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REVIEW ARTICLE

Senescence and senolysis in cancer: The latest findings

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Abstract

Aging is a life phenomenon that occurs in most living organisms and is a major risk factor for many diseases, including cancer. Cellular senescence is a cellular trait induced by various genomic and epigenetic stresses. Senescent cells are characterized by irreversible cell growth arrest and excessive secretion of inflammatory cytokines (senescence-associated secretory phenotypes, SASP). Chronic tissue microinflammation induced by SASP contributes to the pathogenesis of a variety of age-related diseases, including cancer. Senolysis is a promising new strategy to selectively eliminate senescent cells in order to suppress chronic inflammation, suggesting its potential use as an anticancer therapy. This review summarizes recent findings on the molecular basis of senescence in cancer cells and senolysis.

KEYWORDS
aging, cancer, GLS1, senescence, senolysis

1 | INTRODUCTION

Aging is a major risk factor for many human diseases, including cancer, cardiovascular diseases, and neurological disorders. Hayflick and Moorhead first discovered in 1961 that cultured human cells cannot proliferate indefinitely, resulting in cellular senescence.[1] Cellular senescence is a cellular trait induced by various genomic and epigenetic stresses such as telomere dysfunction, activated oncogenes, reactive oxygen species, and DNA damage. Senescent cells are characterized by irreversible cell growth arrest and excessive secretion of inflammatory cytokines[2–4] (Figure 1). Induction of senescence per se is now thought to act as an antitumorigenic barrier due to its inherent property of permanently arresting cell proliferation.[5,6] However, the senescence-associated secretory phenotype (SASP), a potent secretion of numerous growth factors, cytokines, proteases, and other proteins, supports a variety of pathophysiological phenotypes in age-related diseases, including chronic inflammation, destruction of tissue structure, and cell growth stimulation.[7] Other hallmarks of senescence include upregulation of the cell cycle inhibitors $p16^{Ink4a}$, p21, and p53, induction of senescence-associated β-galactosidase (SA-β-gal), and depletion of Lamin B1 from the nuclear envelope.[8,9]

In 2011, Baker et al. developed INK-ATTAC mice in which the INK-ATTAC gene capable of selectively inducing apoptosis in $p16^{Ink4a}$-expressing cells by the administration of AP20187, a synthetic drug that induces dimerization of a membrane-bound myristoylated FK506-binding protein-caspase 8 (FKBP-Casp8) fusion protein, was introduced into the promoter of $p16^{INK4a}$, currently the most reliable marker of cellular senescence.[10] In the BubR1 progeria mouse background, removal of $p16^{Ink4a}$-positive senescent cells from mice in a drug-dependent manner delayed the progression of various age-related disorders. Subsequently, the elimination of naturally occurring senescent cells not only suppressed the development of age-related organ dysfunction such as renal failure and atherosclerosis,

Abbreviations: ATTAC, apoptosis through targeted activation of caspase; BPTES, bis-2-(5-phenyl-acetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide; CAR, chimeric antigen receptor; CDK, cyclin-dependent kinase; Fbxo22, F-box only protein 22; KDM, histone lysine demethylase; MAPK, mitogen-activated protein kinase; NASH, non-alcoholic steatohepatitis; SCF, SKP1–CUL1–F-box protein.

