Review article

Cellular senescence in lung cancer: Molecular mechanisms and therapeutic interventions

Saurav Kumar Jha [a], Gabriele De Rubis [b,c], Shankar Raj Devkota [d], Yali Zhang [e], Radhika Adhikari [f], Laxmi Akhileshwar Jha [g], Kunal Bhattacharya [h,i], Samir Mehndiratta [b,c], Gaurav Gupta [j,k], Sachin Kumar Singh [c,l], Nisha Panth [m], Kamal Dua [b,c,*], Philip M. Hansbro [m,**], Keshav Raj Paudel [m,**]

[a] Department of Biological Sciences and Bioengineering (BSBE), Indian Institute of Technology, Kanpur, Uttar Pradesh 208016, India
[b] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW 2007, Australia
[c] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, Australia
[d] Monash Biomedicine Discovery Institute, and Department of Biochemistry and Molecular Biology, Monash University, Clayton, VIC 3800, Australia
[e] School of Chemical Engineering, University of Adelaide, Adelaide 5005, Australia
[f] College of Pharmacy and Natural Medicine Research Institute, Mokpo National University, Jeonnam 58554, Republic of Korea
[g] Naraina Vidya Peeth Group of Institutions, Faculty of Pharmacy, Dr. A. P. J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh 0208020, India
[h] Pratiksha Institute of Pharmaceutical Sciences, Guwahati, Assam 781026, India
[i] Royal School of Pharmacy, The Assam Royal Global University, Guwahati, Assam 781035, India
[j] Centre for Global Health Research, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[k] Centre of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates
[l] School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi G.T Road, Phagwara, Punjab, India
[m] Centre for Inflammation, Centenary Institute and University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, NSW 2007, Australia

ARTICLE INFO

ABSTRACT

Lung cancer stands as the primary contributor to cancer-related fatalities worldwide, affecting both genders. Two primary types exist where non-small cell lung cancer (NSCLC), accounts for 80–85% and SCLC accounts for 10–15% of cases. NSCLC subtypes include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Smoking, second-hand smoke, radon gas, asbestos, and other pollutants, genetic predisposition, and COPD are lung cancer risk factors. On the other hand, stresses such as DNA damage, telomere shortening, and oncogene activation cause a prolonged cell cycle halt, known as senescence. Despite its initial role as a tumor-suppressing mechanism that slows cell growth, excessive or improper control of this process can cause age-related diseases, including cancer. Cellular senescence has two purposes in lung cancer. Researchers report that senescence slows tumor growth by constraining multiplication of impaired cells. However, senescent cells also demonstrate the pro-inflammatory senescence-associated secretory phenotype (SASP), which is widely reported to promote cancer. This review will look at the role of cellular senescence in lung cancer, describe its diagnostic markers, ask about current treatments to control it, look at case studies and clinical trials that show how senescence-targeting therapies can be used in lung cancer, and talk about problems currently being faced, and possible solutions for the same in the future.

1. Introduction

One of the deadliest diseases with a high death rate is lung cancer, which also happens to be the most common cause of tumor-related deaths (Global Burden of Disease Cancer et al., 2015; Shtivelman et al., 2014). The principal types of lung cancer are non-small-cell lung cancer (NSCLC), small-cell lung cancer, (SCLC), mesothelioma, sarcoma, and carcinoid based on the histological evaluation (Malyla et al., 2020; Sahu et al., 2023). While the prevalence of other kinds of lung cancer has remained rare, SCLC and NSCLC are the most frequent, accounting for

over 90% of all cases (Litzky, 2008; Zorzetto et al., 2012). NSCLC includes four subtypes: squamous cell carcinoma, adenocarcinoma, large-cell undifferentiated carcinoma, and Pancoast tumor (Panagopoulos et al., 2014; Pikor et al., 2013). SCLC is a rapidly expanding tumor that falls under the combined categories of small-cell and "oat cell" cancer (Field and Withers, 2012; Jiang et al., 2016). The foundation of the present treatment regimens relies on conventional approaches such as surgery resection, radiation, and chemotherapy, either alone or in combination (Huang et al., 2017; Paudel et al., 2020; Regassa et al., 2022). Nevertheless, several reports highlight significant side effects while using these conventional therapy techniques. Additionally, radiation poses risks to adjacent healthy cells. Thus, it is not a recommended course of treatment for patients whose pulmonary systems are already significantly affected (Huang et al., 2017; Regassa et al., 2022). This might result in the loss of lung functions. Recent times have also seen the use of radiation in conjunction with chemotherapy and surgery (Hirsch et al., 2016). Chemotherapy mainly acts by inhibiting the production of DNA and mitosis, leading to the rapid control over proliferation of cancerous cells and their ultimate demise. (Sharma et al., 2023). The non-selective nature of chemotherapy medicines is among the principal causes of high mortality among cancer patients. This is caused by the undesired negative side effects on nearby normal cells. In addition, the administration of anticancer drugs is accompanied by drug-free intervals between cycles (breaks), a critical factor in facilitating the recovery of non-selectively affected cells. Nevertheless, these disruptions possess the capacity to progressively replenish the malignant cells that the treatment was intended to weaken or eliminate. initially, and leads to the chemoresistance (Sharma et al., 2023).

The recognition of cells undergoing senescence may be traced back to the year 1961. Based on a study conducted by Paul Moorhead and Leonard Hayflick from the Wistar Institute of Anatomy and Biology, it has been shown that the division ability of normal human cells is constrained after a certain limit is reached (Hayflick and Moorhead, 1961).

Senescence is the term for the new, nondividing stage that the cells underwent when that limit was reached, as opposed to dying (Fig. 1). Subsequently, Hayflick suggested that this may be a type of cellular aging and hence important to the aging of the entire organism (Hayflick, 1965). For almost a decade, the scientific community mainly disregarded Hayflick's results because they were obstinate in their opinion that improper culture conditions, instead of any property of the cells themselves, were the source of cell growth inhibition (Watts, 2011). Over time, scientists studying cancer and aging developed a keen interest in this phenomenon and started delving further into it. Investigators found that a wide range of stressing stimuli such as oncogene activation, DNA damage, oxidative stress, and chemotherapy- or radiotherapy-induced DNA damage and other stressors, can induce cellular senescence (Gorgoulis et al., 2019). At least initially, senescence helps prevent the formation of malignancies by stopping damaged or defective cells from multiplying (Campisi, 2005). The concern lies in the fact that senescent cells, despite their replicative quiescent nature, actively secrete a potent combination of chemicals which include proinflammatory agents, proteases, and growth factors. The term senescent-associated secretory phenotype (SASP), describes this. These molecules can sometimes stimulate the immune system to eradicate cells undergoing senescence. Still, if this process is unsuccessful, the SASP can cause other cells to age as well, which may accelerate the development of cancer and act as a host of other age-related illnesses, such as frailty and ailments affecting the cardiocirculatory system (Banerjee et al., 2021; Boccardi and Mecocci, 2020; Coppe et al., 2010; Prata et al., 2018). Cells that experience cellular senescence become "senile" or incapable of dividing, losing their capacity to divide and multiply. Although this phenomenon is frequently linked to aging, it can also be prematurely brought on by several stresses, such as DNA damage, oxidative stress, or oncogenic alterations (Wadhwa et al., 2020). Moreover, most anticancer drugs are administered systemically, raising the possibility of senescence in several tissues or compartments.
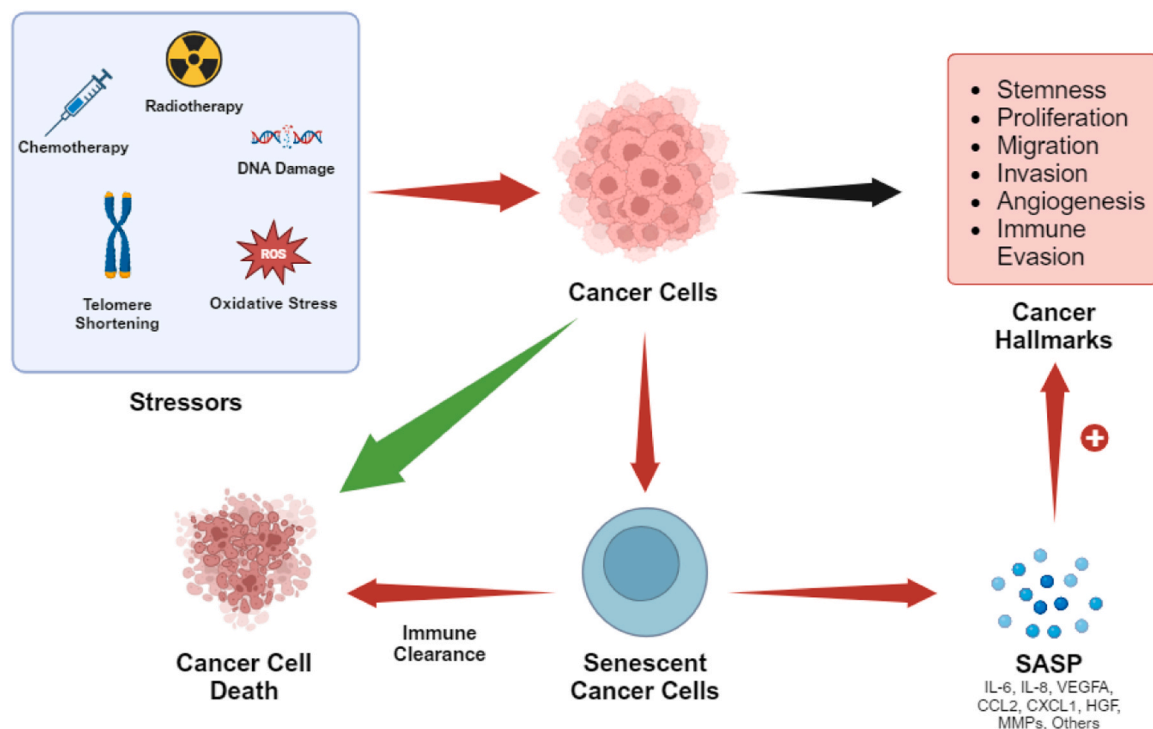

Fig. 1. Non-cancerous or malignant cells may release senescence-related molecules that influence subsequent effects on tumor growth after intrinsic or treatment stressors induce senescence. Various SASP variables increase the oncogenic potential of the cancer cell by influencing tumor stemness, proliferation, migration, and metastasis. Furthermore, factors associated with senescence influence the tumor microenvironment by encouraging tumor angiogenesis and impeding immune cells' ability to fight cancer. Matrix metalloproteinase (MMP) and senescence-associated secretory phenotype (SASP) are acronyms. Figure were drawn using Bio-render.com.

Preclinical models employ many methods to promote senescence, such as alkylating drugs (such as temozolomide, cyclophosphamide, and cisplatin), topoisomerase inhibitors (such as camptothecin, etoposide, and doxorubicin), and γ-irradiation (Rodier et al., 2009; Schmitt et al., 2022), microtubule inhibitors (*e.g.*, docetaxel and paclitaxel). Evaluation of biopsy from patients receiving mitoxantrone-treated prostate cancer divulged increased expression of senescence markers such as p21 and p16INK4a, as well as the SASP components interleukin (IL)-6 and IL-8. When samples from breast cancer patients underwent staining following different chemotherapeutic regimens, several markers of senescence (such as SA-β-gal, p16INK4a, p21, and p53) were found inside malignant tumors (te Poele et al., 2002). In another case, it was shown that chemotherapy results in longer-lasting increases of the SASP factor VEGFA and CCL2 as well as greater levels of p16INK4a in the hematopoietic compartment among patients affected by breast cancer (Schmitt et al., 2022). The ramifications of senescence are more complex than cell death due to the numerous impacts these cells may have on their environment, which significantly changes cellular activity (Schmitt et al., 2022). Currently, the prevailing notion is that harnessing the advantage of senescence to get rid of drug-exposed cancer cells, which haven't undergone apoptotic cell death but have contributed to the initial treatment response by halting proliferation, is considered the most effective approach for eliminating tumors because it has been shown to work (Schmitt et al., 2022). This review will encompass the subsequent subjects: the importance of cellular senescence in lung cancer; suitable indicators for identifying cellular senescence; therapeutic interventions aimed at regulating senescence in lung cancer; case studies and clinical trials illustrating the application of senescence-targeting therapies in lung cancer; existing obstacles and prospective strategies to overcome them.

2. Systemic survey of literature

Two leading search platforms, PubMed and Scopus were used to search the scientific literature for this review. Initially, we searched "cellular senescence" and found 36,478 papers from 1918 to the present. Next, we searched for cellular senescence and lung cancer and found 789 articles from 1968 to 2023. Furthermore, we were interested in the availability of literature on senolytic medications. Therefore, we entered the term senolytic drug and received 525 publications from 2014 to the present. This discovery revealed that while cellular senescence is a phenomenon which has been known for several decades and is an extensively investigated issue, using anti-senescent treatment to heal various diseases does not have a lengthy history. On the other hand, we were interested in the study being conducted on cellular senescence biomarkers and discovered 44 papers from 1995 to 2023. Furthermore, we wanted to investigate the available clinical trials-based literature on senolytic drugs on clinical trials, and we found 7 articles in search engines. This means senolytic drugs should be screened further, and numerous clinical studies will be essential to establish senolytic drugs in primary therapy regimens.

