

Cellular senescence in cancer: Unveiling dual roles, tumor microenvironment dynamics and therapeutic innovations (Review)

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Abstract. Cellular senescence exerts context-dependent effects in cancer, functioning as both a tumor suppressor and promoter. Tumor suppression occurs through p53/p16-mediated cell cycle arrest, whereas tumor promotion is driven by the senescence-associated secretory phenotype (SASP), which reshapes the tumor microenvironment. SASP, comprising inflammatory cytokines such as IL-6 and IL-8 alongside matrix-remodeling factors, fosters immune evasion, angiogenesis and therapeutic resistance. Individual SASP components exert distinct effects on tumor progression across cancer types, which underscores the importance of context-specific analyses. For instance, IL-6 is associated with metastasis in breast cancer, whereas IL-8 is notably associated with therapy resistance in lung cancer. This heterogeneity highlights the need for personalized strategies targeting specific SASP factors. The primary aim of the present review is to systematically dissect the context-dependent mechanisms underlying cellular senescence in cancer including the heterogeneity of SASP and its cancer-type-specific roles, evaluate emerging senotherapeutic modalities, and discuss key challenges and future directions to guide precision oncology approaches. Recent advances in senotherapy, including senolytics such as dasatinib and quercetin, senomorphics and Traditional Chinese Medicine-derived agents such as resveratrol, aim to eliminate pathological senescence while preserving its beneficial roles. Nonetheless, key challenges persist, particularly in biomarker identification and optimizing combinations with immunotherapy. Future research can leverage single-cell technologies to dissect senescence heterogeneity, enabling the potential development of precision oncology approaches.

The primary aim of the present review is to systematically dissect the context-dependent mechanisms underlying cellular senescence in cancer-including the heterogeneity of the SASP and its cancer-type-specific roles and evaluate emerging senotherapeutic modalities, and discuss key challenges and future directions to guide precision oncology approaches. To further advance this aim, future research can leverage single-cell technologies to dissect senescence heterogeneity at the cellular and molecular levels; this will help distinguish protective senescent populations from pathogenic ones, thereby enabling the potential development of precision oncology approaches tailored to tumor-specific senescence landscapes.

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1. Introduction

Cellular senescence exhibits a paradoxical dual role in cancer biology, acting both as a barrier to tumorigenesis and as a facilitator of tumor progression (Fig. 1) (1). In early tumor development, senescence serves as a key tumor-suppressive mechanism by enforcing stable cell cycle arrest through the p53/p21 and p16/ribosome (Rb) pathways, thereby restricting the proliferation of damaged cells (1,2). By contrast, increasing evidence indicates that the senescence-associated secretory phenotype (SASP), comprising inflammatory cytokines (such as IL-6 and IL-8), growth factors and matrix-remodeling enzymes, can paradoxically foster tumorigenesis through extensive remodeling of the tumor microenvironment (TME) (2,3).

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Despite these advances, several critical questions remain unresolved: How do distinct components of the SASP differentially influence tumor progression across cancer types? How can we harness the cytoprotective properties of senescence while avoiding its pro-tumorigenic effects? Recent findings underscore the context-dependent nature of interactions between senescent cells and the TME, which highlights the need for precision strategies in senescence-targeted interventions (4-6). The present review aims to address these gaps by dissecting SASP heterogeneity and its therapeutic implications, and by evaluating emerging modalities, including senolytics and SASP modulators, that hold the potential to reshape cancer treatment paradigms.

Precise molecular targeting remains central to therapeutic success, particularly in virus-associated malignancies. For instance, hepatitis B virus X protein (HBx) drives hepatocellular carcinoma (HCC) via regulating the expression of microRNAs, underscoring the critical role of viral proteins in promoting malignant transformation (5); additionally, distinct genotypes of human T-cell lymphotropic virus type-1 (HTLV-1)-a virus closely associated with adult T-cell leukemia/lymphoma-exhibit varying prevalence among populations with 1.5% among blood donors in Iran) and correlate with differential cancer susceptibility, which supports genotype-based stratified screening for this hematological malignancy (6-9). These observations underscore the necessity for tailored screening and intervention strategies.

Within the TME, SASP-driven remodeling orchestrates immune evasion, angiogenesis and therapeutic resistance, compounding the complexity of cancer management (2,10,11). In advanced disease, the persistent accumulation of senescent cells and their secretome fosters an immunosuppressive niche through recruitment of myeloid-derived suppressor cells and T-cell dysfunction, while promoting metastatic dissemination (12,13).