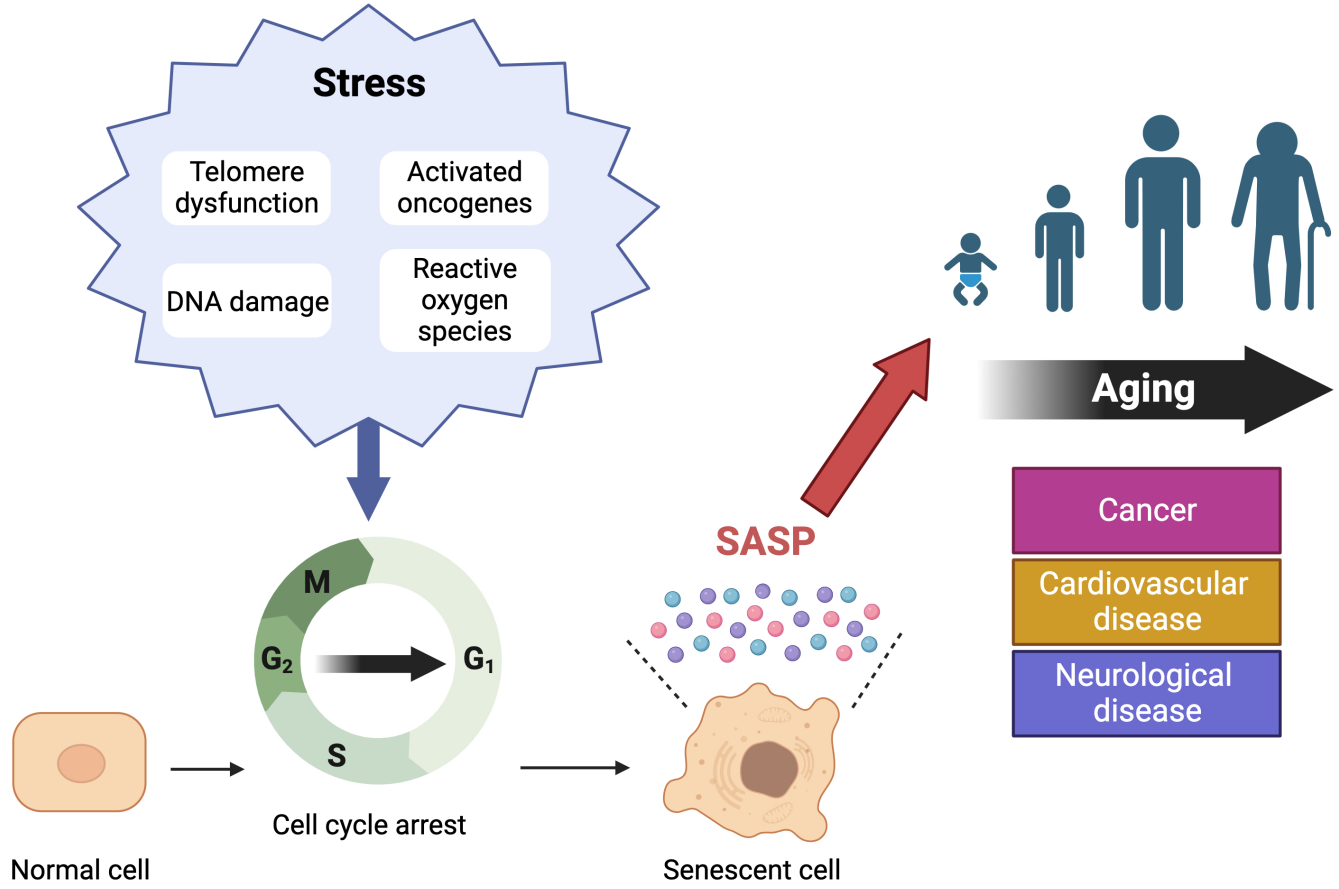

FIGURE 1 Characteristics of "cellular senescence" and "aging." Cellular senescence is one of the molecular mechanisms underlying aging. Cellular senescence is characterized by irreversible cell growth arrest and secretion of senescence-associated secretory phenotype (SASP).

but also delayed the progression of neoplastic disease, independent of genetic background or diet.[10–12] These findings suggest that selective elimination of senescent cells may be a potential strategy for cancer suppression.

2 | A MECHANISM UNDERLYING SENESCENCE INDUCTION

We have demonstrated that normal human diploid fibroblasts (HDFs) exposed to various senescence-inducing stimuli undergo a mitosis skip before entering permanent cell cycle arrest.[13] Activation of p53 in G2 in response to senescence-inducing stimuli induces p21, which suppresses the activities of both Cdk1 and Cdk2. This suppression leads to premature activation of APC/C^{Cdh1}, which degrades various mitotic regulators and triggers accumulation of Cdt1. Activated p53 also enhances the function of RB1, suppressing the transcription of mitotic regulators. Both pathways cooperate to ensure mitotic skipping and induce senescence. Recently, it was also reported that replication stress due to elevated cyclin E promotes p53-dependent mitotic bypass, leading to cell cycle escape at S/G2 phase and induction of cellular senescence by a similar mechanism.[14]

Furthermore, we have revealed that SCF^{Fbxo22}-KDM4A is a senescence-associated E3 ligase targeting methylated p53 for degradation.[15] p38MAPK is critically needed for SASP induction, but activated p53 suppresses p38MAPK function.[16] Thus, activation of p53 is necessary for induction of senescence, but SASP and $p16^{Ink4a}$ induction requires it to be downregulated at the late phase of the senescence process. We found that FBXO22 is essential for this downregulation of p53. SCF^{Fbxo22} specifically ubiquitinates methylated p53, which forms a complex with KDM4A for degradation during the late phase of senescence. The formation of a ternary complex between FBXO22, methylated p53, and KDM4A promotes ubiquitination of p53 by the SCF complex. Downregulation of methylated p53 by SCF^{Fbxo22} at the late phase of the senescence process leads to induction of $p16^{Ink4a}$ and SASP.

