 2015). Senolytics and senomorphics are two types of senotherapeutics. Senolytics are the therapeutic interventions that specifically target and eliminate senescent cells, and senomorphics reduce harmful effects of the pathological SASPs, promoting senostasis (Childs et al., 2017). Following treatment approaches can be used in COPD by targeting cellular senescence:

7.1. Senolytics drugs

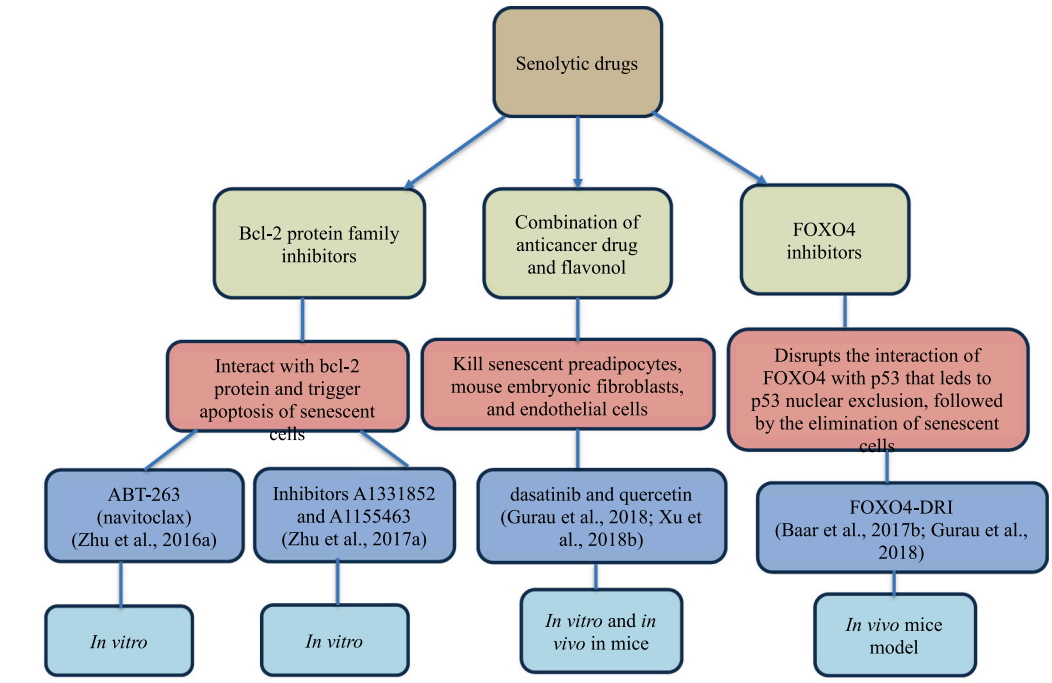
Senolytics drugs works by eliminating senescent cells selectively. These compounds induce apoptosis in the senescent cells while having barely any impact on proliferating cells (Kirkland et al., 2017).

The Bcl-2 protein family comprises proteins like; Bcl-W, Bcl-XL, Bcl-2, and Mcl-1. These proteins inhibit apoptosis and autophagy, and their levels are elevated in senescent cells (Calcinotto and Alimonti, 2017). Therefore, compounds that target and inhibit these proteins in senescent cells may serve as potential therapeutic agents to modulate senescence in COPD. Bcl-2 protein inhibitor, called ABT-263 (navitoclax), was identified and found as effective senolytic agent (Zhu et al., 2016b). However, these medications can have significantly higher toxicities in patients (Roberts et al., 2012; Wilson et al., 2010). So, novel compounds, like A1331852 and A1155463 were identified and studied as more promising candidates for clinical use (Zhu et al., 2017).