This dynamic interplay between the protective and deleterious facets of senescence has spurred the development of targeted senotherapies (10,13). Current approaches encompass the following: i) Senolytic agents, which selectively ablate detrimental senescent cells (e.g., dasatinib-quercetin combinations); ii) senomorphic compounds, which attenuate harmful SASP components without eliminating senescent cells; and iii) novel candidates inspired by Traditional Chinese Medicine (e.g., resveratrol), which may fine-tune senescence responses (10,13,14). Yet, notable challenges persist in clinical translation, including the identification of biomarkers to distinguish protective from pathogenic senescent subsets, mitigation of therapy-induced SASP-mediated resistance and optimization of therapeutic timing to maximize benefit while limiting harm (2,11).

Emerging evidence suggests that integrating senescence-targeted agents with established treatments, such as immunotherapy, may potentiate therapeutic efficacy (12). Advancing these strategies will require robust preclinical models that accurately recapitulate the complexity of the human TME (15,16). Furthermore, incorporating single-cell profiling technologies and systematically evaluating combination regimens, including those pairing traditional Chinese and Western medicines, will be key to fully exploit the therapeutic promise of senescence modulation in oncology (14).

A nuanced understanding of cellular senescence in cancer underscores its dualistic nature and positions it as an attractive yet challenging therapeutic target. Future research can delineate the molecular determinants that dictate whether senescence exerts tumor-suppressive or tumor-promoting effects in specific contexts, paving the way for precision interventions that may potentially offer clinical benefit (1,2,11,12).

2. Dual-faced nature of cellular senescence in cancer

Cellular senescence exerts a paradoxical influence on cancer, functioning as both a tumor suppressor and promoter (17) (Fig. 2). In the early stages of tumorigenesis, senescence operates as a key defense mechanism, arresting the proliferation of damaged cells via the p53/p21 and p16/Rb pathways, thereby preventing malignant transformation (2,18-21). This protective effect is mediated by cell-autonomous processes such as growth arrest and by non-cell-autonomous mechanisms through SASP, which remodels the TME via cytokines, chemokines and matrix-degrading enzymes (21-24). For instance, in HCC, senescent cells suppress tumor initiation through activation of p53-p21-Rb signaling, whereas SASP-derived IL-24 recruits cytotoxic T cells to eliminate premalignant cells (5,25).

By contrast, at advanced stages, the SASP paradoxically fosters tumor progression by establishing an inflammatory niche conducive to metastasis and therapeutic resistance (15,26-33). This duality is shaped by tumor-specific microenvironmental contexts, resulting in divergent outcomes that can either restrain or accelerate cancer progression (34,35). In gastric cancer (GC), SASP-derived IL-6 and C-X-C motif chemokine ligand 12 (CXCL12) promote immune evasion and extracellular matrix (ECM) remodeling by recruiting myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs) (5,25). Similarly, in lung adenocarcinoma, SASP-driven upregulation of secreted phosphoprotein 1 (SPP1) and Tenascin enhances invasion and immune escape through CD44 and integrin signaling (26,31). Furthermore, senescence-associated epigenetic alterations, such as the demethylation of histone 3 lysine 9 dimethylation (H3K9me2, a key repressive histone modification), can reactivate oncogenes such as yes-associated protein 1 (YAP1), driving chemoresistance in GC (36).

The TME further modulates these outcomes, producing cancer type-specific consequences (15,26-29,31,32). In melanoma, the expression of senescence-associated genes, including BRCA2, is associated with increased CD8⁺ T-cell infiltration and favorable prognosis (37). By contrast, in HCC, high senescence scores are associated with elevated tumor mutational burden and poor survival, mediated by immunosuppressive SASP components (38,39). Long non-coding RNAs (lncRNAs) also influence this dynamic; for instance, nuclear paraspeckle assembly transcript 1 (NEAT1) suppresses senescence in HCC by stabilizing kinesin family member 11 (KIF11) and repressing CDK inhibitor 2A (CDKN2A) transcription (5), which underscores the context-dependent regulation of senescence across malignancies.