3 | SENESCENCE AND CANCER

3.1 | Oncogene-induced senescence (OIS)

Induction of cellular senescence requires functional p53 and RB1, which are frequently oncogenic mutations in the majority of human cancers.[17–19] The activation of oncogenes such as $HRAS^{V12}$

causes OIS. This was first demonstrated in vivo in 1997.[20] These observations have suggested that senescence induction is a cancer-suppressing mechanism that effectively prevents the accumulation of cells activating oncogenes.[8,21] However, the resulting senescent cells may promote carcinogenesis by inducing chronic inflammation in surrounding tissues via SASP.[8,22] Thus, cellular senescence is now considered to be a double-edged sword for cancer.

3.2 | Therapy-induced senescence (TIS)

Therapy-induced senescence is now recognized as a response to various anticancer therapies, including conventional chemotherapy, cell cycle inhibitors, telomerase inhibitors, and radiation therapy.[23,24] TIS occurs only in a subset of the treated cells.[23] Like OIS, TIS can be initially beneficial by inducing tumor suppressors such as p53, p21, p27, and PTEN.[25–31] Cells with functional Rb and p53 appear to be more sensitive to stress and oncogene activities that stimulate senescence.[23,32] However, even in SAOS-2 osteosarcoma and DU145 prostate cancer cells, lacking Rb and p53, doxorubicin induced senescence in more than 50% of the cells in vitro.[33,34] In comparisons of TIS in cancer cells containing or lacking functional p53, both demonstrated similarly strong responses, suggesting that induction of other senescence-inducing genes, such as p21, mediated by p53 independent pathway in drug-induced senescence.[35,36]

Low doses of chemotherapy induce senescent cell state, especially in human cancer cells, whereas high doses induce apoptosis.[37] Indeed, in various preclinical models, exposure to chemotherapeutic agents or radiation increased the presence of senescence marker-positive cells.[38] Cytotoxic chemotherapeutic agents with different mechanisms of action, alkylating agents, topoisomerase inhibitors, and microtubule inhibitors, were all identified as senescence-inducing agents in preclinical models.[39] In fact, analysis of biopsy-derived samples from prostate cancer patients treated with the topoisomerase 2β inhibitor mitoxantrone also revealed upward regulation of the senescence markers $p16^{INK4a}$ and p21 and the SASP factors IL-6 and IL-8.[4] Areas of increased SA-β-gal staining were observed in breast tumors after neoadjuvant chemotherapy.[40] This staining was restricted to tumor cells and was not detected in normal tissues. It is important to note that while a significant number of existing chemotherapeutic agents have the ability to induce senescence, the apoptotic response is predominant in most cancers.[8]

CDK4, CDK6, and their activating partners, D-type cyclins, link the extracellular environment to central cell cycle mechanisms.[41] Constitutive activation of cyclin D-CDK4/6 drives tumorigenesis in several types of cancer. Small-molecule inhibitors of CDK4/6 have been used with great success to treat hormone receptor-positive breast cancers and are in clinical trials against many other tumor types.[41] In addition to blocking cell proliferation, inhibition of CDK4/6 can also cause tumor cell senescence, which is dependent on RB1 and FOXM1.[42–44] Cyclin D-CDK4/6 phosphorylates and activates FOXM1, which has antisenescence activity.[43,45] p53 is not required for cells to enter or maintain cell cycle arrest in the continued presence of Cdk4/6 inhibitors, but p53 is essential for maintaining arrest after drug removal.[46–48] Because cyclin A2/CDK2 activity depends upon CDK4/6 activity throughout the cell cycle, not just in G1 phase, loss of CDK4/6 activity in S/G2 phase causes cells to replicate their DNA but prevents subsequent cell division, inducing cell cycle exit.[49]

Replicative senescence occurs in response to telomere loss. Cancer cells most commonly circumvent this by reactivating telomerase activity.[50] Telomerase is overexpressed in 80%–95% of cancers and is present at very low levels or barely detectable in normal cells.[51] Inhibition of telomerase can cause a decrease in telomere length, leading to cellular senescence and apoptosis in telomerase-positive tumors. To date, a number of compounds, including BIBR15 and GRN163L, that inhibit the telomerase complex have been identified as candidates for anticancer therapy and are in clinical trials.[8,52]