A flavonoid present in apples, quercetin is found to stimulate AMPK as well as act as senolytic agent by preventing mice from developing lipopolysaccharide (LPS) induced emphysema (Ganesan et al., 2010; Schafer et al., 2017a) – Fig. 4C. One of the FDA–approved anticancer drug, Dasatinib is recognized for its ability to trigger apoptosis. Intriguingly, when it is combined with Quercetin, the combined drug agents can work as senolytic compound (Gurău et al., 2018). The combination has proven to be efficient in eliminating *in vitro* endothelial cells, mouse embryonic fibroblasts (MEF) and senescent preadipocytes (Zhu et al., 2016b). In ageing mice, the senolytic combination of dasatinib and quercetin decreased senolytic cells and the SASP response, while intermittent therapy boosted lifespan by 36 % and lowered mortality risk by 65 % (Xu et al., 2018a).

The other strategy involves targeting Forkhead box protein O4 (FOXO4), is a protein which helps to sustain the viability of senescent cells by binding to p53 (Gurău et al., 2018). For inhibiting this protein, a FOXO4 peptide, FOXO4-DRI developed which disrupts the interaction of FOXO4 with p53 that led to p53 nuclear exclusion, followed by the removal of senescent cells. The doxorubicin-forced rapid ageing was counteracted by FOXO4-DRI peptide and recovered mice's fitness, density of fur, and also renal function in mice (Baar et al., 2017a). In spite of this, such therapeutic peptides exhibit some notable disadvantages, including issues with stability and relatively short half-life (Fosgerau and Hoffmann, 2015). These peptides could also be used when treating COPD, however, further invitro, preclinical and clinical studies is required to fully explore their potential in COPD treatment. In addition, biopharmaceutics studies are required to optimize their long-term stability and develop them with a suitable half-life.

There are some other compounds that are found with having potential senolytic properties. Although, studies of these compounds aren't specifically done in COPD related cells, they can be the potential agent for COPD treatment as they are found being effective as senolytics agents. For instance, piperlongumine, a natural compound has demonstrated to trigger caspase-mediated apoptosis in senescent cells (Zhang et al., 2016). Another potential compound is Nicotinamide riboside which is a nicotinamide adenine dinucleotide (NAD^+)'s precursor enhances cellular levels of NAD+ that enhances DNA repair, thereby activating sirtuins. When ageing mice were given treatment with nicotinamide riboside, it was discovered to be useful in prolonging life and rejuvenation of muscle stem cells (Zhang et al., 2016). Furthermore, a synthetic steroid, Danazol can be also potential drugs for COPD. It can