3. Defining cellular senescence and the related molecular underpinnings

The principal and most noticeable hallmark of senescence is the fact that senescent cells reach a stable growth arrest that prevents damaged and aged cells from proliferating is the hallmark of senescence. Still, numerous other phenotypic changes linked to the senescent program are important to comprehending the pathophysiological roles of senescent cells (Salama et al., 2014). For example, senescent cells experience chromatin remodeling, metabolic reprogramming, and morphological alterations. They also release a chemical, primarily proinflammatory, known as the SASP. At first, cellular senescence was understood as a by-product of tissue culture. Abundant evidence, however, shows that senescent cells affect normal tissue homeostasis and aging and illness

(Munoz-Espin and Serrano, 2014). Furthermore, senescence can occur throughout the physiological development of an organism (Munoz-Espin et al., 2013; Storer et al., 2013), and it is also required for the phenomenon of tissue remodeling. Senescent cells, for example, are briefly induced during wound healing and play a role in wound resolution (Demaria et al., 2014; Jun and Lau, 2010). Senescence may also be a stress reaction that is protective. Senescence is best recognized for boxing a robust anticancer mechanism that inhibits the growth of preneoplastic cells, hence preventing cancers (Collado and Serrano, 2010). But aging and several illnesses related to old age are also caused by the buildup of senescent cells (Childs et al., 2015; van Deursen, 2014). The early evidence supporting the connection of senescence and aging came from studies of the build-up of senescent cells within aged tissues (Krishnamurthy et al., 2004). Senescence of stem and progenitor cells was proposed to impair tissue homeostasis as we age by preventing tissues from repairing and regenerating. Over the past ten years, there has been a notable expansion in our comprehension of the detrimental consequences of senescence on aging. This awareness has been made possible by two areas of research. First, a systematic identification of senescent cells in numerous diseases characteristic of old age has been made possible using transgenic models that facilitate the detection of these cells (Munoz-Espin and Serrano, 2014). Second, pivotal studies have led the development of genetic and pharmaceutical methods to specifically eradicate senescent cells, showing that senescent cells can be a causative factor in aging and associated illnesses (Herranz and Gil, 2018; van Deursen, 2014). One of the latest investigations examined the transcriptome profiles of senescence brought on by endothelium replication and senescence induced by TNF-α to comprehend these molecular alterations. The researchers have previously documented the pattern, routes, and processes linked to elevated transcripts during TNF-α-stimulated senescence. The group discovered several p53/p16-RB-E2F-DREAM targets inhibited in senescent cells yet necessary for the progression of mitosis, proliferation, DNA damage repair, maintenance of chromatin integrity, and synthesis of DNA. They demonstrate how the stable nature of the senescent arrest is influenced by the collective suppression of many target genes (Kandhaya-Pillai et al., 2023).

Senescent cells are characterized by numerous distinctive morphological and metabolic features. Identifying senescent cells in experimental model has proven possible by looking for these markers. A conspicuous Golgi apparatus, numerous larger nuclei in expanded cells, and occasionally vacuolated cytoplasm are the characteristic features of senescence phenotype (Fig. 1, Fig. 2). Senescent cells collect higher amounts of protein in the cytoplasm and nucleus, as demonstrated by a recent breakthrough technique to quantify protein levels using fluorescence microscopy (Becker and Haferkamp, 2013; De Cecco et al., 2011). Measuring the lysosomal β-galactosidase activity using a straightforward biochemical test is the most popular technique for identifying senescent cells and looking for distinctive morphological changes (Dimri et al., 1995). In senescent cells, the enzyme β-galactosidase, commonly called as senescence-associated beta-galactosidase (SA-β-gal), is more expressed and more active because of an expansion of the lysosomes (Lee et al., 2006; Narasimhan et al., 2022). Elevated β-gal activity is not a dependable indicator of senescence, as it can also be observed *in vitro* when cells are serum starved or over confluent, stimulated with TGF-β, heparin, or TPA therapy (Cristofalo, 2005; Lee et al., 2006; Severino et al., 2000; Untergasser et al., 2003; Yegorov et al., 1998). Because they mediate senescence and cell cycle arrest, the tumour suppressors p16INK4a and p21Waf1 are frequently employed as biomarkers. Since p16INK4a and p21Waf1 are not necessarily necessary for the initiation or upkeep of the senescence pathway, their combined predictive power is constrained. Senescence-associated heterochromatic foci (SAHF), or condensed heterochromatic areas, are a distinctive characteristic of senescent cells. These heterochromatin areas have been employed as markers of SAHF (Adams, 2007; Narita et al., 2003).

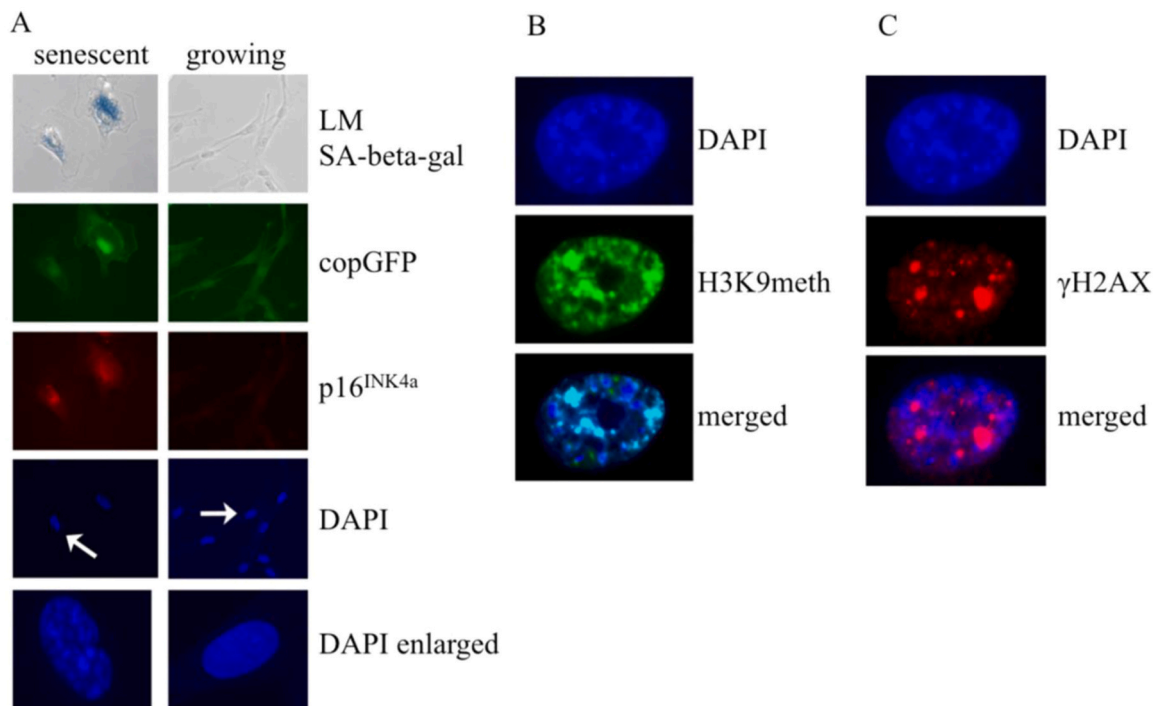The clinical proof of the occurrence of cellular senescence within in

Fig. 2. A) After N-RASQ61K induces senescence, larger cells with numerous or expanded nuclei are characteristic of the senescence phenotype, and there is a noticeable rise in SA-β-gal activity. Lentiviruses expressing copGFP control or N-RASQ61K were used to transduce human diploid fibroblasts (HDF). CopGFP co-expression was used to regulate transduction efficiency, which was continuously above 90%. Fifteen days after infection, the expression of p16Ink4a the condensation of chromatin (highlighted by the DAPI), and the emergence of elevated activity of SA-ß-Gal were assessed and measured. Arrows point to chromatin foci stained for DAPI in larger cells. B, C) HDF that were made to senesce using N-RASQ61K were stained with DAPI and an antibody against either γH2AX or H3K9meth to show DNA damage foci or senescence-associated heterochromatin foci, respectively. H2AX belongs to the H2A family of histones that forms foci at DNA break sites and is rapidly phosphorylated following DNA damage. The figure was reproduced with permission and without modification from Becker and Haferkamp (2013).

the tumoral lesions of cancer patients has been largely overlooked since there are presently no clear and all-encompassing biomarkers for senescent cells. This is due in part to the difficulty in identifying this evidence. Cellular senescence was initially thought to act as a protective process that would suppress the formation of tumors, stopping wounded cells from multiplying and becoming malignant, thereby preventing cancer. However, in the last two decades, there has been a heightened comprehension of cellular senescence as mechanism involved in the pathogenesis of tumors and in treatment response. Senescent cells are difficult to identify and measure in cancer patients in a therapeutic setting because there are no universally recognized markers for them (Gorgoulis et al., 2019; Kohli et al., 2021). Further, there has been a greater emphasis in the recent decade on cellular senescence in human tissue as a developing cancer trait (Gorgoulis et al., 2019; Hanahan, 2022), and efforts are being put to identify them in cancer patients appropriately. Increased activity of acidic lysosomal galactosidase represents a distinctive feature of cellular senescence because lysosomes enlarge in number and size with cellular aging (Debacq-Chainiaux et al., 2009; Evangelou et al., 2017; Robbins et al., 1970). Despite being discovered to be a non-universal indicator of cellular senescence, the quantification of the activity of SA-β-gal still regarded as the reference for detecting cells undergoing senescence. (Dimri et al., 1995). While SA-β-gal activity is lacking in the majority of quiescent and proliferating cells (Kohli et al., 2021), it is present in specific cell, *i.e.,* macrophages (Hall et al., 2016), bone marrow cells (Kopp et al., 2007), and *in vitro* when cells are serum starved or over confluent (Childs et al., 2015; Georgakopoulou et al., 2013; Severino et al., 2000; Yang and Hu, 2005). Furthermore, SA-β-gal is unnecessary for senescence since cells can become senescent even if they do not express it (Lee et al., 2006). To address the limitations of SA-β-gal, an analogue of biotin-linked Sudan Black B (SBB) was created to identify the accumulation of lipofuscin in cells undergoing senescence. (Evangelou et al., 2017). Lipofuscin

accumulates in the lysosomes of cells undergoing senescence because of age-related lysosomal dysfunction (Campisi, 2013; Gorgoulis et al., 2019; Hernandez-Segura et al., 2018). Unlike enzymatic SA-β-gal activity, lipofuscin is maintained in stable materials (Georgakopoulou et al., 2013). Therefore, the identification of cellular senescence in archival tissue samples such as formalin-fixed paraffin-embedded (FFPE) specimens can be achieved through utilization of SSB histochemical stain. (Evangelou et al., 2017). Due to the minute size of lipofuscin aggregates and the possibility of background contaminants being misinterpreted as SBB-positive lipofuscin aggregates, thereby reducing sensitivity, the test requires considerable interpretation expertise (Evangelou et al., 2017). In human liver tissue samples obtained by biopsy, endogenous lipofuscin—which has been associated with the development of chronic liver disease—can be identified using autofluorescence (Chang et al., 1999; Saif et al., 2020). With regards to cellular senescence, this can be identified in patient samples using lipofuscin autofluorescence. Most senescence-inducing events activate the pathways inhibiting the cell cycle such as p53/p21WAF1/Cip1 and p16INK4a, making them extensively used indicators of senescence (Paez-Ribes et al., 2019). Thus, in cellular senescence, lipofuscin autofluorescence may be used to identify senescence in patient samples (Alcorta et al., 1996; Beausejour et al., 2003; Kohli et al., 2021). The expression of p21WAF1/Cip1 indicates the onset of senescence, while expression of p16INK4a indicates a more mature and persistent senescence response (Kohli et al., 2021). However, non-senescent cells can express p21WAF1/Cip1 as a response mechanism to DNA damage (Karimian et al., 2016), and the genes encoding for p21WAF1/Cip1 (*CDKN1A*) and p16INK4a (*CDKN2A*) were not found in the transcriptomic signature of senescent cells (Hernandez-Segura et al., 2017). The detection of senescent cells without the need for a multi-marker approach is now supported by a potential proof-of-concept method for senescent cell identification using image flow cytometry that was

recently developed (Malavolta et al., 2022) (Fig. 3). This method measures autofluorescence and morphological parameters, utilizing machine learning and artificial intelligence algorithms (Malavolta et al., 2022). Reverse transcription-polymerase chain reaction (RT-PCR) (Kohli et al., 2021) can detect indirect markers of cellular senescence (Freund et al., 2012). Nevertheless, because both techniques need tissue dissociation, case-specific reference materials, and the inability to provide information about the spatial distribution of senescent cells inside the tissue, their therapeutic use for the treatment solid tumors is restricted. Even though many senescence core genes have been identified (Hernandez-Segura et al., 2019), the senescent transcriptome and proteome is dynamic and varied, depending on the tissue from which cells origin and on the specific stimulus that induced senescence (Coppe et al., 2008; Domen et al., 2022b; Hernandez-Segura et al., 2019). The essential gene expression patterns that need to be present to validate cellular senescence in specific tissues and diseases still need to be determined (Kohli et al., 2021). The SENCAN classifier is a machine learning-based gene expression classifier identifying senescence in cancer sample data. Transcriptome data was used to train the SENCAN classifier to identify senescent cancer cells. Regretfully, even though the SENCAN classifier can identify senescence in various cancer cells *in vitro*, it is still unclear how accurate it is in identifying senescence in cancer samples obtained *in vivo* (Jochems et al., 2021). To sum up, cellular senescence contributes to cancer development in two ways. Although its persistence and the accompanying SASP is known to contribute to the tumor microenvironment and assist later carcinogenesis stages, it can initially function as a tumor suppressor through the limitation of the proliferation of injured cells. Comprehending the context-specific impacts of cellular senescence is essential for creating focused and efficacious cancer treatments.