These opposing roles highlight the necessity of nuanced therapeutic strategies. Recent advances in senotherapy aim to exploit this complexity by selectively eliminating deleterious senescent cells using senolytics (e.g., dasatinib plus quercetin), attenuating SASP signaling via senomorphics or integrating

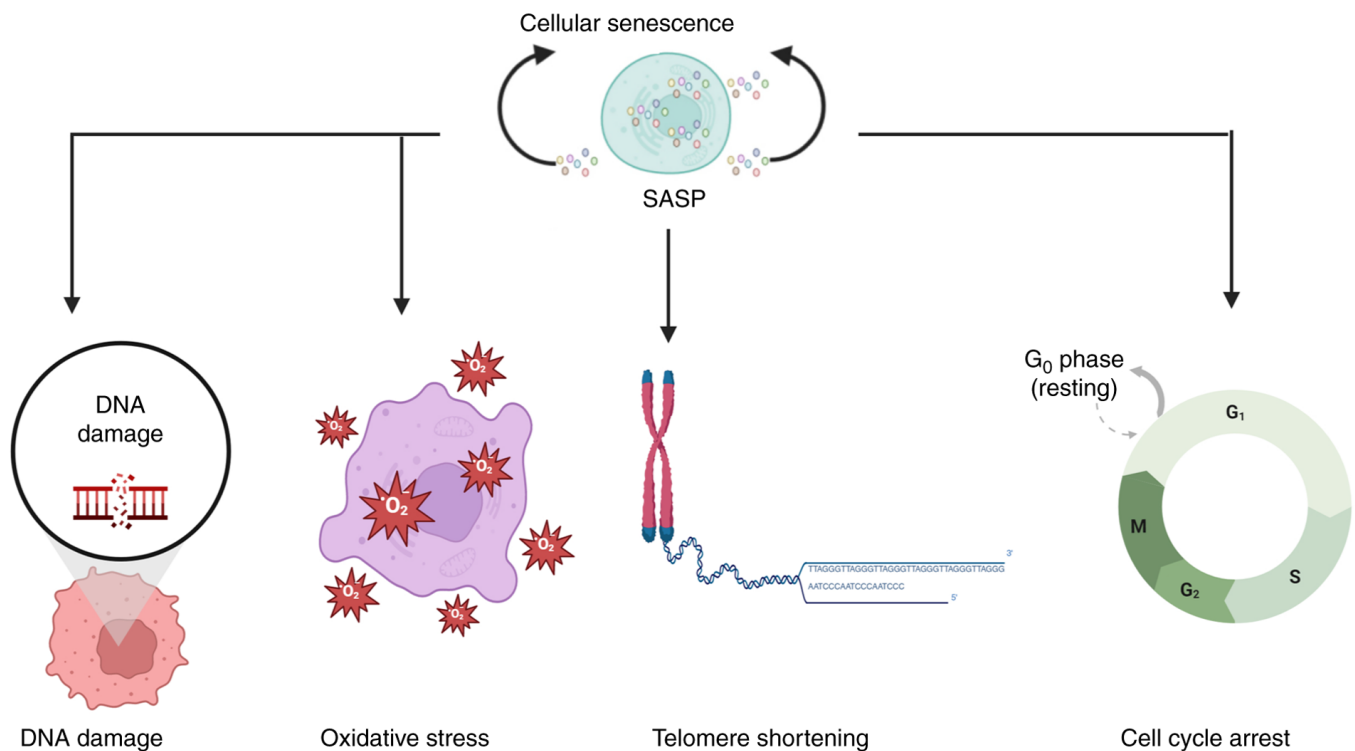


Figure 1. Mechanism of cellular senescence. The schematic illustrates the principal mechanisms driving cellular senescence, including DNA damage, Oxidative stress, Telomere shortening and Activation of cell cycle arrest pathways. The black arrows in this figure indicate the causal and regulatory relationships between the drivers of cellular senescence, downstream signaling pathways and the senescence process: i) They point from DNA damage, oxidative stress and telomere shortening to the activation of cell cycle arrest pathways, visually showing how these stressors trigger downstream signaling to induce cellular senescence via stable cell cycle arrest. ii) They may also link the senescence process to SASP, aligning with the document's statement that SASP is a key phenotypic feature of senescent cells. SASP, senescence-associated secretory phenotype.

these approaches with standard treatments (40,41). Key challenges include distinguishing beneficial from pathological senescence and mitigating therapy-induced senescence in normal tissues, which may drive recurrence (42). Future directions emphasize the development of: i) Biomarkers for senescent subpopulation profiling; ii) temporal control of senescence induction; and iii) combinatorial regimens to optimize efficacy while minimizing adverse effects. Successfully addressing these hurdles could transform cancer therapy by harnessing the protective potential of senescence while neutralizing its pro-tumorigenic properties (39,41). However, notable barriers remain before these strategies can be translated into safe and effective clinical applications.