Radiation therapy, like chemotherapy, is widely applied in the treatment of multiple types of cancer due to its ability to induce rapid DNA damage. This anticancer therapy can induce an irreparable DNA damage response that activates ATM/ATR and p53-p21 pathway-mediated apoptosis and cellular senescence.[53,54] Indeed, radiation has been shown to induce senescence in human head and neck squamous cell carcinoma-derived cells.[22,55] Radiation induced senescence even after exposure to relatively high doses (10 Gy) and lower doses (0.5 Gy).[56,57]

3.3 | Role of senescence in cancer

3.3.1 | Senescence in precancerous lesions

The sustained cell cycle arrest caused by cellular senescence serves as a first barrier to tumorigenesis.[58] Cells experiencing DNA damage would enter cell cycle arrest to prevent abnormal proliferation, thereby inhibiting cancer development.[8,58] Senescent hepatocytes induced by oncogenes promote CD4-positive T cell infiltration and clearance of senescent cells, preventing further progression of the precancerous state.[59] In the case of $KRas^{G12V}$-driven lung neoplasia, the presence of the senescence markers $p16^{INK4a}$ and SA-β-gal in precancerous lung adenomas and the absence of senescence markers and increased expression of the proliferation marker Ki67 in lung adenocarcinomas reflect the importance of OIS in suppressing tumorigenesis.[60] Nevertheless, once the cells become senescent cells, proinflammatory SASPs cause chronic inflammation in the surrounding tissues and promote cancer.

3.3.2 | Senescence in advanced cancer

Characteristics of advanced cancer include accelerated angiogenesis, tumor invasion, and metastasis.[58] Epithelial–mesenchymal

transition (EMT) is a cellular transformation that helps tumor cells acquire greater migratory and invasive potential.[61] Further investigation of the components of SASP revealed that IL-6 and IL-8 are the primary drivers of SASP-mediated EMT and invasiveness of premalignant and malignant tumor cells.[4] The increased tumor vascularization observed when tumorigenic epithelial cells and senescent fibroblasts were coinjected subcutaneously into mice suggests that senescence may promote tumorigenesis by stimulating angiogenesis.[62] Vascular endothelial growth factor (VEGF) only partially promotes angiogenesis, and senescence-conditioned medium pretreated with VEGF-neutralizing antibody failed to completely block endothelial cell invasion into the basement membrane, suggesting the presence of other angiogenic factors in the SASP.[62] In contrast to immune surveillance of premalignant cells through senescence, SASP in advanced cancer creates an immunosuppressive environment and promotes tumor growth. Senescent fibroblasts secrete small amounts of anti-inflammatory factors (e.g., IFN-α, IFN-γ, IL-3, IL-5) and massive amounts of proinflammatory factors (e.g., IL-6, IL-8, MCP-1).[63,64] Senescent fibroblasts may affect the balance of myeloid cells, lymphocytes, and macrophages in the tumor environment, such that cancer cells coinjected with aged fibroblasts into immunocompetent mice induced larger tumor volumes than cancer cells coinjected with nonsenescent fibroblasts; however, coinjection into immunocompromised nude mice caused comparable tumor growth, regardless of fibroblast status.[65] These studies provide evidence of the role of senescence in promoting tumor invasion and metastasis and have important clinical implications for both local and distant tumor control.

However, there are also recent reports that immunization by senescent cancer cells upregulates MHC-I and IFNγ receptors and promotes prophylactic and therapeutic CD8 T cell-dependent antitumor immune responses in tumors.[66,67] This was also the case in human patient-derived cancer cells during TIS. Thus, senescent cells in advanced cancer may play a dual role in promoting not only tumor progression but also antitumor immunity. Therefore, further studies are urgently needed to determine whether the elimination of cancer senescent cells is beneficial or harmful.

4 | SENOLYTICS FOR ANTICANCER THERAPY

The strong link between cellular senescence and multiple aging pathologies, including cancer, has prompted the search for small-molecule compounds called "Senolytics," which selectively eliminate senescent cells[8,9] (Table 1). The persistence of therapy-induced senescent cells after cancer treatment may create a tissue environment that promotes recurrence and metastasis.[63] In cancer, a "one-two punch" approach to cancer treatment is effective: First use one drug to induce senescence of cancer cells, and then use a second drug to eliminate the senescent cancer cells.[68]

TABLE 1 Senolytic or senomorphic treatments in cancer.