4. The double-edge sword nature of cellular senescence

Researchers have mostly focused on the negative connotations of senescent cells; however, despite their unfavourable reputation, senescent cells, or at least those with senescence-associated markers, can occasionally be advantageous. Senescence-related cells appear crucial for embryonic development but can also aid in skin, heart, and lung regeneration (Demaria et al., 2014; Feng et al., 2019; Munoz-Espin et al., 2013; Reyes et al., 2022). Contrarily, other research revealed that getting rid of senescent cells is advantageous and that they can even cause harm to those same tissues (Chaib et al., 2022b). How can scientists make sense of these seemingly incompatible outcomes? Ideally, the pro-inflammatory factors released by the senescent cell trigger immune system cells to eliminate it, which removes the SASP factors. In these situations, senescence serves as a means of not only stopping the damaged cell from proliferating but also communicating and coordinating its elimination and replacement. This mechanism may fail with aging and disease; senescent cells continue to bombard their neighbours with SASP molecules because they are not eliminated. This can have deleterious effects. For instance, cells treated with the cancer medication abemaciclib by Demaria's lab researchers had several characteristics of
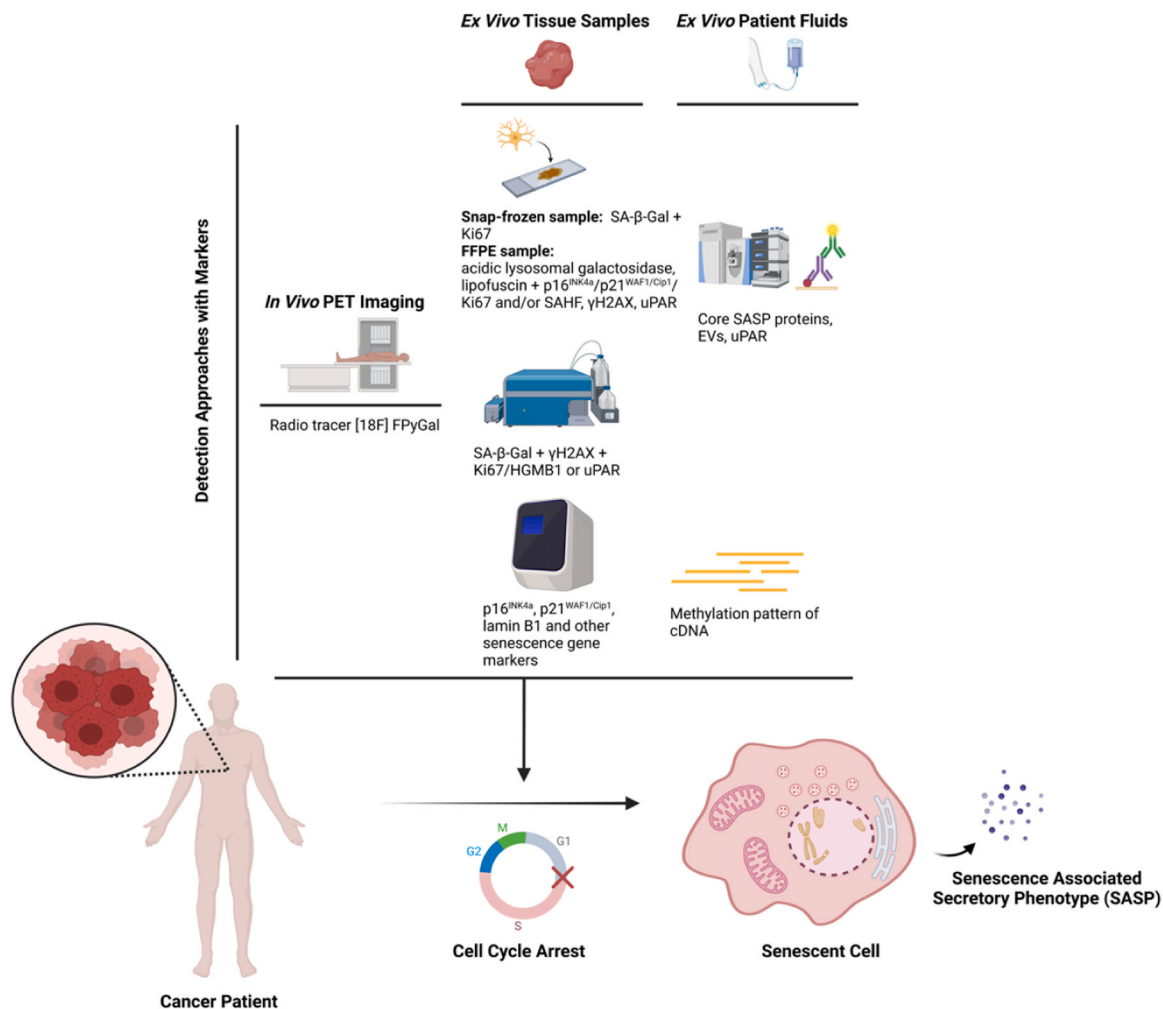

Fig. 3. Current approaches for identifying cellular senescence in both *ex vivo* and *in vivo* along with the markers of aging associated with cancer patients. Figure were drawn using BioRender.com.

senescence, but they also generated distinct molecules from other senescent cells. Demaria named the factors secreted as the p53-associated secretory phenotype (PASP) since it appeared that the transcription factor p53 oversaw this senescence program. Numerous proinflammatory signaling molecules typically generated by senescent cells were absent from the PASP; Demaria demonstrated that NF-κB controlled these inflammatory factors triggered by different cancer medications. Known as the NASP, this secretory profile seems more detrimental than the PASP (Wang et al., 2022a). We must precisely comprehend which cells are targeted by these many transgenic models and senolytics. The heterogeneity of senescent cells has huge clinical significance. Increasing knowledge of diverse communities may aid scientists in comprehending their involvement in different diseases and creating medications that specifically target those groups. Developing a more profound knowledge of the underlying biology of senescent cells is crucial for developing more focused and effective therapies, even in the face of the fact that first-generation senolytics are already undergoing human trials. Both beneficial and destructive senescence exist, and senolytics may target both. However, senolytics in the advantageous group have never been thoroughly examined, and the degree of similarity between the two senescence populations is unknown. Better knowledge of this, in my opinion, should enable us to develop more effective medications or, at the very least, identify those that target the harmful senescence.

5. Cellular senescence in lung cancer

With regards to lung cancer, as well as other types of cancer, we can distinguish three general types of senescence: replicative senescence, triggered by the reduction of telomeres length occurring upon multiple cycles of cell replication and is aimed at preventing DNA replication errors (Hansel et al., 2020); oncogene-induced senescence, which is triggered by activating genomic alterations occurring at the level of oncogenes (Zhu et al., 2020); and stress-induced senescence, which is considered a "premature" type of senescence that is activated upon exposure to stressors such as increased reactive oxygen species (ROS) levels, mitochondrial dysfunction, and damage to the DNA (Debacq-Chainiaux et al., 2016; Hansel et al., 2020). The latter form of senescence is particularly relevant, as it includes therapy-induced senescence which occurs when cancer cells are exposed to chemotherapy and radiation. This occurs in many types of cancer, including lung cancer (Ewald et al., 2010b). Regarding the pathophysiological significance of senescence, cellular senescence is a well-characterized homeostatic mechanism aimed at eliminating damaged cells from a tissue, minimizing the risk of cancerous transformation of pre-cancerous cells (Gorgoulis et al., 2019). On the other hand, emerging evidence revealed the cancer hallmark-promoting capabilities of cellular senescence across different types of cancer (Domen et al., 2022c), to the point that cellular senescence itself is now considered a hallmark of cancer (Hanahan, 2022). This paradoxical so-called "antagonistic pleiotropy" of senescence as a phenomenon having opposing anti-cancer and tumor-promoting effects (Campisi and d'Adda di Fagagna, 2007) has been thoroughly discussed in the previous section of this review. In the present section, we provide an updated characterization of the intricate relationship between cellular senescence and lung cancer.

5.1. Senescence role in lung cancer suppression

Senescent cells exhibit a condition of stable cell cycle arrest, which serves as an inherent impediment to the development of tumors. The senescence program known as OIS is primarily influenced by active oncogenes, with a particular emphasis on genes belonging to the RAS and BRAF families. The mitogenic stimuli overpower the growth control systems of non-malignant cells by stimulating abnormal signaling pathways and, specifically, unplanned DNA replication (Braig et al., 2005; Schmitt et al., 2022). The biological reaction to the detection of pro-mitotic activity is to initiate a rapid cessation of cell division, emphasizing the direct protective function of senescence as a mechanism to inhibit the genesis and progression of tumors. Research conducted on several rodent models, together with supporting data from tissue samples obtained from humans, has emphasized the tumor-suppressing function of OIS (Michaloglou et al., 2005; Schmitt et al., 2022). Crucially, the ability of senescence to control tumors is also strengthened by processes that occur outside of the cell. Senescent cells possess the capability to stimulate the occurrence of senescence in neighboring cells via exposure to the SASP as well as via direct cell-to-cell contacts. Consequently, they also restrict the spread of non-senescent premalignant or completely malignant cells in their immediate vicinity. SASP factors may induce apoptosis or necrosis in neighboring cells in some instances. As an example, TNFα, which is part of the SASP, can cause apoptosis in human-derived cancer cell lines, while IL-6 initiates apoptosis ex vivo in neoplastic T lymphocytes (Kim et al., 2010; Kuilman et al., 2008; Regis et al., 2009; Schmitt et al., 2022). Therefore, senescence functions as a protective barrier against tumors in living organisms, and the regulation of possible precursor lesions in the surroundings via SASP-mediated paracrine control further strengthens its resilience. There is a growing amount of information that confirms the significant function of senescent cells driven by oncogenes in enhancing cancer immunosurveillance. The immune system seems to be prepared to eradicate premalignant senescent cells. For instance, in mice, macrophages are recruited by the release of CCL2 and then activated with the support of CD4+ T cells (Kang et al., 2011; Regis et al., 2009). This process effectively eliminates NrasG12V-senescent premalignant hepatocytes. When HRAS[G12V]-induced senescent human cultured fibroblasts were injected into mice, it was observed that the super-enhancer landscape in these cells underwent global remodeling (Regis et al., 2009; Tasdemir et al., 2016). This was achieved by recruiting bromodomain-containing protein 4, a chromatin reader, to super-enhancer sites that are adjacent to the SASP gene. This process played a vital role in immunosurveillance. The suppression of the SASP program and the disruption of immune clearance of premalignant OIS cells were seen with inhibition of bromodomain-containing protein. The p53-p21 axis, which functions as a tumor suppressor, independently regulates the immune response to oxidative stress (OIS). Additionally, it facilitates communication between immune and senescent cells, likely via the SASP pathway (Schmitt et al., 2022; Ventura et al., 2007). In contrast to apoptosis-mediated tumor suppression, the investigation of senescence-mediated tumor suppression poses challenges in p53-dependent environments. This phenomenon has been examined through genetic analysis in a mouse model of Myc-driven lymphoma (Rane et al., 2002; Schmitt et al., 2022). In this model, the activation of macrophages by apoptotic remnants of lymphoma cells triggered macrophages to secrete senescence-promoting TGFβ, which subsequently triggered tumor-suppressive senescence within the lymphoma cell compartment. The rapid development of lymphoma in vivo may be attributable to two factors: the inhibition of lymphoma cells via apoptotic blockage mediated by Bcl2, or the incapability of macrophages through senescence triggered by Suv39h1 knockout, and the interference with TGF synthesis in macrophages. The migration of macrophages to tumor locations in vivo was seen because of pharmacological suppression or genetic blockade of H3K9me3 demethylases, which restored melanoma senescence as a response to the reactivation of p53 and/or p21 (Schmitt et al., 2022; Yu et al., 2018). In murine models of aggressive B cell lymphomas characterized by mutations dysregulating NF-κB, the activation of Card11 or Myd88 mutations resulted in an increased rate of lymphomagenesis, even if a significant number of E[1]-myc lymphoma cultured cells exhibited the enforcement of OIS. In contrast, these cells formed the immunogenic tumor population associated with senescence, which was specifically and directly eliminated by primed CD8+ T cells when PD-L1 was inhibited (Reimann et al., 2021; Schmitt et al., 2022). This study presented the first evidence of an immunogenic transition in senescent cells that is acknowledged by the

adaptive immune system, resulting in a postponement of tumor advancement in mice. Anticancer treatment may also exhibit immunogenic effects, namely in tumors that undergo therapy-induced senescence (TIS) because of various antineoplastic drugs. The concurrent administration of MEK and CDK4/6 inhibitors resulted in a significant induction of cellular senescence, together with NF-κB-mediated SASP, in a murine lung cancer model driven by Kras mutations (Ruscetti et al., 2018; Schmitt et al., 2022). The animals exhibited a subsequent activation of NK cell-mediated immunosurveillance, which led to tumor reduction, because of TNFα and ICAM1. In a mouse model of Kras-mutant pancreatic ductal adenocarcinoma, the simultaneous inhibition of CDK4/6 and MEK resulted in the manifestation of senescence phenotypes. Significantly, the secretion of SASP factors by senescent PDAC cells played a crucial role in the process of vascular remodeling. This remodeling enabled the transport of drugs and led to the accumulation of CD8+ T cells (. The cytotoxicity of these CD8+ T cells may be improved by inhibiting PD-1 *via* antibody-mediated mechanisms (Ruscetti et al., 2020; Schmitt et al., 2022).