Underlying mechanisms of context-dependent cellular senescence in cancer. Cellular senescence exhibits pronounced context dependency in cancer, functioning as either a tumor-suppressive barrier or a tumor-promoting factor depending on the specific biological and microenvironmental context. This paradox stems from the interplay between tumor-specific biology, SASP heterogeneity and dynamic remodeling of the TME. The present review delineates the core mechanisms underlying these contradictions, drawing on evidence from specific cancer types highlighted below.

The SASP is highly heterogeneous; its composition, cytokines, chemokines and matrix-remodeling enzymes show a marked variation across cancer types, like breast cancer, gastric cancer, lung adenocarcinoma, HCC, melanoma,

colorectal cancer and glioma, shaping the functional outcome of senescence. In melanoma, senescent cells secrete factors that enhance antitumor immunity. For instance, senescence-associated genes such as BRCA2 are associated with increased infiltration of CD8⁺ T cells, a hallmark of effective immune surveillance (37). Consistent with this, the SASP in melanoma tends to favor pro-inflammatory cytokines that recruit cytotoxic lymphocytes, which may potentially promote tumor suppression (25).

By contrast, HCC exhibits a pro-tumor SASP profile. High senescence scores in HCC are associated with elevated immunosuppressive factors that attract MDSCs and CAFs (38,39). These factors remodel the TME, promoting immune evasion and ECM deposition, thereby converting senescence into a tumor-promoting force. Such disparities underscore that SASP-driven outcomes depend on its specific components: Pro-immune vs. immunosuppressive factors determine whether senescence restrains or accelerates tumor growth.

The immune architecture of the TME further amplifies these contradictions, as senescent cells recruit distinct immune subsets via SASP signaling. In melanoma, senescence-associated cues bolster adaptive immunity; as noted, senescence-related genes are associated with enhanced CD8⁺ T-cell infiltration, suggesting a pro-inflammatory, antitumor milieu (37). By contrast, in other malignancies, senescence dampens immune surveillance. In GC, senescent cells foster immune suppression via SASP. SASP-derived IL-6 and CXCL12, for instance, recruit MDSCs and regulatory