Treatments	Targets or drug mechanisms
Dasatinib[69,70]	Inhibits PI3K
Quercetin[69,70]	Inhibits PI3K
Fisetin[71]	Inhibits PI3K
Navitoclax (ABT263)[72]	Inhibits BCL-2, BCL-XL, and BCL-W
Nav-Gal[73]	Inhibits BCL-2, BCL-XL, and BCL-W
ARV825[74]	Degrades BET family proteins
Digoxin[75,76]	Inhibits Na^+/K^+ pumps
Ouabain[75]	Inhibits Na^+/K^+ pumps
BPTES[77]	Inhibits GLS1
CAR T cells[78]	T cell immune responses
PD1 or PDL1 blocking antibodies[79]	T cell immune responses
Metformin[80]	Inhibits NF-κB
Rapamycin[81]	Inhibits mTOR
Temsirolimus[82]	Inhibits mTOR
AZD8055[83]	Inhibits mTOR
Siltuximab[84]	Inhibits IL-6
Canakinumab[85]	Inhibits IL-1β

4.1 | Senolytic small compounds

In 2015, Zhu et al. showed that transcriptome analysis revealed increased expression of the antiapoptotic prosurvival signaling network in senescent cells, including ephrins (EFNB1 or 3), PI3K, p21, BCL-XL, and plasminogen-activated inhibitor-2 (PAI-2).[69] They tested whether drugs targeting gene products that protect against senescent cell antiapoptotic pathways (SCAPs) are senolytics in vitro, and of the 46 drugs tested, dasatinib (D), an inhibitor of multiple tyrosine kinases, and quercetin (Q), a natural flavonol, were identified as the first senolytics.[69] The DQ combination therapy as the first-in-human senolytic therapy was effective in the treatment of idiopathic pulmonary fibrosis, a fatal disease associated with senescent cells in the lungs.[70] Fisetin, another natural flavonol similar to quercetin, has more potent senolytic activity than quercetin.[71] The efficacy of fisetin alone or in combination with other anticancer agents has been studied in a wide variety of cancers. Fisetin treatment has antiproliferative and proapoptotic effects in cancer cells in vitro and in mice and suppresses inflammation, migration, and metastasis in vivo.[86]

Senescent cells often have elevated levels of the antiapoptotic BCL-2 family of proteins.[87] Compounds targeting this protein family have been extensively studied for senolytic therapy. Several studies have shown that navitoclax (also known as ABT263), a selective inhibitor of BCL-2, BCL-XL, and BCL-W, effectively eliminates several types of senescent cells, including senescent cancer cells, by reactivating the apoptotic pathway.[68,72,88,89] Although navitoclax has demonstrated high efficacy, several previous clinical trials have

shown significant side effects of navitoclax related to on-target effects in blood cells, including thrombocytopenia and neutropenia.[90] Nav-Gal, a galacto-conjugated navitoclax prodrug, remains inactive in the prodrug form but becomes active when the galacto moiety is cleaved by SA-β-gal. Because senescent cells have high levels of SA-β-gal, navitoclax delivered via Nav-Gal is activated by SA-β-gal only in senescent cells, thus limiting off-target effects in other cells.[73]

ARV825, a proteolytic targeted chimeric (PROTAC) drug, consists of a potent inhibitor of the bromodomain and extraterminal domain (BET) proteins BRD2, BRD3, and BRD4 and the E3 ligase-binding agent pomalidomide.[74] ARV825 inhibited nonhomologous end-joining (NHEJ), the main mechanism of DNA double-strand break repair, by promoting the degradation of BRD4, and also induced autophagy, thereby inducing senolysis through two independent pathways.[74] ARV825 effectively eliminated senescent hepatic stellate cells in the liver of obese mice, thereby reducing the development of liver cancer.[74]

The cardiac glycosides digoxin and ouabain have been identified as senolytic agents with activity in several cancer models.[75,76] The cardiac glycosides can inhibit Na^+/K^+ ATPase pump activity, resulting in an imbalance in the intracellular electrochemical gradient, leading to depolarization and acidification. Senescent cells have depolarized plasma membranes and high concentrations of hydrogen ions, making them more susceptible to cardiac glycosides.[76]

Glutaminase 1 (GLS1), the rate-limiting enzyme of glutaminolysis is a gene essential for the survival of human senescent cells.[77] In senescent cells, loss of proteostasis occurs due to increased production of mistranslated, misfolded, or incomplete proteins.[9] In general, aggregated proteins are degraded in lysosomes, while an excess of aggregated proteins damages the lysosomal membrane, resulting in leakage of intralysosomal H^+, subsequent intracellular acidosis, and induction of apoptosis.[91] However, GLS1 expression is increased in senescent cells, resulting in accelerated glutaminolysis, induced ammonia production, neutralized pH, and enhanced survival of senescent cells.[77] Thus, the results suggest that senescent cells are dependent on glutaminolysis and that their inhibition offers a promising strategy for inducing senescent cell degradation in vivo (Figure 2).