5.2. The role of senescence in lung cancer progression

In the lungs, the presence of senescent cells has been firstly identified by Holz et al., who detected senescent fibroblasts in lung biopsies of emphysema patients (Holz et al., 2004). Successively, Tsuji et al. also identified a greater number of senescent type II alveolar and endothelial cells, defined as p16INK4a$^+$ / p21CIP1/WAF1/Sdi1$^+$, in lung biopsies of patients with emphysema, suggesting that cellular senescence might be the driving force underlying the abnormal cellular turnover at the root of the loss of alveolar cells observed in the lungs of emphysematous patients (Tsuji et al., 2006). Following these early reports, cell senescence is now regarded as a pivotal hallmark of diseases of accelerated aging, which include COPD and pulmonary fibrosis (Gulati and Thannickal, 2019; Jessamine et al., 2024; MacNee, 2016). This has the potential to explain the reason why the incidence of common COPD comorbidities such as type 2 diabetes, metabolic syndrome, and ischemic heart disease correlates with the age of COPD patients (Barnes, 2017). Another important comorbidity of COPD is lung cancer. COPD patients have a 6-fold higher chance of developing lung cancer compared to healthy individuals, and COPD is a well-known
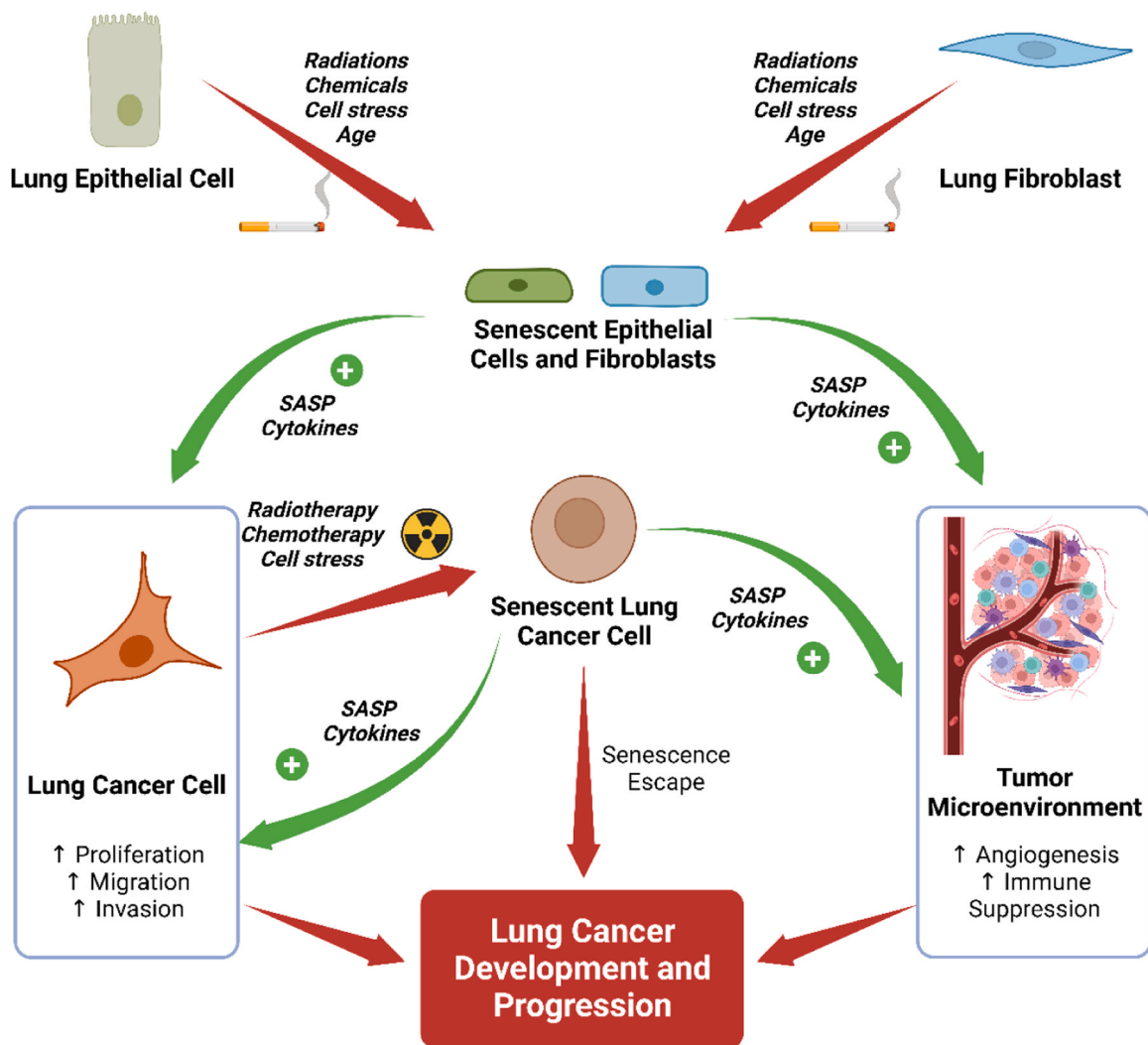

Fig. 4. Mechanisms through which cellular senescence is known to promote lung cancer development and progression. In healthy lung epithelial cells and fibroblasts, cell senescence is triggered by various factors, including age and exposure to chemicals and other DNA-damaging stimuli, and in lung cancer cells by the DNA damage and cell stress caused by chemotherapy and ionizing radiation therapy. Senescent cells produce senescence-associated secretory profile (SASP) cytokines, which promote lung cancer development and progression by (i) increasing proliferation, migration, and invasion capacity of non-senescent cancer cells and (ii) promoting angiogenesis and immune suppression within the tumor microenvironment. Finally, senescent cancer cells can escape senescence and resume proliferating, further contributing to lung cancer progression. Figure were drawn using BioRender.com.

independent risk factor of lung cancer development (Young et al., 2009). Considering that cigarette smoking is one of the most common factors underlying the development of both COPD and lung cancer (De Rubis et al., 2023b; Liu et al., 2022; Paudel et al., 2023), it could be argued that a greater incidence of lung cancer among COPD patients would be a mere reflection of a higher rate of cigarette smoking (Malyla et al., 2023b). However, numerous studies have shown that COPD is associated with a higher risk of developing lung cancer independently from the patient's smoking status (Calabro et al., 2010; Kishi et al., 2002; Mannino et al., 2003; Mehta et al., 2020; Wasswa-Kintu et al., 2005). This led some authors to hypothesize that COPD-related cellular senescence may represent one of the factors which contributes to the development of lung cancer among COPD patients (Kuznar-Kaminska et al., 2018a). Furthermore, considering that prolonged exposure to cigarette smoke is known to induce cellular senescence in lung fibroblasts and epithelial cells (Nyunoya et al., 2006; Paudel et al., 2022c), it may be argued that cellular senescence might represent another pathophysiological factor linking cigarette smoking and the incidence of lung cancer.

Cellular senescence can contribute to lung cancer pathogenesis in numerous ways, and the effect of different senescent cells may overlap in promoting this process. This is summarized in Fig. 4. First, an important contribution to lung cancer development could be provided by senescent healthy cells, such as epithelial cells and fibroblasts within the lung, *via* SASP components secretion (Hansel et al., 2020). These cells normally accumulate in adult lungs with age and, together with a reduced ability of the immune system to effectively remove senescent cells from the lungs, are among the main factors contributing to tissue aging and lung diseases correlated to advanced age (Xie et al., 2018). The exposure of lung tissues to cellular stressors further contributes to the increase of the number of senescent cells in the lung. These cellular stressors include activation of oncogenes, deactivation of tumor suppressors, DNA damage, and oxidative stress, commonly triggered by cigarette smoke and environmental pollutants (Nyunoya et al., 2006; Xie et al., 2018). Another factor contributing to increased cellular stress-induced senescence of lung cells is exposure to chemotherapy and ionizing radiation (Sriratanasak et al., 2022; Tabasso et al., 2019), which represent the mainstay therapeutic approach for most lung cancer cases (De Rubis et al., 2023b). The presence of senescent lung cells, such as lung fibroblasts, has been shown to affect adjacent cells, including pre-malignant and malignant cells, *via* the secretion of numerous components of the SASP that promote a pro-tumorigenic status, stimulating cell proliferation, EMT, and cell invasiveness (Hansel et al., 2020). IL-6 and IL-8 are among the main contributors to the promotion of the pro-tumorigenic status (Chien et al., 2011; De Rubis et al., 2024; Hansel et al., 2020; Wunderlich et al., 2017). The positive contribution of cells undergoing senescence to cancer development through the action of SASP components has also been demonstrated in a work by Kuźnar-Kamińska and colleagues, which showed that exposure of human bronchial epithelial cells to the serum of COPD patients resulted in an increase in senescence markers such as SA-β-gal activity, histone γ-H2A.X expression, and p21 expression, concomitantly with increased ROS production and augmented secretion of SASP factors including CXCL5, VEGF, and IL-8 in the conditioned medium (Kuznar-Kaminska et al., 2018b). Furthermore, the conditioned medium derived from these cells accelerated A549 human lung adenocarcinoma cells proliferation, migration, and adhesion to epithelial cells, highlighting the direct tumor-promoting activity of SASP factors in lung cancer (Kuznar-Kaminska et al., 2018b).

Besides the direct effects that SASP factors exert on lung cancerous or pre-cancerous cells, elements of the SASP also indirectly influence the tumor microenvironment, stimulating angiogenesis and developing a generally tumor-promoting and immune-suppressing environment (Gonzalez-Meljem et al., 2018). In a recent work, Matsuda and colleagues studied the role of TGF-β in the induction of an immune-suppressive microenvironment in lung cancer, showing that (i) in the presence of low oxygen concentration, typical of the tumor microenvironment, TGF-β induces a state of deep senescence in A549

cells; (ii): A549 cancer cells undergoing deep senescence secrete a specific signature of 14 SASP cytokines, and the presence of this signature correlates with remodeling of the tumor immune microenvironment towards an immune-suppressive phenotype in lung cancer patients, and (iii): NSCLC patients treated with immune checkpoint inhibitors whose tumors express the 14-gene SASP signature exhibit significantly poorer clinical outcomes in terms of progression-free survival compared to patients who do not extensively express the SASP signature (Matsuda et al., 2023). In another work, Lin and colleagues identified and validated a senescence-related signature (SRS) of 1164 senescence-related genes in lung adenocarcinoma, showing that patients with high expression of this signature exhibited elevated expression of SASP, together with an immunosuppressive phenotype. Furthermore, the SRS status was prognostic of clinical outcomes (Lin et al., 2021). Furthermore, the prognostic potential of senescence-associated gene expression signatures was also demonstrated in a report by Domen and colleagues, who showed that the presence of a immunohistochemical signature of four markers (lipofuscin, Ki67, p21WAF1/Cip1, and p16INK4a) correlated with overall survival and disease-free survival in NSCLC patients (Domen et al., 2022a).

Finally, another indirect mechanism used by cellular senescence to contribute to lung cancer development, and particularly to tumor reoccurrence/progression, involves tumor escape from senescence (Evangelou et al., 2023). Although senescence is considered an irreversible phenomenon whereby cells exit from the cell cycle and cannot resume it, cancerous cells may acquire the ability to escape the senescent state and resume proliferation upon accumulation of advantageous mutations (Evangelou et al., 2023; Saleh et al., 2019). This phenomenon has been associated with cancer stem cells (Sabisz and Skladanowski, 2009). In a study conducted on p53-null and p16-deficient H1299 human NSLCL cells, Roberson and colleagues showed that about 1 in 10^6 cells that enter cellular senescence upon camptothecin treatment acquire the ability to resume the cell cycle, retaining a gene expression signature which is more representative of senescent cells compared to that of parental cells, and that this escape was mediated by the overexpression of Cdc2/Cdk1 (Roberson et al., 2005). The investigator also observed increased expression of this cyclin-dependent kinase in human samples following chemotherapy, proposing that this type of escape may contribute to lung cancer reoccurrence (Roberson et al., 2005). More recently, in an *in vitro* investigation on human and murine lung cancer cells, hypoxia was found to promote cell escape from cisplatin-induced senescence, and this was reversed by treatment with the autophagy inhibitor hydroxychloroquine, thus suggesting the involvement of autophagy in senesce escape (Olszewska et al., 2021). Furthermore, Deng and colleagues showed, using NSCLC organoid models, that a subset of cells expressing high levels of DNA methyltransferase 3 A (DNMT3A) exhibited resistance to tyrosine kinase inhibitor treatment by entering an early, reversible senescent-like state-mediated by the overexpression of inhibitor of apoptosis (IAP) proteins, further highlighting the role played by senescence in lung cancer progression and reoccurrence (Deng et al., 2023).