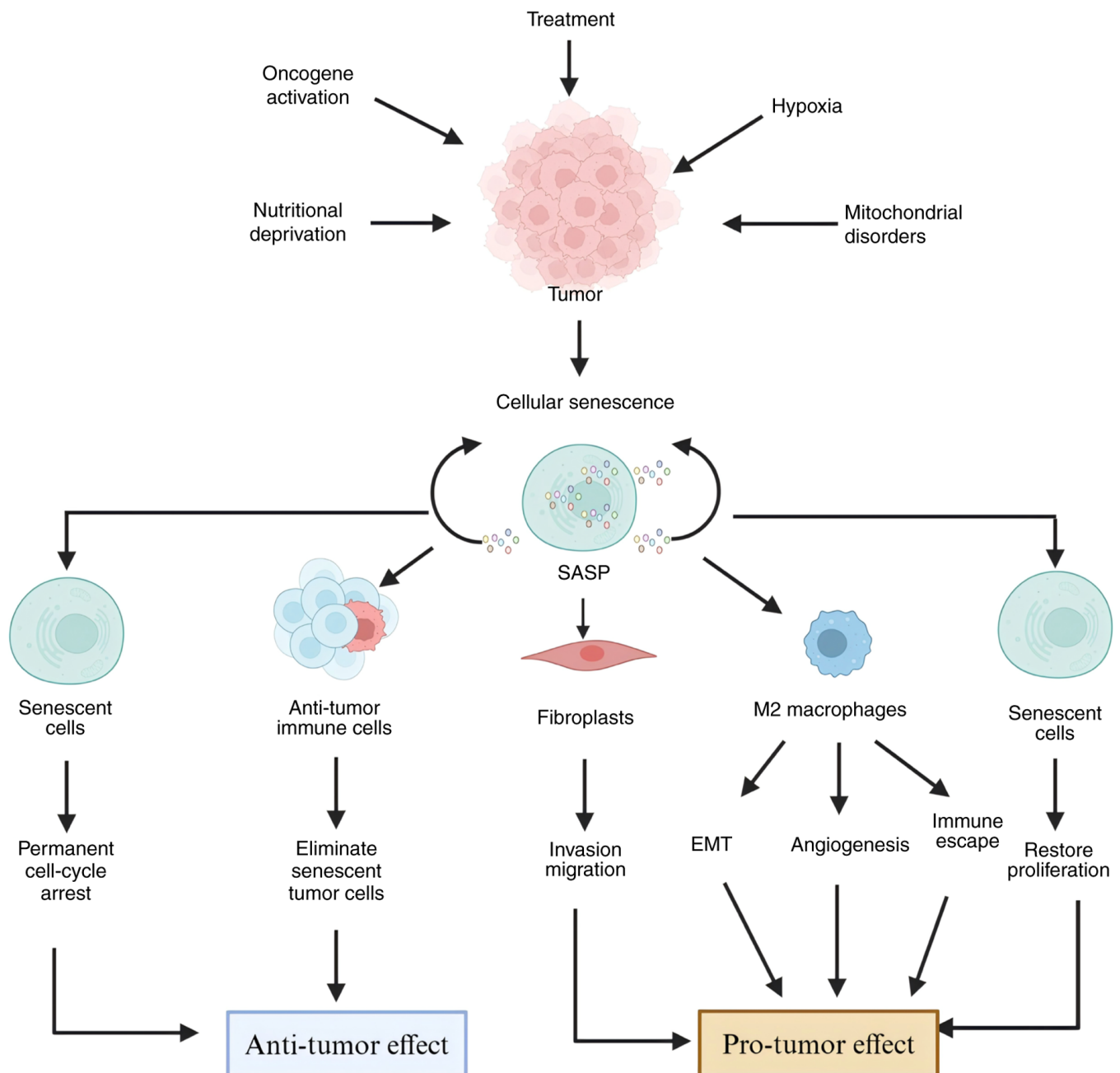


Figure 2. Dual roles of SASP in the TME. The schematic depicts the dual functions of the SASP within the TME, demonstrating its capacity to both promote and inhibit tumor progression. The black arrows in this figure visually distinguish the two opposing roles of SASP in the TME: i) Arrows for tumor-inhibiting effects point from the SASP to the recruitment of cytotoxic immune cells for clearing premalignant cells, consistent with the finding that SASP-derived IL-24 exerts tumor-suppressive effects in HCC. ii) Arrows for tumor-promoting effects point from the SASP to pro-tumor processes, such as recruiting myeloid-derived suppressor cells or cancer-associated fibroblasts and driving EMT or invasion, which are key pro-tumor mechanisms of SASP. SASP, senescence-associated secretory phenotype; EMT, epithelial-mesenchymal transition; TME, tumor microenvironment.

T cells (Tregs), blunting cytotoxic T-cell activity and enabling immune escape (27,28). Similarly, in lung adenocarcinoma, SASP-induced SPP1 and Tenascin interact with CD44 and integrins on immune cells, impairing their cytotoxicity and promoting evasion (26,31). These examples demonstrate that the net effect of senescence hinges on the immune subsets it recruits, cytotoxic vs. immunosuppressive.

Intrinsic genetic and epigenetic programs further govern this context dependency by modulating senescence pathway activity. In HCC, the lncRNA NEAT1 represses senescence by stabilizing KIF11 and inhibiting CDKN2A

transcription, a key senescence inducer (5). This epigenetic silencing diminishes the tumor-suppressive capacity of senescence, which allows malignant cells to evade growth arrest. By contrast, such repressive mechanisms appear less pronounced in melanoma, enabling senescence to exert anti-tumor effects. In glioma, TNF receptor-associated factor 7 knockdown induces senescence and synergizes with lomustine to suppress tumor growth (43). This contrasts with HCC, where senescence pathways are often epigenetically silenced, conferring resistance to similar strategies. Thus, the genetic and epigenetic landscape, including lncRNA

networks and senescence gene expression, notably determines whether senescence serves as a barrier or is co-opted for tumor progression.