Regarding the anticancer activity of GLS1 inhibitors, glutamine metabolism is one of the hallmarks of cancer. In various cancers, GLS1 shows higher expression in tumor tissues than in normal tissues, and high GLS1 expression is also associated with tumor progression and poor prognosis.[92] In addition, the inhibition or knockdown of GLS1 can lead to cell death and induce apoptosis.[92] A GLS1-specific inhibitor, BPTES, was shown to substantially inhibit cancer cell growth in vitro and in mouse tumor models.[92–95] These results suggest that BPTES may have dual antitumor activities: one is the inhibition of cancer cell per se and the other is elimination of stromal senescent cell in the tumor. Indeed, GLS1 inhibition by BPTES has been shown to induce apoptosis in pancreatic ductal adenocarcinoma cells induced to senescence by low concentrations of gemcitabine.[96] In vivo, areas of decreased SA-β-gal staining was also observed with the combination of gemcitabine and BPTES compared with low-dose gemcitabine alone. Although many other GLS1 inhibitors have been discovered in addition to BPTES, at present there are only a limited number of small-molecule GLS1 inhibitors that are selective and effective against cancer.[92] Despite their preclinical efficacy, only a few of these inhibitors have advanced to early clinical trials.[97]

4.2 | Immune response-mediated senolysis

The immune system may also induce endogenous senolytic effects following TIS.[22] Urokinase-type plasminogen activator receptor (uPAR) was identified as a protein widely induced on the surface of senescent cells.[78] Chimeric antigen receptor (CAR) T cells can induce specific T cell responses to the antigen of interest.[98] uPAR-specific CAR T cells effectively eliminated senescent cells and significantly delayed tumor growth in vitro and in a mouse model of lung cancer in which senescence was induced by a combination of MEK and CDK4/6 inhibitors.[78] Recent studies also suggest that

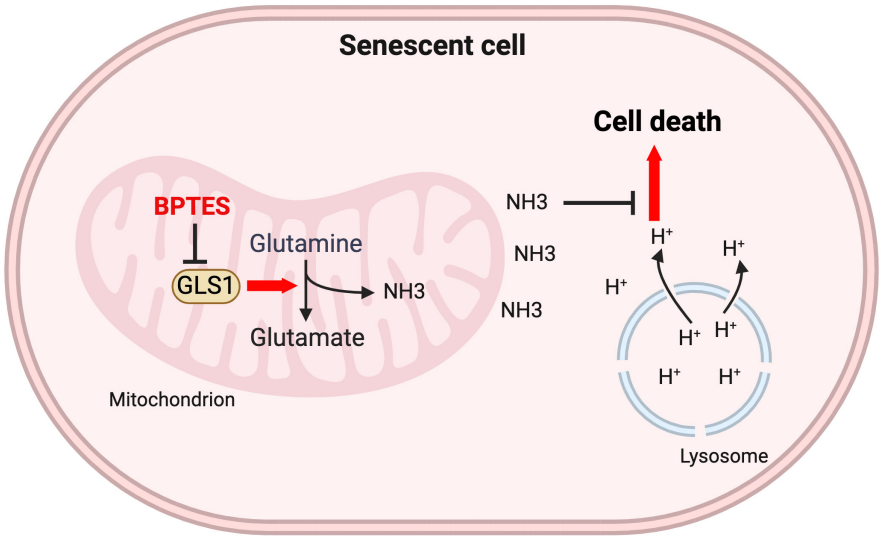

FIGURE 2 Ammonia production by GLS1 is essential for survival of senescent cells. GLS1 induces ammonia (NH3) production and neutralizes the proton (H^+). Intracellular acidification induces cell death.