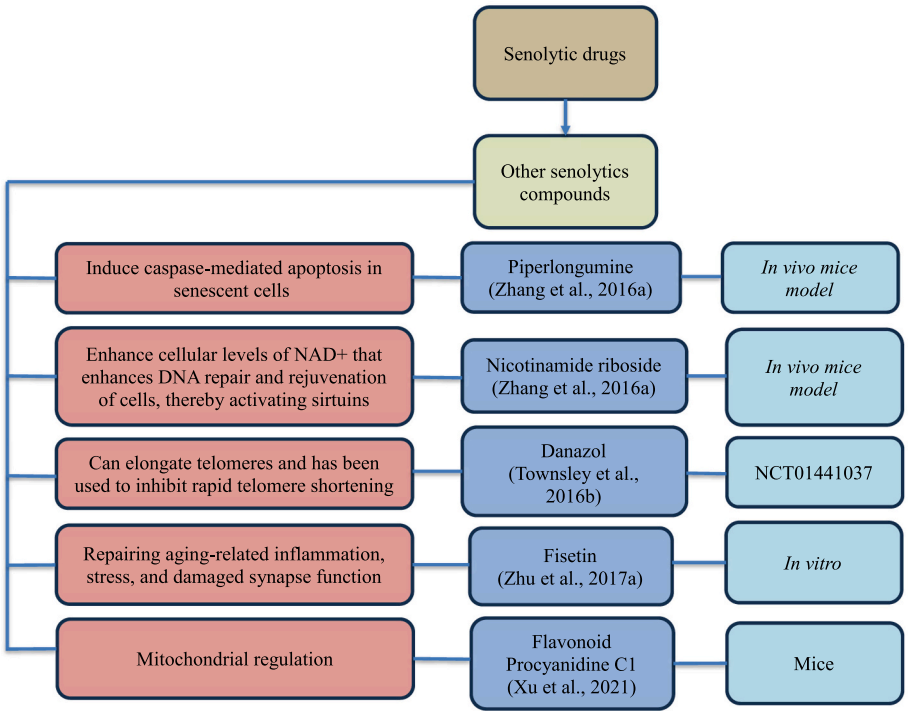


Fig. 4. A. Represents senolytic drugs: Classification Mechanism Citation Experiment model. B Represents senolytic drugs: Classification Mechanism Citation Experiment model. C Represents senolytic and senomorphic drugs Classification Mechanism Citation Experiment model. D Represents senomorphic drugs Classification Mechanism Citation Experiment model. E Represents other formulations: Classification Mechanism Citation Experiment model.

elongate telomeres and inhibits rapid shortening of telomere (Townsley et al., 2016a). Moreover, Fisetin, a type of plant polyphenol, which lowers cognitive decline in older mice by repairing impaired synaptic function, stress, and inflammation related with ageing (Zhu et al., 2017).

While many of the senolytic agents mentioned above have not been specifically studied in the context of COPD-related cells, they have shown their potential as senolytic compounds in other models. These agents may be useful for promoting senolysis and inhibiting the progression of the COPD (Fig. 4A and B). However, most of the research to date has been limited to *in vitro* studies, and there is a significant gap in clinical data for COPD-specific applications. So, further study is needed under these senolytics compounds for using them clinically as potential