Senescence also evolves with the tumor stage, shifting from protective in early disease to deleterious in advanced stages. Initially, senescence acts as a barrier to transformation through p53/p21- and p16/Rb-mediated cell cycle arrest (1,2). In premalignant lesions, SASP factors, like IL-6, TNF- α , p21/p16, SPPI, MMPs and YAP1, may trigger immune-mediated clearance of damaged cells (5,27). At later stages, persistent senescence and chronic SASP reshape the TME to foster metastasis and therapy resistance. In lung adenocarcinoma, late-stage senescent cells upregulate SPPI, which enhances invasiveness (31), while in GC, senescence-driven H3K9me2 demethylation reactivates oncogenes such as YAP1, which promotes chemoresistance (36). This stage-dependent shift underscores the dynamic nature of senescence and its adaptation to the evolving tumor ecosystem.

In summary, the opposing roles of cellular senescence in cancer arise from SASP heterogeneity, immune composition of the TME, cancer-specific regulatory networks and disease stage. Deciphering these context-dependent mechanisms is essential for precision strategies that exploit the tumor-suppressive effects of senescence while mitigating its pro-tumor consequences. These insights underpin the rationale for SASP-targeted interventions, such as inhibiting the IL-6/STAT3 pathway in breast cancer or blocking the IL-8/CXCR2 axis in lung cancer (33,34) (Table I), to enable more effective senotherapy.

Tumor-specific mechanisms underlying SASP component heterogeneity. The heterogeneity of SASP components across cancer types reflects tumor-specific signaling networks and interactions within the TME, as exemplified by IL-6 and IL-8.

In breast cancer, IL-6 promotes metastasis through context-dependent pathways. Preclinical evidence demonstrated that IL-6 activates downstream cascades regulating epithelial-mesenchymal transition (EMT) and matrix remodeling, both key for metastatic dissemination. Consistently, IL-6-driven signaling is associated with aggressive phenotypes in breast cancer, where senescent cells secrete IL-6 to reinforce a pro-metastatic niche.

In GC, IL-6 primarily reshapes immune landscapes within the TME. Acting through chemokine networks such as chemokine (C-C motif) ligand 2 (CCL2)/C-C chemokine receptor 2, it recruits MDSCs and CAFs, fostering immunosuppression and enabling immune evasion (31,32). This divergence from breast cancer partly reflects distinct IL-6 receptor (IL-6R) distribution, with GC enriched for IL-6R on stromal and immune cells compared with tumor cells.

IL-8 exhibits similarly context-dependent functions. In lung adenocarcinoma, SASP-derived IL-8 underpins therapy resistance by sustaining drug-tolerant cell survival via CXC receptor 1/2 (CXCR1/2) signaling, thereby maintaining tumor persistence despite treatment (26,29). By contrast, in colorectal cancer, IL-8 primarily drives angiogenesis by stimulating vascular endothelial proliferation and migration, which enhances tumor perfusion and growth.

These functional disparities arise from three principal factors: i) Cell-type specificity of SASP receptor expression

(e.g., IL-6R on tumor vs. stromal cells); ii) preferential activation of downstream pathways (e.g., EMT-related cascades in breast cancer vs. immune-modulatory pathways in GC); and iii) TME composition, which dictates whether SASP factors engage tumor, immune or stromal compartments (15,33-36). Collectively, these mechanisms highlight the need for context-specific targeting of SASP components in cancer therapy.

Targeting IL-6 illustrates the following principle: Neutralizing IL-6 or blocking its downstream signaling (e.g., anti-IL-6 antibodies or STAT3 inhibitors) may suppress metastasis in breast cancer, whereas in GC, such interventions may primarily mitigate immunosuppression by reducing MDSC recruitment (37-43), consistent with strategies outlined in Table I. Similarly, the divergent roles of IL-8 underscore the therapeutic value of CXCR1/2 blockade in lung adenocarcinoma to disrupt cancer stem cell maintenance and therapy resistance, whereas in colorectal cancer, inhibiting IL-8-mediated hypoxia inducible factor-1 α upregulation could attenuate angiogenesis. These approaches align with the SASP-modulating therapies summarized in Table I, emphasizing that therapeutic efficacy depends on matching interventions to the dominant IL-8-driven pathway in each type of cancer.

3. Relationship between cellular senescence and the TME

Cellular senescence exerts profound, context-dependent effects on the TME, which shapes cancer progression through complex interactions. The accumulation of senescent cells within the TME promotes tumor development by secreting pro-inflammatory and pro-tumorigenic factors collectively known as the SASP (3,44,45). SASP components remodel the ECM and establish a malignant niche by driving cancer cell proliferation, invasion and immune evasion (45,46). Furthermore, SASP factors recruit and activate stromal cells, such as CAFs, further reinforcing a tumor-permissive microenvironment (17,44,47). Senescent immune cells also contribute to immune dysfunction by disrupting metabolic balance (e.g., glucose competition) and amplifying immunosuppressive signals (e.g., cAMP), thereby facilitating immune escape (48).