Considering the fact that chemo- and radiotherapy are known to induce cell senescence, and the prominent role played by cellular senescence in the promotion of lung cancer progression, therapy-induced senescence is considered a phenomenon that facilitates neoplastic growth, reducing the efficacy of these therapeutic approaches (Ewald et al., 2010a; Wang et al., 2020). This provides a solid rationale for developing anti-senescence drugs such as senolytics and senomorphics, discussed in a later section of the present review.

6. Therapeutic interventions targeting cellular senescence

Therapeutic approaches aimed at addressing cellular senescence have attracted considerable attention owing to the dual function that senescence serves in the context of cancer. Although senescence may inhibit the development of tumors by stopping the growth of damaged

cells, it can also facilitate the advancement of tumors *via* other mechanisms, such as the release of pro-inflammatory chemicals. Senolytics are pharmaceutical substances that specifically trigger apoptosis, or the death of cells, in senescent cells. The objective of senolytics is to mitigate the pro-tumorigenic consequences of senescence and facilitate tissue regeneration by eliminating senescent cells (Wissler Gerdes et al., 2020). Dasatinib and quercetin, which are senolytic medicines, have shown potential in preclinical investigations for many forms of cancer, including lung cancer (Islam et al., 2023; Nambiar et al., 2023). These pharmaceutical agents have a specific affinity for senescent cells while minimizing harm to healthy cells, making them very appealing contenders for the treatment of cancer. Reversing or avoiding the senescent phenotype is another strategy. One approach to doing this is by influencing signaling pathways that are associated with aging, such as the p53 and p16 pathways (Rubin de Celis and Bonner-Weir, 2023). Researchers are looking at small-molecule inhibitors that target these pathways to see whether they might restore cell proliferative ability and reverse senescence. For example, MDM2 inhibitors for p53 and CDK4/6 inhibitors for p16 are examples of such inhibitors (Shangary and Wang, 2009). Nevertheless, it is crucial to thoroughly assess how reversing senescence impacts tumor development since it has the potential to enhance the growth of pre-existing malignancies. Since SASP contributes to the pro-tumorigenic effects of senescence, inhibiting SASP factors represents another therapeutic strategy (Lau and David, 2019). This can be achieved using anti-inflammatory agents or specific inhibitors targeting key components of the SASP, such as IL6 and IL-8. By dampening the inflammatory milieu in the tumor microenvironment, SASP inhibition may help mitigate the tumor-promoting effects of senescence. Harnessing the immune system to target senescent cells represents another promising approach (Takasugi et al., 2022). Immunotherapies, such as immune checkpoint inhibitors, aim to enhance the immune response against cancer cells, including senescent cells. By activating cytotoxic T cells, these therapies can help eliminate senescent cells and prevent their accumulation in the tumor microenvironment. Additionally, strategies to enhance the phagocytic activity of immune cells, such as macrophages, may facilitate the clearance of senescent cells (Takasugi et al., 2022). Given the complex interplay between senescence and tumor progression, combination therapies targeting multiple aspects of senescence and cancer biology may offer the most effective approach. For example, combining senolytics with conventional chemotherapy or immunotherapy could enhance treatment efficacy by targeting both senescent and proliferating cancer cells (Bhatt et al., 2024; Bousset and Gil, 2022a). By creating unique mice that were meant to respond to a chemical stimulus, researchers initially tested the theory of specifically targeting senescent cells to trigger apoptosis, which caused the cells to undergo apoptosis and die (Baker et al., 2011). Eliminating these death-resistant cells increased the mice's longevity and quality of life. It sparked a hunt for medications and treatments that would accomplish the same goal without modifying the test subject. These have been shown to express more pro-survival genes, which gives them a strong resistance to apoptosis (Zhu et al., 2015). The quest for medications that might specifically target these cells began, and soon after, the first medications that did so were found to target these "death-resistant" cells. Senolytics is the term given to this novel family of medications (Zhu et al., 2015). Subsequent research revealed that age-related deterioration and poor health might be slowed down in mice by eliminating only thirty percent of the cells (Tchkonia et al., 2013; Zhu et al., 2014, 2015). This supports the idea that eliminating senescent cells therapeutically might help treat some age-related illnesses. These cells appear to be at least largely responsible for vascular aging, and their elimination enhances vascular health (Roos et al., 2016). Additionally, evidence points to their possible involvement in osteoarthritis (Roos et al., 2016), skin aging (Velarde et al., 2013), type 2 diabetes (Palmer et al., 2021), atherosclerosis (Childs et al., 2016; Xu et al., 2017), and respiratory disease (Paudel et al., 2022a). Several industries are progressing with senolytic therapies; some are undergoing clinical trials to translate mice

studies into humans. The therapeutic removal of senescent cells using a senolytic agent or blocking their SASP to slow down or prevent aging disorders are potential fields of therapy. Other approaches to managing senescent cells include boosting the immune system to drive them out or, more recently, modifying the SASP *via* signaling pathways like KDM4 to lessen its deleterious effects (Zhang et al., 2021a). One promising new treatment avenue to control senescence and lessen its role in age-related illnesses, such as cancer, is KDM4 targeting (Wu et at., 2022). The following section will describe senescence cell targeting drug therapies. In general, therapeutic treatments that specifically target cellular senescence have potential for the treatment of cancer, including specifically lung cancer. Nevertheless, further investigation is required to strategically improve treatment approaches, mitigate possible adverse reactions, and augment therapeutic effectiveness within clinical contexts.

6.1. Senolytics

Senolytics are a category of drugs or substances that specifically focus on and remove senescent cells from the body. Senolytics function by selectively triggering apoptosis, a process of programmed cell death, in senescent cells, thereby eliminating them from the body (Hickson et al., 2019; Rad and Grillari, 2024). Animal models have demonstrated that the targeted elimination of senescent cells improves several aspects of well-being and extends longevity. Senolytics have the potential to enhance the performance of aging tissues and organs by eliminating senescent cells, thus restoring some characteristics of young physiology. Senescent cells have a role in the emergence of age-related illnesses, including cancer, heart disease, and neurological disorders (Nehlin, 2023). By eliminating these cells, senolytics have the potential to postpone the initiation or advancement of various diseases. Studies conducted on animal models have shown that the administration of senolytics may increase the duration of life and enhance health span, which refers to the time of life that is devoid of severe illness and incapacity. Senolytics have the potential to increase the overall quality of life of aging adults by enhancing tissue function and postponing the development of age-related illnesses. (Fig. 5). Due to the activation of pro-survival and anti-apoptotic pathways, senescent cells exhibit a higher degree of resistance to apoptosis than their counterparts in good health, even in the presence of cellular stressors. One of the most popular senolytics strategies involves blocking pro-survival pathways, such as PI3K/AKT pathway and the BCL-2 protein family. In a 2021 study, Novais et al. discovered that age-dependent intervertebral disc degeneration in mice was lessened by the long-term treatment of the senolytic medications quercetin, a naturally occurring flavonoid, and dasatinib, a tyrosine kinase inhibitor. After receiving the treatment combination for nearly two years, mice showed fewer senescent-related biomarkers, such as matrix metalloproteinase (MMP)-13, p16Ink4a-positive senescent cells, and SASP molecules like interleukin (IL)-6, as well as a decreased incidence of disc degeneration. Crucially, the extracellular matrix (ECM) at the spinal disc was maintained in drug-treated animals by having a greater collagen I and chondroitin sulfate composition. Nevertheless, this treatment effect was limited to mice between the ages of 6 (young) and 14 (middle-aged), not 18 (elderly) months, indicating an age-dependent effectiveness. Because of the immune system's ability to eliminate senescent cells, there is growing interest in using modified immune cells for senolytic reasons, in addition to using senolytic medications. For example, it has been discovered that CD4+ T lymphocytes collaborate with monocytes and macrophages to eliminate senescent hepatocytes. It has also been demonstrated that natural killer cells aid in removing senescent-activated stellate cells from the liver, which results in the resolution of fibrosis. Although senolytic medicines, including BCL-2 family inhibitors, have demonstrated encouraging results in eliminating senescent cells, clinical translation is still restricted due to safety concerns. Senolytics are usually medications used to treat other conditions that have been repurposed to destroy senescent cells, which is
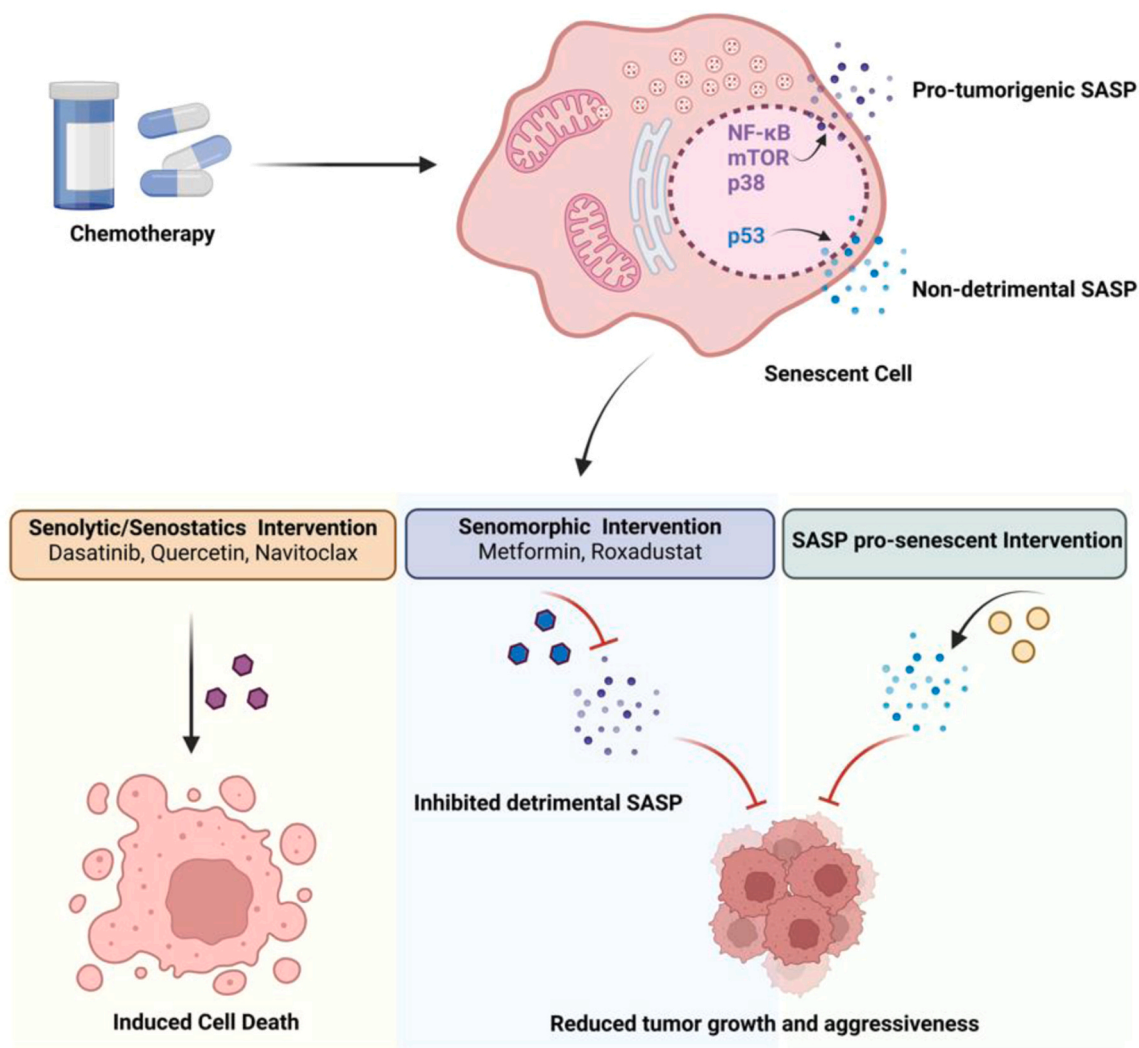
Fig. 5. Approaches for targeting senescent cells in cancer. (a) Senolytic therapies selectively eliminate senescent cells, which play a detrimental role in tumor formation. (b) Senomorphic therapy targets the suppression of certain senescence-associated secretory phenotype (SASP) factors that support tumor growth, along with signaling pathways like NF-κB, mTOR, and p38, which regulate SASP. (c) Cancer treatments promoting senescence may stimulate the production of SASP factors that are less harmful, resulting in a non-deleterious senescence phenotype. Abbreviations used in above diagrams: DDR, DNA damage response; DSB, double-strand break; dsDNA, double-stranded DNA; SASP, senescence-associated secretory phenotype; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK binding kinase 1; IRF3, interferon regulatory factor 3; IFN, interferon. Figure were drawn using BioRender.com.