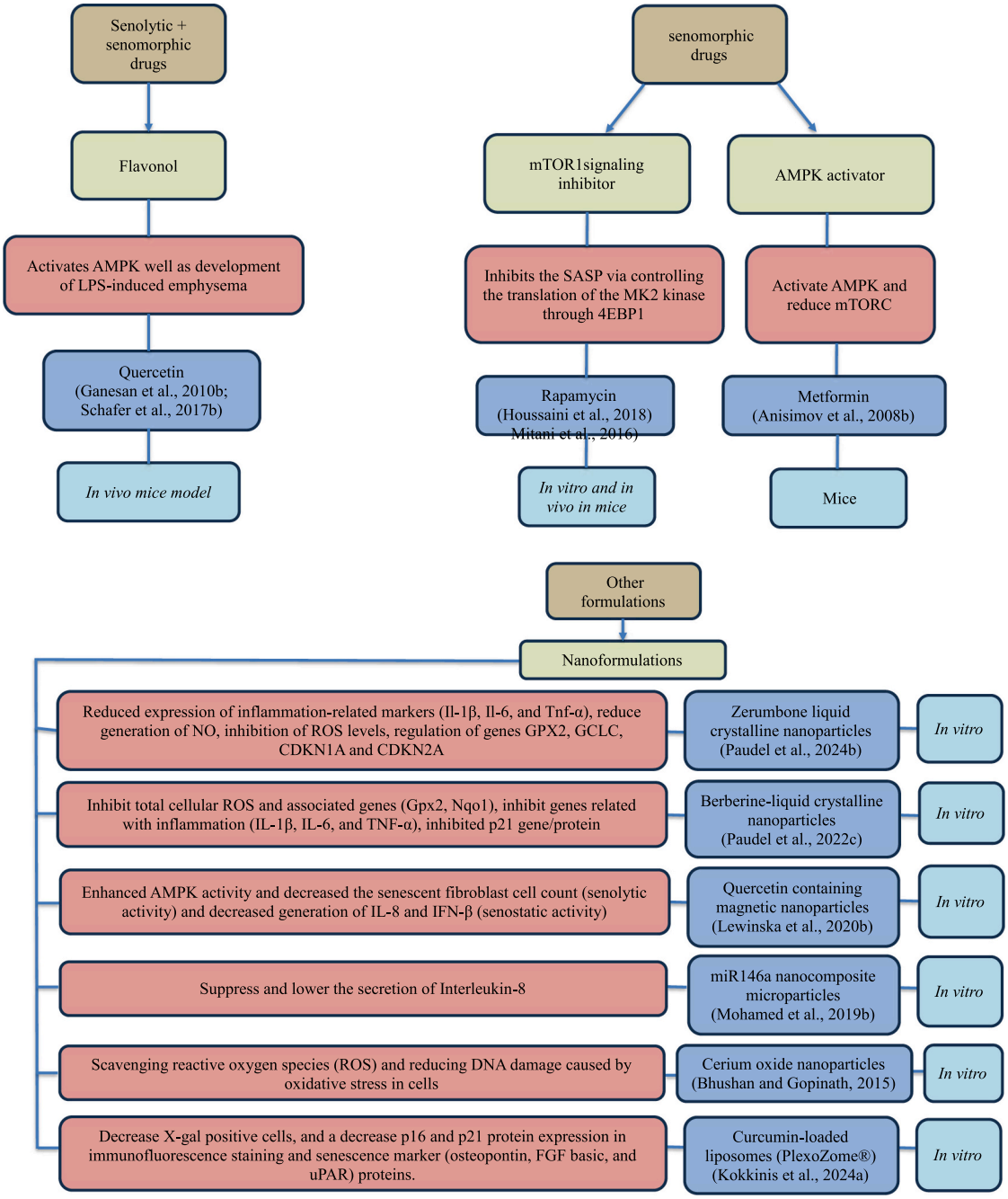


Fig. 4. (*continued*).

drugs in COPD.

7.2. Senomorphics drugs

Senomorphics are the agents that attenuates the pathological SASPs to cause senostasis (Childs et al., 2017). The mechanism of senomorphics primarily involves preventing autocrine and paracrine senescence by reprogramming the SASPs in different ways.

As discussed earlier, mTOR complex 1 (mTORC1), is triggered in COPD cells. mTORC1 is triggered in peripheral blood mononuclear cells (PBMCs) and peripheral lungs of COPD, given that elevated levels of phosphorylated S6 kinase. Rapamycin, an immunosuppressant drug efficiently blocks mTORC1 activation in COPD cells both *in vitro* and *in vivo* in mouse models (Houssaini et al., 2018; Mitani et al., 2016). In a tobacco smoke-exposed mouse model of COPD, Rapamycin is found effective in reducing senescence-associated-b-galactosidase (SA-bGal), SASP mediators and a reduction in emphysema (Houssaini et al., 2018). Rapamycin reduces the SASP by controlling the conversion of the MK2 kinase *via* 4EBP1. (Herranz et al., 2015). However, rapamycin doesn't block mTORC2, a component of mTOR complex. When mTORC1 is inhibited by rapamycin, it may lead to increased activity of mTORC2. So, the development of drugs that selectively suppress both mTORC1 and mTORC2 could be more effective in treating chronic conditions involving cellular senescence (Barnes et al., 2019). Additionally, rapamycin possess several adverse effects including, constipation, diarrhoea, mouth ulcers, headache, fever, nausea, abdominal pain, anaemia, arthralgia, hypertension, hypercholesterolaemia, hypertriglyceridemia, and elevated level of creatinine (Lee et al., 2024). This has resulted in creation of less harmful analogues known as rapalogs, like everolimus and temsirolimus. But the study in these drugs have been limited for

identifying them as potent senomorphics compound for COPD treatment (Mannick et al., 2014, 2018).