Dual roles of senescent cells in the TME. The influence of senescent cells within the TME is highly dynamic. While SASP components can elicit antitumor responses by enhancing immune surveillance and suppressing angiogenesis in certain contexts (49,50), specifically referring to four scenarios supported by preclinical and clinical evidence: First, in premalignant lesions or early-stage tumors, where senescent cells secrete immune-activating SASP factors to trigger clearance of abnormal cells—for instance, in HCC premalignancy, senescent hepatocytes release IL-24 to recruit cytotoxic CD8⁺ T cells for eliminating premalignant cells (5,15,25-34). Second, in cancer types with high immunogenicity, such as melanoma, senescent cells express senescence-associated genes and secrete pro-inflammatory SASP factors that promote CD8⁺ T-cell infiltration, correlating with favorable patient prognosis (37). Third, in the acute phase after therapy-induced senescence, short-term SASP secretion from acutely senescent tumor cells activates immunogenic cell death, recruiting natural killer

Table I. Therapeutic strategies harnessing context-specific senescence mechanisms.

Therapeutic strategy	Mechanism of action	Target cancer types	Key findings	(Refs.)
Senolytics (exisulind)	Induces apoptosis in senescent cells; synergizes with palbociclib	GC	Reduces SASP-mediated immunosuppression; enhances response to senescence induction	(83)
Senescence induction (FEN1-PBX1 inhibition)	Inhibits FEN1-PBX1 axis to trigger senescence via ROS accumulation	Breast cancer	Suppresses tumor growth by activating p53/p21 pathways	(84)
LncRNA modulation (NEAT1 knockdown)	Promotes KIF11 degradation, activating CDKN2A-mediated senescence	HCC	NEAT1 upregulation is associated with senescence evasion; knockdown reduces tumor progression	(85)
Senescence-related gene targeting (EZH2 inhibition)	Reactivates CDKN2A by reversing H3K27me3-mediated silencing	HCC	EZH2 inhibitors reduce tumor growth and enhance immune infiltration	(86,87)
Combination therapy (TRAF7 knockdown + lomustine)	TRAF7 knockdown induces senescence; lomustine enhances senescent cell clearance	Glioma	Reduces recurrence by synergizing senescence induction with chemotherapy	(43)
Traditional Chinese Medicine (Jianpi Huayu decoction)	Suppresses senescence via p53-p21-Rb pathway	Colorectal cancer	Inhibits tumor growth by reducing SASP and stabilizing the TME	(83)

GC, gastric cancer; lncRNA, long non-coding RNA; HCC, hepatocellular carcinoma; EZH2, enhancer of zeste homolog 2; CDKN2A, CDK inhibitor 2A; Rb, ribosome; KIF11, kinesin family member 11; TRAF7, TNF receptor-associated factor 7; SASP, senescence-associated secretory phenotype; TME, tumor microenvironment; H3K27me3, histone H3 lysine 27 trimethylation; NEAT1, nuclear paraspeckle assembly transcript 1; FEN1, flap endonuclease 1; PBX1, pre-B cell leukemia factor 1; ROS, reactive oxygen species.

(NK) cells and dendritic cells to enhance antitumor immunity (18,51). Fourth, in tissues rich in innate immune cells, the tissue-specific TME amplifies the antitumor effect of SASP—for example, senescent hepatic stellate cells in the liver induce M1 macrophage polarization via SASP, inhibiting liver fibrosis and early tumorigenesis (49). They more frequently drive tumor progression through chronic inflammation, immunosuppression and metastasis, as persistent senescence in advanced cancers leads to accumulated immunosuppressive SASP components that recruit myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs), fostering immune evasion and metastatic dissemination (30,31,36). They more frequently drive tumor progression through chronic inflammation, immunosuppression and metastasis (51). This paradox extends beyond oncology; in neurodegenerative models, such as MAPTP301SPS19 mice, clearance of senescent cells improves cognitive function (51). These observations highlight the broad pathological impact of senescence and its potential as a therapeutic target in cancer and aging-related diseases.