one of the main causes. Senescent cells were discovered to be very susceptible to senolytics, even though they were employed for other purposes. The issue with this is that many of these medications have side effects. "Therefore, significant side effects are likely to be associated with current senolytics, which would severely restrict their clinical use." One of the best examples of a senolytic chemical displaying panolytic action is Navitoclax, which induces off-target death in cell types other than senescent cells. Clinical studies discovered that navitoclax causes non-senescent cells, such as neutrophils and platelets, to undergo apoptosis, which causes neutropenia and thrombocytopenia (Mohamad Anuar et al., 2020). Because of the hazards that are linked with it, the FDA has not cleared it for clinical usage. Researchers are now investigating the development of second-generation senolytics, which are more selective towards senescent cells than healthy cells, to improve the specificity of drug delivery. Materials targeting senescence biomarkers have been developed by researchers for this aim. Mesoporous silica nanoparticles encapsulating cargo were created by Agostini et al. and capped with galacto-oligosaccharides, a substrate of SA-β-gal that functions as a molecular gate. It was discovered that cells with strong SA-β-gal activity, which mediates the enzymatic hydrolysis of the cap,

preferentially release the cargo (Agostini et al., 2012). They also suggested in their study that senescent cells `modified biophysical phenotype may influence intracellular medication delivery and can be used to influence drug delivery. Furthermore, they recommend that more focused delivery towards senescent cells might be accomplished by adjusting the parameters employed in these approaches depending on cellular biophysical features (Agostini et al., 2012). Beyond biochemical methods such as nanoparticles, various physical methods of membrane disruption, such as electroporation and high aspect-ratio nanostructures, are also included in the category of intracellular delivery approaches. The use of biophysical markers to offer a configurable physical foundation for targeting may be more advantageous, especially for physical delivery systems when targeting biomolecular markers will be difficult (Li et al., 2023). Biophysical and biomolecular markers can be used in tandem further to improve the selectivity of intracellular delivery by Chen et al. (2019) nanoparticles. Senescent cells maybe more receptive to the absorption of stiffer nanoparticles that decrease the energy barrier for endocytosis uptake if their membranes are more rigid. The development of senolytics is becoming ever more important as the population ages. Though still in its infancy, the rapid advancement

towards second-generation senolytics to improve their safety and efficacy for therapeutic application is encouraging (Park and Shin, 2022). More knowledge of the traits and behavior of senescent cells will be necessary, and this fits in well with several newly developed analytical techniques, including next-generation biophysical cytometry and single-cell RNA sequencing. This will lead to the development of more focused and selective senolytics, which would improve human longevity and health. Dasatinib, Quercetin, Fisetin, and Navitoclax were the first senolytic medications found employing a hypothesis-driven approach. Senescent cells accumulate with age and at the sites of various chronic conditions, including diseases that represent most of the morbidity, mortality, and health-care costs (Kirkland and Tchkonia, 2020). The most hazardous senescent cells have an increased expression of anti-apoptotic pathways and are resistant to apoptosis, which allows them to live while eradicating nearby cells. Senolytics cause apoptosis in senescent cells with a tissue destructive SASP by momentarily inhibiting these SCAPs. Senolytics can be given as a "hit-and-run" method, as senescent cells take weeks to reaccumulate (Wissler Gerdes et al., 2020). In preclinical models, senolytics postpone, prevent, or improve frailty, cancers, and issues related to the heart, brain, liver, kidneys, musculoskeletal system, lung, eyes, blood, metabolism, and skin (Kirkland and Tchkonia, 2020). They can also mitigate the effects of radiation, organ transplantation, and cancer therapy. Senolytics were found to be promising to alleviate over 40 conditions in preclinical studies and offer a new avenue for treating age-related dysfunction and diseases (Kirkland and Tchkonia, 2020). This is expected for agents that target the fundamental aging mechanisms that are 'root cause' contributors to multiple disorders. In early pilot studies, senolytics appear to decrease inflammation, lessen senescent cells, and improve human frailty. Clinical studies are being conducted or will soon begin for the following conditions: diabetes, idiopathic pulmonary fibrosis, Alzheimer's disease, COVID-19, osteoarthritis, osteoporosis, eye disorders, bone marrow transplant, and children cancer survivors (Kirkland and Tchkonia, 2020). Senescence can be either advantageous or destructive. And there's a worry that senolytics could target both desired and normal cells. However, senolytics in the advantageous group have never been thoroughly examined, and the degree of similarity between the two senescence populations is unknown. The investigation of senolytics is now in its preliminary phase, and more research is required to comprehensively comprehend their impacts and possible adverse consequences in people. Nevertheless, they provide a hopeful method for tackling the root causes of aging and disorders associated with old age (Hickson et al., 2019).

6.2. Senomorphics

Senomorphics, also known as senostatics, are chemicals that prevent senescence without killing senescent cells or decrease the harmful effects of SASP. Most senomorphics work by blocking SASP transcriptional regulators, including ataxia telangiectasia mutated, p38 MAPK, JAK/STAT, NF-κB and mTOR pathways (Zhang et al., 2021b, 2023). Senomorphics may have the disadvantage of needing continuous administration, whereas senolytics require sporadic administration because of their hit-and-run action (Kirkland and Tchkonia, 2020). Fascinatingly, several medications have been demonstrated to have both senomorphic and senolytic effects, contingent upon the kind of cell and dosage administered. For example, procyanidin C1, a polyphenolic flavonoid produced from grape seed extract, is senomorphic at low doses but senolytic at larger ones (Xu et al., 2021; Zhang et al., 2022).

6.3. Galactose-based prodrugs

Lysosomal galactosidase activity is greater in senescent cells, and this enzyme has been utilized as a senescence marker (senescence associated galactosidase activity). Using this enzyme activity, galactose-based prodrugs can be created by covalently attaching galactose or acetyl galactose groups to a cytotoxic molecule. Following cellular absorption, senescent cells exhibit preferential metabolism of the fused galactoside prodrugs, which release active cytotoxic drugs and cause senescent cells to be selectively killed. Several prodrugs based on galactose, including SSK1, prodrug A (JHB75B), and Nav-Gal (Cai et al., 2020; Gonzalez-Gualda et al., 2020; Guerrero et al., 2020; Zhang et al., 2022), have proved the feasibility of this technique. Surprisingly, the cytotoxic moieties of these prodrugs are all chemotherapeutic chemicals, including gemcitabine (Cai et al., 2020), duocarmycin (Guerrero et al., 2020), and 5-fluorouracil and navitoclax (Gonzalez-Gualda et al., 2020). Theoretically, the prodrug approach enhances the specific demise of senescent cells relative to proliferative and non-senescent normal cells. For instance, Nav-Gal has less platelet toxicity than the original drug Navitoclax (Gonzalez-Gualda et al., 2020).

6.4. Proteolysis-targeting chimera (PROTAC)

A PROTAC (Proteolysis-Targeting Chimera) is a kind of molecule that is developed for targeted protein degradation. In contrast to typical medications that block or alter protein function, PROTACs operate by triggering the breakdown of target proteins within cells (Burslem and Crews, 2020; Zhang et al., 2022). Three parts make up PROTACs, which are trifunctional compounds: an E3 ligase recruitment ligand, a ligand that attaches to a target POI, and a flexible linker that connects the two ligands. As a result, an E3 ligase may create a stable ternary complex with a PROTAC and a POI (Bondeson et al., 2018), resulting in the POI's ubiquitination and proteasomal destruction. PROTACs are an attractive method for developing senotherapeutics because of their many benefits, which include higher potency, more specificity, longer activity, and reduced toxicity (Lai and Crews, 2017). There are currently several PROTAC-based anti-senescent therapies available. For example, PZ15227 was created by coupling the anti-senescent drug navitoclax (ABT-263) to the cereblon (CRBN) E3 receptor, which is hardly expressed in healthy platelets (He et al., 2020). As expected, PZ15227 outperformed navitoclax regarding efficacy and potency in clearing senescent cells while producing less cytotoxicity to platelets (He et al., 2020). An additional instance is the binding of the BET inhibitor OTX015 to the E3 ligase binder pomalidomide, which results in the production of ARV825, a novel bifunctional PROTAC that functions as a BET family protein degrader (Wakita et al., 2020). ARV825 increased BRD4 degradation and demonstrated significant senolytic action in senescent cells at nanomolar concentrations, as well as the ability to eradicate senescent cells in mice models (Wakita et al., 2020). Other SCAP targets can predictably be used to produce new PROTAC senotherapeutics. PROTACs, on the other hand, have a greater molecular weight than typical small molecules, which means they may have less optimal pharmacokinetic features and may be inappropriate for oral administration. Another factor to consider in bivalent PROTAC toxicity studies is that they may display reduced degradation at high doses, a phenomenon known as the hook effect (Bondeson et al., 2018; Burslem and Crews, 2020). Resistance to PROTAC effects can also emerge if the POI or the core components of E3 ligase complexes are altered (Jiang et al., 2021; Zhang et al., 2022, 2019a).

6.5. Nanocarriers

Nanotechnology allows for the regulated release and distribution of various payloads to targeted cells because of its tunable physiochemical properties. Because of this, it is a technology that facilitates the detection and treatment of cancer (Imran et al., 2022; Jha et al., 2023, 2022; Maharjan et al., 2019; Panthi et al., 2023). The drugs, decoy oligonucleotide, or chemical compound loaded in nano-formulations show better efficacy than its pure compound (without loading into nano-formulations) against lung cancer (De Rubis et al., 2023a; Kannaujiya et al., 2023; Kumari et al., 2023; Malyla et al., 2023a; Manandhar et al., 2023; Paudel et al., 2022b, 2024). Many nanomaterials

have been specifically designed to act as nanocarriers for detecting senescent cells and curative therapies, most notably nanoparticles (NPs) (Jha et al., 2024; Morsli et al., 2022). Because of their vast surface area, nanoparticles (NPs) may be covalently modified with various targeting groups, including peptides, antibodies, and nucleic acids. Additionally, the special SA-β-gal may be used to create NPs conjugated with galacto-oligosaccharides, which will aid in preferential trafficking into senescent cells. NPs were loaded with doxorubicin and navitoclax, for instance, to create the senolytic nanoparticles GalNP(dox) and GalNP (nav) (Munoz-Espin et al., 2018). These NPs selectively killed senescent cells while sparing normal healthy cells after cellular uptake by endocytosis, fusion with lysosomal vesicles, and hydrolysis of the galacto-oligosaccharide coat by SA-β-gal (Munoz-Espin et al., 2018). It has also been reported that modifying self-assembling peptides with -galactose groups enable senescent cells to absorb them. This is followed by a particular cleavage of SA-β-gal, which leads to an enzyme-directed process of self-assembly that creates intracellular nanofibers and hydrogels, ultimately inducing death in senescent cells by initiating their apoptotic pathways (Xu et al., 2019). An additional layer of selective NP delivery to senescent cells is added when lactose encapsulation and the senescent surfaceome are combined. For instance, rapamycin was encapsulated in calcium carbonate NPs coated with lactose and paired with a monoclonal antibody directed against CD9, a protein that is overexpressed in some senescent cells. In aged human dermal fibroblasts, the dual-functional CD9-Lac/CaCO3/Rapa NPs showed significant absorption by senescent cells *via* surface recognition and anti-senescence actions upon intracellular drug delivery (Brack et al., 2007; Thapa et al., 2017). Molecularly imprinted nanopolymers (nanoMIPs) (Dar et al., 2020; Zhang et al., 2019b) were also developed to target cellular senescence *via* the 2-microglobulin (B2M) epitope, which is found on another senescent surfaceome protein (Althubiti et al., 2014). Dasatinib-loaded B2M nanoMIPs displayed selective death of senescent cells over growing cells and enhanced potency over dasatinib alone, reducing dasatinib off-target toxicity (Ekpenyong-Akiba et al., 2019). Further, Molybdenum disulfide nanoparticles (Ke et al., 2018), zinc oxide nanoparticles (Wiesmann et al., 2021), and quercetin surface-functionalized magnetite Fe_3O_4 nanoparticles (Lewinska et al., 2020) are examples of other NPs. They were not, however, functionalized to target senescent cells preferentially.

6.6. Immunotherapy based on the senescent cell surfaceome

The immune system plays a vital role in the removal of senescent cells. Furthermore, in physiological settings, senescent cells can initiate both innate and adaptive immune responses by secreting SASP factors or boosting certain surface antigens to attract immune cells for clearance, such as neutrophils, macrophages, T lymphocytes, and NK cells (Burton and Stolzing, 2018; Sagiv and Krizhanovsky, 2013; Zhang et al., 2022). Immunosenescence results in decreased immunosurveillance. To bypass recognition from the immune system, senescent cells may also develop immune suppression mechanisms. These could result from tissue senescent cell accumulation and related tissue dysfunctions. As a result, an alternative senotherapeutics approach is immunotherapy, which is predicated on enhancing immune cells' capacity to attack Senescent cells. Senescent surfaceome proteins are preferentially upregulated on the surface membrane of senescent cells and are typically utilized by such immunotherapies. These proteins include urokinase-type plasminogen activator receptor (uPAR), glycoprotein nonmetastatic melanoma protein B (GPNMB), B2M, dipeptidyl peptidase 4 (DPP4) CD9 receptor, NOTCH receptors, and others (Ge et al., 2021; Hoare et al., 2016). The technique of genetically modifying T cells to generate a synthetic receptor antigen that aids in recognizing and destroying specific cancer cells is known as chimeric antigen receptor (CAR) T cell therapy. Using CAR-T cells as senolytics instead of small drugs has several advantages, primarily their high durability and effectiveness. The main challenge is the high level of heterogeneity of senescent cells.