As discussed above in 4, AMPK is the primary regulator that inhibits mTORC1. So the drugs that activates AMPK that can be the possible therapeutic approach FOR targeting senescence in COPD cells. Metformin has been found to activates AMPK, which inhibits mTOR and extends life (Anisimov et al., 2008a). In mice, metformin has found to decrease inflammation, senescence and growth of elastase-induced emphysema (Cheng et al., 2017). The potential senotherapies for COPD has been summarized in schematic diagram Fig. 4D and Fig. 5. The list of recent clinical trials related to age related diseases/ conditions including the drug or combinations of the drugs used is shown on Table 2.

Table 2 summarizes recent ongoing and completed clinical trials of senotherapeutics, including those targeting respiratory tract infections including COPD, and other chronic diseases, highlighting the expanding scope of senotherapeutic research beyond COPD alone. Nicotinamide riboside (Norheim et al., 2024) is found to reduce the airways inflammation associated with COPD in patients aged 60 or older. Another drug, Mepolizumab (Sciurba et al., 2025) is found to reduce COPD exacerbations in patients with high eosinophil levels. While it didn't improve symptoms or quality of life, its ability to lower inflammation may help reduce the harmful effects of cellular senescence in this COPD subgroup. Even though other drugs like; Fisetin (FIS), Dasatinib + Quercetin listed above have not been specifically researched in COPD, they have shown promise in related chronic and age-associated diseases, including other respiratory conditions such as Osteoarthritis and Alzheimer's Disease (Gonzales et al., 2023; NLM, 2020). This highlights the potential of senotherapeutics as a broader strategy for managing aging-related diseases including respiratory diseases. However, further research and well-designed clinical trials are necessary to establish their efficacy and safety specifically in COPD.

7.3. *Nanoformulations targeting senescence in COPD*

Nanotherapeutics that precisely and efficiently target the senescence indicators could be a potential strategy for managing the progression of COPD. These nanotherapies might be made to reduce the senescence markers or to increase the expression of antiageing molecules like SIRT, to prevent the PI3K-mTOR pathway, to stop specific miRNAs or to delete senescent cells with senolytic therapies. (Paudel et al., 2022a). Nanotechnological approaches that precisely target the expected cells/pathways in the lungs through a variety of nanocarriers can be coupled with senotherapeutics (Dua et al., 2019).

The study conducted by Bhushan and Gopinath (2015) have proposed that cerium oxide–based nanoparticles have a potential to be used for treatment of COPD due to their senostatic activity by scavenging reactive oxygen species (ROS) and reducing oxidative DNA damage to cells. (Mohamed et al., 2019c) developed miR146a nanocomposite microparticles to suppress IRAK1(Interleukin-1 Receptor-Associated Kinase 1) target gene expression. It was discovered that IRAK1 expression was decreased by 40 %, and the secretion of Interleukin-8 was also lowered by these nanoparticles. Another possible way to treat for COPD might be quercetin containing magnetic nanoparticles. Lewinska and colleague (Lewinska et al., 2020a) developed quercetin containing nanoparticles that are magnetic and found it enhanced AMPK activity and decreased the quantity of fibroblasts that had become senescent due to hydrogen peroxide (senolytic activity). Additionally, they decreased secretion of IL-8 and IFN-β (senostatic activity).

Furthermore, when berberine-loaded liquid crystalline nanoparticles (berberine-LCNs) were studied in human broncho-epithelial cells (16HBE) and mice macrophage (RAW264.7) macrophages Cells, they showed strong antioxidant effects by inhibiting cellular ROS and regulated linked genes (*Gpx2, Nqo1*) in both cells. They were found to inhibit genes associated with inflammation (*IL-1β, IL-6,* and *TNF*-α), showing anti-inflammatory activity and also inhibited p21 gene/protein expression, showing potential antisenescence activity in 16HBE cells exposed with 5 % cigarette smoke extract to induced senescence (Paudel et al., 2022b). The study indicates that berberine-LCNs could be also a promising nanotherapeutic approach for treatment of COPD.