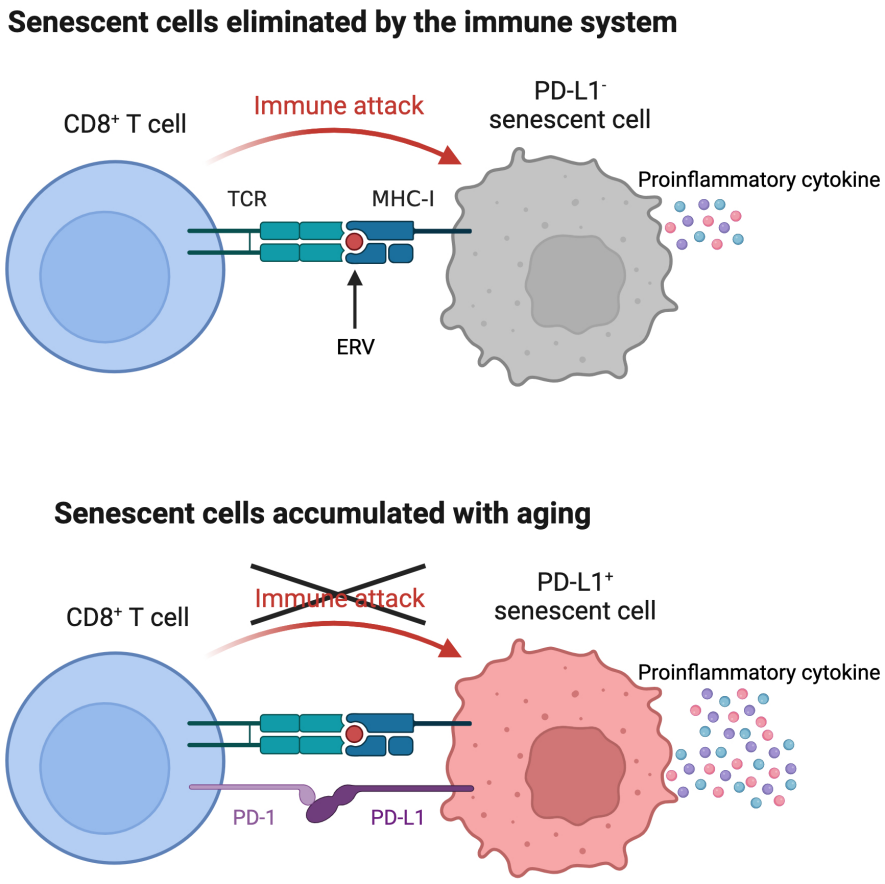

FIGURE 3 Accumulation of PD-L1$^+$ senescent cells with aging. PD-L1$^-$ senescent cells are eliminated by activated CD8$^+$ T cells. On the other hand, PD-L1$^+$ senescent cells escape immune surveillance by binding to PD-1 molecules on CD8$^+$ T cells and suppressing the activity of CD8+ T cells, resulting in accumulation.

uPAR-targeting CAR T cells can persist in vivo for long periods of time to continuously target and eliminate uPAR-expressing senescent cells and ameliorate age-related metabolic and physical dysfunction.[99] Targeting uPAR-positive cells with CAR T cells may be both a cancer prevention and a cancer treatment in humans.

Senescent cells heterogeneously express the immune checkpoint protein programmed death-ligand 1 (PD-L1), and PD-L1$^+$ senescent cells accumulate with age in vivo.[79] PD-L1$^-$ cells are sensitive to CD8$^+$ T cell surveillance, whereas PD-L1$^+$ cells are resistant, even in the presence of SASP. PD-L1 expression in senescent cells induces escape from T cell immunity. Taken together, the results suggest that the heterogeneous expression of PD-L1 has an important role in the accumulation of senescent cells and inflammation associated with aging, and the elimination of PD-L1$^+$ senescent cells by immune checkpoint blockade may be a promising strategy for antiaging therapy (Figure 3).

Immune checkpoint blockade, such as treatment with monoclonal antibodies to PD-1 or PD-L1, has contributed to substantial advances in cancer immunotherapy over the past decade, successfully treating a variety of malignancies by redirecting T cells to PD-L1-expressing cancer cells.[100] Interestingly, CDK4/6 inhibitors are known to induce tumor cell senescence.[41,46] Treatment of mice bearing autologous breast cancers or cancer allografts with CDK4/6 inhibitors and anti-PD-1/PD-L1 antibodies increased the efficacy of immune checkpoint blockade and resulted in complete tumor regression in a high proportion of animals.[101–103]

However, NASH model mice treated with anti-PD-1 therapy for a relatively long period of time (8 weeks) had an increased incidence of liver cancer.[104] Due to the diversity of T cell populations and the ability of these cells to infiltrate most organs, immune checkpoint inhibitors (ICIs) can cause a wide range of immune-related adverse events, which can affect virtually any organ.[105] Furthermore, 10%–30% of patients treated with ICIs may experience "Hyper Progressive Disease," in which the tumor grows rapidly and the disease worsens.[106,107] Therefore, the use of immunotherapy for age-related diseases, including cancer, requires optimization of dosage and frequency of administration, balancing enhanced immune clearance, resistance to acute inflammation, and rate of tissue repair.