Their dependencies, the surface molecules they upregulate, and the soluble chemicals they generate vary significantly depending on the kind of cell and senescence trigger (Kim et al., 2017). This makes the search for senolytic techniques that work well in every situation exceedingly challenging. In a recent study, senescent surface protein uPAR was recognized by CAR T cells, which were then reprogrammed to precisely target and eradicate senescent cells in various *in vitro* and *in vivo* senescence settings. CAR NK cells or CAR macrophages will be produced in a similar way to boost cytotoxic activity against senescent cells (Poblocka et al., 2021; Suda et al., 2021; Zhang et al., 2022). In conclusion, senescent cell surfaceome-based immunotherapy shows potential for treating age-related illnesses. More study is required to better understand the biology of senescent cells, pinpoint certain surface indicators, and create secure and efficient immunotherapies that specifically target senescent cells.

6.7. Chemotherapy/Radiotherapy–aging– and senolytic drug

According to literature, cancer is becoming a more treatable illness, and over the past several decades, the death rate from the disease has significantly decreased in industrialized nations (Siegel et al., 2023). Approximately 2 million individuals in the United Kingdom have survived cancer, and many of them experience early memory loss and accelerated onset of several illnesses that mimic premature aging. Regrettably, there is no recognized therapy for these conditions nor a cure. Efforts to enhance the quality of survival following successful cancer treatment have started to change in several disciplines, as many cancer types now have high cure rates. This is essential because long-term cancer survivors in childhood and adulthood experience a variety of detrimental health and quality of life changes that raise their risk of frailty, multi-morbidity, and death relative to the general population (Morrison-Jones and West, 2023). It is believed that DNA-damaging cancer medicines, which kill cancer cells but also harm healthy cells, are the root cause of early aging in cancer survivors (Torgovnick and Schumacher, 2015). Therapy-induced cell senescence has been identified as one of the several biological mechanisms that have been suggested as the drivers of this. Senolytics are an intriguing breakthrough in the biology of aging because they target the survival processes of senescent cells, which are missing in normal cells and destroy them (Prasanna et al., 2021). In mice, they have been demonstrated to delay or even cure age-related illness or incapacity. In the recently published research, the scientists examined the effects of a few well-known first-generation senolytics (Dasatinib + quercetin and Navitoclax) in a mouse model of early aging brought on by whole-body radiation. "Premature frailty is a well-documented, clinically important problem of long-term cancer survivors, so we focused on it as a primary outcome," the authors said (Fielder et al., 2022). In irradiated male mice, the scientists also evaluated a 10-week course of metformin, a senostatics drug rather than a senolytic one. The mice recovered from the therapy one month after finishing radiation treatment, but before the treatment was initiated, there was significant evidence of radiation-induced senescence in different tissues (Fielder et al., 2022). This study demonstrated that animals given senolytic medications shortly after radiation therapy did not experience early aging, and even those treated after they began exhibiting early aging symptoms also had better health outcomes later. The authors concluded that the results demonstrate the positive effects of a short-term senolytic intervention, even when implemented at an advanced age, on the early development of frailty and cognitive impairment caused by radiation exposure (Fielder et al., 2022). Metformin-related study results were also positive. They observed that metformin and senolytics were equally effective. These data suggest that multiple domains of radiation-induced premature aging in mice are rescued by a relatively brief treatment with the senostatics metformin, and the effects last for at least 10 months after the intervention is stopped. The researchers concluded that brief senolytic or senostatics interventions could effectively rescue premature

progressive frailty and accelerated aging induced by whole-body irradiation over a significant part of the life history in male mice. These findings suggest a call for more work to be done to convert senolytic and senostatics therapies into adjuvant treatment for patients who have long-term tumor survivorship.

6.8. Extracellular vesicles from stem cells

Extracellular vesicles (EVs) are membrane-bound, microscopic bubbles that cells release through intercellular communication (Malyla et al., 2023c; Paudel and Kim, 2020). These bubbles can contain a variety of molecular cargo, including proteins, DNA, or RNA (Sharma et al., 2022). Many studies have shown EVs to mimic many of the benefits of cellular therapies, including stem cell treatments, and as a drug delivery system (Manandhar et al., 2022; Weng et al., 2021). To combat cellular senescence, the researchers employed EVs made from human embryonic stem cells (ESC). ESCs are considered a powerful therapeutic tool, but as the authors of the paper point out in the introduction, immunological rejection, tumorigenicity, and ethical concerns restrict their application. It would be a promising way forward if we could cultivate ESCs and employ the EVs they produce in the same way. First, the researchers verified that EVs produced from ESCs can slow cellular senescence *in vitro*. A condition known as "cellular senescence" occurs when a cell ceases to divide because of one or more senescence-inducing stresses. These cells release substances that can cause nearby cells to become inflammatory and senescent. Although senescence plays a part in wound healing and development, it is generally acknowledged that excessive senescence associated with aging is detrimental. The researchers chose mouse embryonic fibroblasts (MEF) that had accumulated seven divisions as their in vitro senescence model because cells become senescent after a specific number of divisions (Ben-Porath and Weinberg, 2004; Wallis et al., 2020). Not only did EV treatment improve p21 and β-galactosidase levels, but it also improved senescence-typical morphology—the flattening and shapelessness of cells—among other senescence indicators. Furthermore, EVs raised the proliferative cell percentage to values like young control cells. So, what cargo were those EVs transporting, and what aspect of it oversaw slowing down MEF senescence? (Ben-Porath and Weinberg, 2004; Wallis et al., 2020) Prior studies have shown that EVs are rich in microRNA (miRNA), which are small RNA snippets, usually 22 nucleotides or less. Even though miRNAs are small, they may have a significant impact (Singh et al., 2024). For example, they can control the creation of proteins by suppressing messenger RNA (mRNA). According to one study, EVs produced by healthy cells in the hypothalamus could slow down the aging process, and this action is partly mediated by miRNA detected in those EVs. As a result, the researchers concentrated on miRNAs and sequenced the EVs' miRNAs. In ESC-EVs, 128 miRNAs were elevated, and 110 were downregulated compared to mouse fibroblasts (Yu et al., 2023). The researchers closely examined the first group, speculating that enhanced miRNAs are most likely responsible for the anti-aging effect. Numerous miRNAs are known to be involved in longevity pathways, such as insulin signalling and mTOR. Ultimately, the list of miRNAs that were downregulated in aged cells and substantially concentrated in ESC-EVs was reduced to only six by the researchers. Two synthetic RNA molecules known as miRNA mimics miR-15b-5p and miR-290a-5p that imitate the actions of naturally existing miRNAs successful reduced the senescent phenotype of the aged MEFs when transfected by the researchers. The question of which those two advantageous miRNAs impact genes remained. 11 miR-15b-5p target genes and 10 miR-290a-5p target genes were found by the researchers; however, only three of them overlapped, and only two of them—Ccn2 and Lurap1—are known to be engaged in age-related processes. Lurap1 activates the powerful inflammatory transcription factor NF-κB, and Ccn2 is a key player in cellular senescence. However, in aged MEFs, the EV treatment only markedly downregulated the latter.

7. Future directions and challenges

7.1. Regulating SASP

Mitochondrial malfunction is one of the main indicators of cellular senescence (Correia-Melo et al., 2016). Research showed that SASP synthesis falls off in senescent cells that have depleted their mitochondria while the cells are still in cell cycle arrest. But mitochondria are also well-known inducers of programmed cell death known as apoptosis (Bock and Tait, 2020). A crucial apoptosis mediator called cleaved caspase inhibits the formation of SASP during apoptosis. Still, significant mtDNA leaking into the cytosol during that process sets off a series of processes that allow the cell to die peacefully without bothering its neighbours. However, only a tiny percentage of peripheral mitochondria experience mtDNA leaking in the context of cellular senescence (Dou et al., 2017). This mechanism is like a lesser form of apoptosis, and the researchers hypothesized that it is necessary for the continual generation of SASP, which is likely the most harmful effect of senescence. Through mitochondrial outer membrane permeabilization (MOMP), the closely related proteins BAK and BAX produce holes in the mitochondrial membrane that allow mtDNA leaking to occur (Riley et al., 2018). Regardless of the cause or form of senescence, the researchers found that BAX activates in senescent cells simultaneously as part of the cell's mitochondria leak mtDNA. When DNA damage occurs in senescent cells, the combined deletion of BAX and BAK inhibited the release of mtDNA and decreased the expression of numerous common SASP genes. It did not, however, change the levels of senescence markers, indicating that BAX and BAK control the SASP but not the cell cycle arrest linked with senescence (Victorelli et al., 2023). The researchers used genetically altered BAK- and BAX-deficient mice and exposed them to a low radiation dosage known to cause cellular senescence in the liver to explore this process further *in vivo* (Victorelli et al., 2023). Senescence indicators were present in the radiation treated animals and many pro-inflammatory substances were much higher than in the controls (Victorelli et al., 2023). This implies that fewer SASPs were made by roughly the same number of senescent cells.

7.2. Examination of potential obstacles and limitations in translating senescence-based therapies into clinical practice

The secretions released by senescent tumor cells in response to antitumor treatments that break DNA can have two key opposing impacts. According to one theory, senescent cells will prevent tumor cells from multiplying, hence slowing the progression of cancer (Fig. 6). Senescent tumor cells emit secretomes that not only directly influence surrounding stromal fibroblasts and cancer cells but also induce the senescence of neighboring tumor cells *via* a paracrine pathway, eventually leading to the recruitment of immune cells to eliminate cancer cells (Asaithamby et al., 2022; Roger et al., 2021). Senescent cells, on the other hand, can stimulate the development and invasion of surrounding tumor cells by producing inflammation, which can contribute to the formation of tumors. Senescent cancer cells can, therefore, lead to chronic inflammation and the development of drug opposition, which can include resistance to targeted therapies and chemotherapy. Additionally, with chemotherapy or targeted therapy, tumor cells may differentiate into stem cells, evade senescence, and develop a greater inclination to form tumors *in vivo* (Roger et al., 2021). Consequently, determining whether senescence is universal or specific to cancers and tumor lineages, particularly malignancies of oncogenotypes, and if senescence is encouraged and caused only by anti-cancer medicines, would be a critical knowledge gap for clinical translation. Since there isn't a single clear sign of senescence, it is challenging to study tumor cell senescence. Furthermore, data analysis of The Cancer Genome Atlas (TGCA) may reveal a single high mRNA expression of CDKN2A (p16INK4a), CDKN1A (p21WAF1/Cip1), and MKI67 (Ki67), but not lipofuscin, another senescence marker (Gorgoulis et al., 2019).
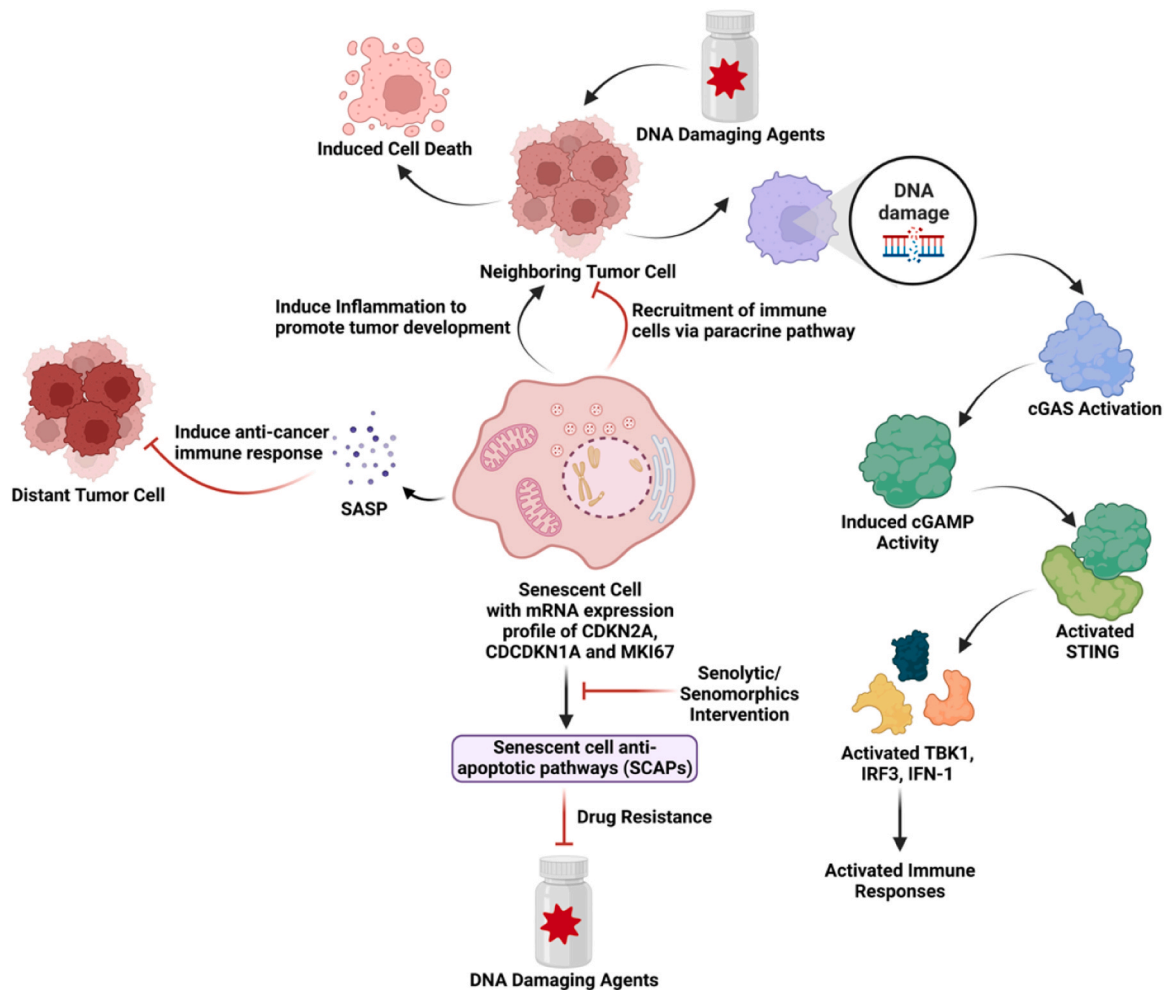
Fig. 6. Diagram depicting the triggering of tumor cell senescence through the activation of cGAS-STING-IRF3-mediated innate immune signaling subsequent to the tumor's exposure to DNA-damaging anti-cancer treatments. The SASP secretome released by senescent tumor cells can affect distant tumors, leading to the stimulation of further anti-tumor immune responses and inducing senescence in both tumor cells and stromal fibroblasts. Timely administration of senolytics (agents targeting senescent cells) and senomorphics (SASP secretome inhibitors) can mitigate the adverse effects of therapy- induced senescent tumor cells on tumor management. DDR, DNA damage response; DSB, double-strand break; dsDNA, double-stranded DNA; SASP, senescence-associated secretory phenotype; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK binding kinase 1; IRF3, interferon regulatory factor 3; IFN, interferon. Abbreviations used above: DDR, DNA damage response; DSB, double-strand break; dsDNA, double-stranded DNA; SASP, senescence-associated secretory phenotype; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK binding kinase 1; IRF3, interferon regulatory factor 3; IFN, interferon. Figure were drawn using BioRender.com.