In another study, Zerumbone liquid crystalline nanoparticles (ZER-LCNs) were found to reduce the expression of pro-inflammatory markers (*Il-6*, *Il-1β* and *Tnf-α*), along with production of nitric oxide in RAW 264.7 cells. In addition, ZER-LCNs reduced oxidative stress by lowering reactive oxygen species (ROS) levels and regulating genes which is crucial in protecting cells from oxidative damage such as *GPX2* and *GCLC*, in human broncho epithelial cells (BCi-NS1.1). There was significant decrease in the expression of *SIRT1*, *CDKN1A*, and *CDKN2A* which exhibited the anti-senescence effects of ZER-LCNs (Paudel et al., 2024a).

Furthermore, curcumin-loaded liposomes (PlexoZome®) exhibited anti-senescent activity when they were assessed in cigarette smoke extract-induced COPD in *in-vitro* model utilizing BCiNS1.1, as evidenced by reduction in X-gal positive cells, and a decrease in p16 and p21 expression in immunofluorescence staining and decrease in inflammatory (GMCSF, EGF, and ST2) and senescence (osteopontin, FGF basic, and uPAR) proteins (Kokkinis et al., 2024b). Till now only, *in vitro* studies have been carried out for nanoformulations in senescence therapy for chronic respiratory diseases, further research is needed so that the formulation studied invitro could be developed into promising therapeutic option for chronic respiratory inflammatory disorders, including COPD. The schematic diagram of nanoformualtions targeted senescence in COPD is shown in Fig. 4E

8. Complications involved

Research cannot ignore the fact that healthy cells can also be damaged by senolytic therapies. Therefore, anti-senescence drugs should target the markers specifically expressed by senescent cells. Targeting the senescence-associated markers by antibodies through specific receptors can be also beneficial. For instance, NK cells target to kill senescent cells through NKG2D receptors (Sagiv et al., 2016). NKG2D- CAR T cell lines eliminate the senescent cells, diminish age associated pathological conditions and improved physical performance in mice. Similar effects were observed in aged non-human primates with NKG2D-CAR T cell treatment (Yang et al., 2023). In addition to that mouse embryonic fibroblasts (MEFs) and astrocytes (AST) used as a senescent model and co-localisation of these with NKG2D-CAR T cells showed cytotoxic effect (Deng et al., 2024).

The progression of COPD can lead to development of cancer. As discussed above, the double edge nature of senescence makes the senescence associated drug development process, challenging in COPD. Although senescence can provide benefits, such as preventing cancer by inhibiting excessive proliferation (Demaria et al., 2017), the prolonged accumulation of senescent cells can lead to chronic inflammation, tissue dysfunction, and impaired lung repair in COPD. In case of COPD developed cancer, two punch approach which have been proposed may be beneficial. This involves the use of senolytic therapies along with pro-senescence therapies to reduce the negative impacts of cellular senescence while preserving any potential benefits (Calcinotto et al., 2019; Xue et al., 2007).

9. Conclusion

Most of the studies conducted on serotherapeutic are only limited to *in vitro* and *in vivo* studies in animal model. Moreover, studies on serotherapeutic for specifically the COPD conditions is also very limited. So, further studies are needed for the development of potential novel senotherapeutics that can be clinically used in COPD patients to prevent exacerbation of symptoms, improve quality of life and prolong lifespan. The identification of more specific senescent markers involved in COPD and development of senotherapeutics targeting those markers could