5 | SENOMORPHICS FOR ANTICANCER THERAPY

Considering that the majority of tumor-promoting and chemotoxicity-promoting functions of senescent cells may be causally related to SASP, controlling the induction of SASP using senomorphic SASP inhibitors is another promising approach to prevent the adverse effects of senescence[22,108] (Table 1). SASP is reported to be induced by multiple mechanisms, including the nuclear factor-κB (NF-κB), cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING), GATA4, CCAAT/enhancer

binding protein-βa (CEBPβ), NOTCH, IL-6, Janus kinase (JAK)-signal transducer and activator of transcription (STAT), p38 MAPK, and mTOR pathways.[3,81,109–116]

Metformin prevents, to some extent, the nuclear translocation of the NF-κB pathway components and subsequent transactivation at target gene promoters, thereby reducing the expression of various SASP factors, which may explain, at least in part, the anti-aging and antitumor effects of metformin in both mouse models and diabetic patients.[80] Although these were small clinical trials using a "window of opportunity" design, a decrease in tumor cell proliferation was observed with metformin treatment in breast and prostate cancer patients.[117,118]

mTOR is an essential regulator of SASP, and mTOR inhibitors have shown senomorphic effects in senescent cancer cells.[81,83,119,120] In various preclinical studies, the mTOR inhibitor, rapamycin, may have the context-dependent potential to reduce NF-κB activity, suppress proinflammatory SASPs at the translational level, and suppress the ability of senescent fibroblasts to stimulate prostate tumor growth in mice.[81] The combination treatment with docetaxel and temsirolimus, an mTOR inhibitor, suppressed the growth of prostate and breast cancer in mice.[82] In addition to its senomorphic effect as an mTOR inhibitor, AZD8055 acted as potent senolytic agents against liver cancer cells induced senescent through CDC7 inhibition.[83]

Antibodies to the SASP factors may also limit deleterious senescence-related functions. Siltuximab, a neutralizing anti-IL-6 monoclonal antibody approved for the treatment of multicentric Castleman's disease, has been tested in clinical trials in a variety of solid tumors.[84] Canakinumab is a human immunoglobulin Gκ monoclonal antibody with high specificity and affinity for IL-1β for use in patients with juvenile arthritis and periodic fever syndrome, and has shown some activity in various trials involving patients with non-small cell lung cancer.[85] Because SASP also has beneficial effects such as wound healing, tissue regeneration, and immune surveillance, detailed follow-up in appropriate model systems and clinical trials will be necessary to accurately identify the specific anticancer effects of drugs targeting SASP.

6 | PERSPECTIVE

There are several methods of senolytics and senomorphics. Senolytics using senescent cell-eliminating vaccines that target proteins highly expressed in senescent cells as antigens have also been reported.[121] Development for future clinical application will be pursued from many directions.

However, one of the key remaining challenges is the lack of gold-standard biomarkers for the senescent state. There is no single marker that can clearly distinguish senescence from other growth arrest states. There is a need to develop a method for quantification of senescent cells other than tissue staining, such as liquid biopsy, as a biomarker to determine the efficacy of senolytic drugs.

Tumor heterogeneity is another challenge. Tumor heterogeneity can lead to a variety of drug responses and limit the effectiveness of inducing senescence within tumors. Since they can lead to resistance and side effects, the development of broadly-acting senolytic agents is desirable.

Therefore, further research on cellular senescence, cancer, and senolysis is warranted.

AUTHOR CONTRIBUTIONS

Yoshimi Imawari: Conceptualization; data curation; formal analysis; writing – original draft. **Makoto Nakanishi:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

M. Nakanishi is a scientific advisor of AIRWEAVE corporation, a Scientific advisor and a shareholder of reverSASP Therapeutics, and an associate editor of *Cancer Science*. Y. Imawari has no conflict of interest.

ETHICS STATEMENTS

Approval of the research protocol by an Institutional Reviewer Board: N/A.
Informed Consent: N/A.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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