Non-degradable aggregates of oxidized lipids and proteins build up in the lysosomes of senescent cells due to lysosomal dysfunction associated with senescence from lipofuscin (Gorgoulis et al., 2019), and there is no equivalent coding gene for the former. Due to these features, it is unknown if senescence happens in response to clinical anti-cancer treatments like radiation and chemotherapy (Prasanna et al., 2021). A previous study utilizing beta-galactosidase staining as a senescence marker discovered that frequent exposure to 400 nM 5-azacytidine combined with carboplatin plus docetaxel treatment promoted senescence in p53 null human lung cancer cells but not untreated cells (Ewald et al., 2010b; Roberson et al., 2005). Senescent cells' innate capacity to promote one or more senescent cell anti-apoptotic pathways (SCAPs) is one of the primary mechanisms by which they evade genotoxic anti-tumor drugs and live longer. Due to this reason, eradicating senescent cancer cells early on using "senomorphics" (drugs that particularly target the SASP secretome) or senolytic medications (drugs that specifically target senescent cells) may aid in cancer management. Clinical research is being conducted on senolytic drugs that target one or more SCAP pathways (Chaib et al., 2022b). Notably, cancer treatment is not the goal of any of the ongoing trials. Senescence-like fibroblasts are

the focus of radiotherapy, which sensitizes NSCLC and lessens radiation-induced lung fibrosis (Asaithamby et al., 2022; Bondeson et al., 2018; Meng et al., 2021). Further pre-clinical research is necessary to identify the anti-senescent molecule(s) that target certain cancer types, and to evaluate the adverse effects of senolytic drugs and the removal of senescent cells from healthy organs. To investigate the efficacy of anti-senescent drug treatments in different tumor lineages and oncogenotypes, and when paired with different chemotherapy, targeted therapy, immune checkpoint inhibition, and radiation techniques, pre-clinical models—particularly with human malignancies—are necessary.

7.3. Consideration of the ethical and societal implications of senescence-based therapies

Numerous genetic, pharmacological, and other treatments can be used to slow down the aging process in laboratory animals, including non-human primates and yeast. Human clinical trials are presently being conducted for two broad kinds of therapies (Table 1). One kind trigger endogenous repair and rejuvenation mechanisms by triggering nutrient signaling pathways. The other class focuses on harmful meta-effects of

Table 1

List of clinical trials evaluating the role of senescence in lung cancer including the drug and combinations of the drugs used (Bousset and Gil, 2022b; Chaib et al., 2022a; Wyld et al., 2020).

Senolytic drug	CT phase	Cancer	Drug Combinations	CT number	Status
Navitoclax	Phase I	SCLC	Etoposide, cisplatin (Bousset and Gil, 2022b)	NCT00878449	Completed
Navitoclax	Phase I	Solid tumours including NSCLC	Erlotinib, irinotecan (Tolcher et al., 2015)	NCT01009073	Completed
Navitoclax	Phase I	Solid tumours including lung carcinoma, NSCLC and SCLC	Gemcitabine (Cleary et al., 2014)	NCT00887757	Completed
Navitoclax	Phase I	Solid tumours including NSCLC and SCLC	Carboplatin and or Paclitaxel (Vlahovic et al., 2014)	NCT00891605	Completed
Navitoclax	Phase I/II	KRAS or NRAS mutation-positive advanced or metastatic solid tumors including lung cancer	Trametinib (Bousset and Gil, 2022b; Corcoran et al., 2019)	NCT02079740	Active
Navitoclax	Phase I	Solid tumours including NSCLC and SCLC	Docetaxel (Puglisi et al., 2021)	NCT00888108	Completed
Navitoclax	Phase I/II	BRAF mutant Solid tumours including lung cancer.	Dabrafenib, trametinib (Sullivan et al., 2018)	NCT01989585	Active
Navitoclax	Phase I	Advanced or metastatic NSCLC	Osimertinib (Bertino et al., 2021)	NCT02520778	Completed

aging, including dysfunctional stem cells or senescent cells. The diabetic medication metformin stimulates aging-related nutritional signalling pathways (Barzilai et al., 2016; Woo et al., 2019). In the US, a sizable randomized controlled study is being prepared to investigate if metformin can postpone age-related multimorbidity. In the lab, inhibitors of the protein-sensing TOR complex can activate pathways for protein repair and increase longevity (Harrison et al., 2009). A clinical experiment recently showed that TOR inhibitors can shield susceptible elderly individuals from respiratory infections (Mannick et al., 2018). Additionally, medications that stimulate NAD-dependent sirtuin enzymes and restore the metabolic signaling molecule NAD are being researched (Tarrago et al., 2018; Verdin, 2015; Woo et al., 2019; Yoshino et al., 2018). In the lab, senescent cell elimination prolongs a healthy lifespan by lowering harmful inflammation (Baker et al., 2016; Xu et al., 2018), and other anti-senescent-cell medications are going through clinical testing (Kirkland et al., 2017). Healthy stem cells can be directly infused into the stem cells to revitalize them, or they can be regenerated in the lab using components from young blood (Villeda et al., 2014). Clinical trials are now investigating strategies for treating dementia and physical frailty (Baker et al., 2011; Sha et al., 2019; Tompkins et al., 2017; Woo et al., 2019). In the future, aging may be treated using direct genome editing (Lau and Suh, 2017). A global alliance strives to expedite the advancement of anti-aging treatments into clinical trials (Newman et al., 2016). Whether or not aging is a disease relies on our conception of health and illness, which is a controversial topic in medical philosophy. According to one perspective, an illness is a deviation from "normal" human functioning. A situation cannot be abnormal if it is widespread and the outcome of inborn biological processes (Boorse, 1977). This method suggests that aging is natural and not an illness because aging occurs in all persons. Contrary to popular belief, any condition that exhibits enough structural similarities to be considered a disease should be considered a disease in and of itself, regardless of whether all people shared it. Some authors contend that aging fits this definition (Izaks and Westendorp, 2003). Considering that there is a medical rationale for slowing down aging, regardless of its status as a disease, may help avoid a difficult issue regarding establishing the medical legitimacy of anti-aging interventions. An increasing number of biogerontologists are arguing that using this approach might help postpone, if not prevent, the onset of illnesses such as cancer, Alzheimer's, or heart disease (Woo et al., 2019). However, the ethical discussion surrounding the general acceptability of this type of intervention remains open since, at least in theory, competing interests may take precedence over the existence of such a medical justification. Nor does it demonstrate that the issue of whether aging is a sickness can be entirely ignored, if only due to the important practical ramifications of society's response to that question, as was previously indicated. However, the preventative justification for anti-aging medications is not consistently considered in the ethical discourse (Woo et al., 2019). Those who argue against interfering with the aging process should provide a justification for why the potential

drawbacks of doing so exceed the intervention's preventative benefits. At the very least, one may observe that they must distinguish between the impacts of biological and chronological aging without passing judgment on their chances of success (Woo et al., 2019). The same cautionary note applies to anti-aging research proponents: they should exercise caution in overestimating the possible influence of such research on age-related disorders; in this regard, the necessary reality check may be provided primarily by scientific professionals (Mykytyn, 2006).

Due to promising outcomes in preclinical studies, many clinical trials of drugs with senolytic effects have been conducted. Some have been completed and some are ongoing (Table 1). Most of these trials are directed toward solid tumour types, including various lung cancers. Early results from these clinical trials warrant evaluating senolytic drugs such as Navitoclax in larger randomized, double-blind, placebo-controlled trials either as monotherapy or in combination.

8. Conclusion

As the cells age, the epithelial barrier breaks, the lung milieu changes, and SASP causes pulmonary inflammation and remodeling. These processes may also promote cellular senescence in the surrounding growing cells. A physiological cycle like this one leads to the pathogenesis of lung inflammation. Breaking this loop with anti-senescence treatments may thus aid in the preventing and treating chronic lung diseases (Xie et al., 2023). Hence, treating both non-cancerous cell senescence and remaining senescent cancer cells in patients undergoing pro-senescent antitumor treatments is challenging. It can be challenging to strike a balance between the "dark" and "bright" aspects of senescence since senescent cancer cells may have both tumor-promoting and tumor-suppressive properties. It is currently impractical in the clinic to identify and precisely target less desirable senescent cell groups using biomarkers nor to conduct a trustworthy quantitative assessment of the potential long-term implications of these effects. While it could be somewhat effective, pharmacological inhibition or modification of the SASP is unlikely to alter the course of a tumor significantly. Premature cancer cell senescence generally produces short-term positive effects but has negative impacts in the long run. Senescence is a side effect that most currently approved cytotoxic and cytostatic cancer therapies cause in some percentage of the cancer cell population that survives, whether on purpose or not. Senolysis appears to be the preferable method for eliminating cancer cells exposed to chemotherapeutics that aided in the first treatment response by proliferative arrest rather than undergoing apoptotic cell death. It seems to be the only effective way to eradicate malignancies completely. Though several promising candidate senolytics have been identified, some of which have advanced to clinical trials, promising results from large-cohort cancer studies have not yet been released (Wang et al., 2022b). The research should clarify if the main goals of therapeutic senolytic techniques are to eliminate organ

function-disabling senescent cells in non-malignant tissues and to prevent post-senescent cancer recurrence. These goals won't be reached for a while since there's still a big hurdle to be cleared: the drug-exposed, death-resistant, and non-senescent cancer cell (Schmitt et al., 2022). There are still many obstacles to overcome when moving from the bench to the bedside, not the least of which is understanding the specific impacts of various illnesses and the relative effects and susceptibilities of senescence for different lung cells. Although the pathophysiology of the sickness may not be explained by age-related damage resulting from the proliferative presence of senescent cells, cells already experiencing senescence may react differently to new stimuli. Further in-depth mechanistic study is needed to comprehend the link between biological aging indicators, the disease's course, and various lung phenotypes. Researching this subject has promising prospects for advancements in respiratory care, considering the creation of medications that address and prevent cell senescence.

Ethics approval and consent to participate

Not applicable.

Funding

CRediT authorship contribution statement

K.R.P, P.M.H, K.D, and S.K.J conceptualized the review. S.K.J, G.D.R, R.A, L.A.J, K.B, N.P, S.M, and K.R.P wrote the manuscript. GDR, S.R.D, Y.Z draw figure using BioRender.com. S.K.S, G.G and all other authors participated in review editing and proof reading. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Not applicable.

Acknowledgements

Consent for publication

All authors have approved to publish this manuscript.

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