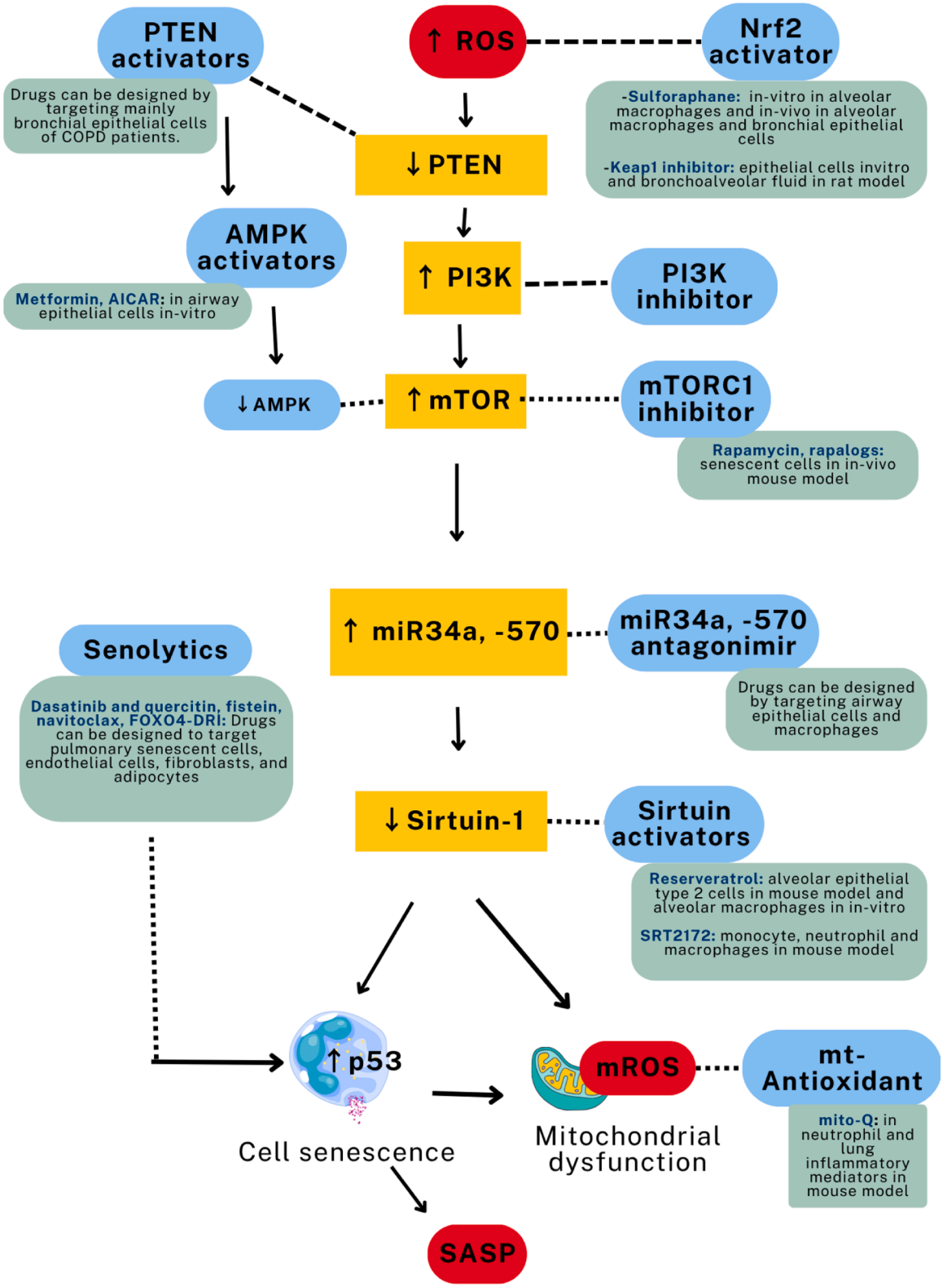


Fig. 5. Therapeutic interventions targeting cellular senescence in COPD. Reactive oxygen species (ROS) suppress phosphatase and tensin homolog (PTEN), which leads to stimulation of phosphoinositide-3-kinase (PI3K) and subsequently the mechanistic target of rapamycin (mTOR), which is suppressed by AMP kinase (AMPK). Stimulation of mTOR triggers microRNAs-34a and −570, which suppress sirtuin-1. This process contributes to cellular senescence and mitochondrial dysfunction, triggering the release of mitochondrial ROS (mROS). Senescent cells further secrete SASP. Various points in these pathways can serve as potential targets for different senotherapeutic agents. These pathways can be inhibited at several points targeting various pulmonary cell types as identified by different studies under *in-vivo* or *in-vitro* experimental conditions. The figure includes drugs and their targets, some of which have not been specifically tested in COPD but may still be relevant and new senotherapeutics target in COPD, based on evidence from similar cell types or disease mechanisms in other organs. Figure is re-produced with slight modification from Barnes (2021).

Table 2
List of recent clinical trials related to age related diseases/ conditions including the drug or combinations of the drugs used.

1	Drug	CT phase	Disease/ Condition	Target Population	CT number	Status
1	RTB101 (BEZ235), an oral mTOR inhibitor (Mannick et al., 2021)	Phase 2	Respiratory tract infections (including COPD)	Adults ≥ 65 years of age	NCT03373903	Active
2	nicotinamide riboside supplementation (Norheim et al., 2024)	Not Applicable	COPD	Older adults (≥60 years) with COPD	NCT04990869.	Completed
3	Mepolizumab, anti-IL−5 monoclonal antibody (Sciurba et al., 2025)	Phase 3	COPD with frequent exacerbations and elevated eosinophils	Adults with COPD on optimized maintenance therapy	NCT04133909	Completed
4	Fisetin (FIS)	Phase 1/2	Osteoarthritis	Adults with mild to moderate symptomatic knee Osteoarthritis	NCT04210986	Completed
5	Dasatinib + Quercetin (Gonzales et al., 2023)	Phase 1/2	Alzheimer's Disease	Adults ≥ 65 years with early symptomatic AD on stable cholinesterase inhibitors	NCT04063124	Completed
5	UBX1325 (foselutoclax)(Crespo-Garcia et al., 2024)	Phase 1	Diabetic Macular Edema (DME)	Patients with advanced DME unresponsive to anti-VEGF (Vascular Endothelial Growth Factor) therapy	NCT04537884	Completed
6	Dasatinib + Quercetin (Farr et al., 2024)	Phase 2	Bone metabolism in postmenopausal women	Postmenopausal women	NCT04313634	Completed

offer valuable insights for managing COPD especially for or those patients who do not respond well to standard treatments. Combination therapies involving existing COPD medications and senolytics represent a promising multimodal treatment strategy. This approach may incorporate anti-inflammatory agents, antioxidants, bronchodilators and corticosteroids alongside senolytics to address both the symptomatic and cellular drivers of the disease. Such a therapeutic combination could not only alleviate hallmark features of COPD but also facilitate the targeted clearance of senescent cells contributing to disease progression.

Additionally, a sequential treatment strategy may prove effective, where senolytic agents are administered initially to eliminate senescence cells, followed by senomorphics to suppress the pro-inflammatory senescence-associated secretory (SASP) and maintain tissue homeostasis.

In Parallel, personalised and precision medicine approach could enhance the efficacy of these treatments by tailoring interventions based on individual patient profiles, including senescence-related biomarkers and molecular characteristics. This targeted approach may be particularly beneficial for COPD patients exhibiting a high burden of senescent cells or poor response to standard therapies. Furthermore, more research is essential to establish safety, potency and efficacy of the senotherapeutics identified.

Authors' contributions

S.S and K.R.P conceptualization. S.S manuscript writing. N.S., R.T., S.B., N.P, G.G., R.M., B.O., K.D., and K.R.P., review editing and proof reading. K.D and K.R.P supervision. All authors read and approved the final manuscript.

Consent for publication

All authors have approved to publish this manuscript.

Ethics approval and consent to participate

Not applicable.

Declaration of Competing Interest

All authors declare no conflict of interest.

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Data availability

No data was used for the research described in the article.

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