Therapeutic strategies targeting senescence in the TME. Addressing these complexities requires therapeutic strategies that precisely modulate senescent cells to enhance antitumor effects while minimizing pro-tumorigenic consequences. Senolytics (e.g., dasatinib and quercetin) represent a promising approach, selectively eliminating harmful senescent cells to reduce SASP-driven inflammation and restore treatment

sensitivity (52–57). Another strategy integrates senotherapies with immunotherapy to reverse immune suppression in the TME, thereby improving tumor recognition while counteracting SASP-mediated resistance (58–63). These approaches underscore the need for precision medicine, tailoring treatment regimens to tumor-specific senescence profiles.

Future research can elucidate mechanisms governing senescence plasticity within the TME, identify biomarkers to distinguish protective from pathogenic senescence and optimize combinatorial strategies that harness antitumor benefits without promoting malignancy. Emerging insights into senescence reprogramming hold the potential to reshape cancer therapy by disrupting tumor ecosystems and improving patient outcomes (64).

4. Biomarkers and therapeutic targeting of senescent cells in the TME

Biomarkers for identification and functional analysis of senescent cells. The identification and functional characterization of senescent cells within the TME rely on robust biomarkers, including cell cycle regulators [e.g., CDKN2A inhibitor (p16INK4a, where INK4a denotes the p16 protein subtype) and p21 wild-type p53-activated fragment 1 (p21WAF1, where WAF1 is the functional alias of the p21 protein)], senescence-associated β -galactosidase activity (SA- β -gal) and specific chromatin modifications such as senescence-associated heterochromatin foci (SAHF) (65,66).

These molecular signatures serve dual purposes: Enabling precise tracking of senescent cell populations across spatial and temporal scales and providing mechanistic insights into their roles in tumor progression and therapeutic response (Fig. 3). Quantitative analysis of these biomarkers has become essential to evaluate the efficacy of senolytic interventions and understanding the dynamic processes of cellular senescence during cancer development (67-69) (Fig. 3).

SASP and its dual roles. Central to the paradoxical effects of senescent cells is the SASP, a complex repertoire of secreted factors-including pro-inflammatory cytokines, chemokines, and ECM-remodeling enzymes whose composition dictates tumor suppression or promotion (64). In glioblastoma, for instance, senescent malignant cells secrete high levels of IL-6 and IL-8, which activate STAT3 signaling in neighboring tumor cells, while MMP-9 released through SASP mediates ECM degradation to facilitate tumor invasion (65-70). This dynamic secretion profile, conserved in patient glioblastomas, underscores how SASP components contribute to the aggressive phenotype of certain cancers, aligning with the notion that senescent cells exert context-dependent influences through their secretory phenotype. While the SASP can initiate tumor-suppressive responses, such as immune activation and inhibition of angiogenesis, it frequently promotes tumor progression by facilitating immune evasion and remodeling the surrounding microenvironment (71). Epigenetic regulation further modulates SASP activity, where chromatin modifications can diminish tumor-suppressive functions of senescence and instead support malignant progression.

Therapeutic strategies targeting senescent cells and future directions. Therapeutic strategies have evolved to address the complex biology of senescent cells through two complementary approaches: i) Senolytic compounds selectively eliminate senescent cells, thereby mitigating the deleterious effects of the SASP-navitoclax achieves this by targeting BCL-xL in senescent cells to induce apoptosis (68), while fisetin preferentially clears senescent populations via p53-dependent pathways (72), consistent with broader senolytic mechanisms reported previously (24,38,73-76); and ii) senomorphic agents, by contrast, modulate specific SASP components to suppress harmful effects while preserving beneficial secretory functions-for example, compounds that inhibit NF- κ B or restore mitochondrial function reduce pro-inflammatory SASP without eliminating senescent cells, maintaining factors critical for tissue repair (77). Combining senolytics with immunotherapy holds promise, enhancing antitumor immune responses by modulating key checkpoints and cytokine networks.

Current research priorities include the identification of predictive biomarkers for patient stratification, optimization of senolytic treatment timing, preservation of physiologically beneficial senescent populations and integration with existing therapeutic modalities (28,76-78). These efforts aim to establish precision senotherapy, tailoring interventions based on comprehensive profiling of tumor-specific senescence landscapes.

Emerging technologies such as single-cell multi-omics and advanced computational modeling are expected to provide further insights into the spatiotemporal heterogeneity of

tumor-associated senescent cells, enabling refined and personalized treatment strategies that consider both neoplastic and microenvironmental factors (77-80).

From a clinical perspective, senescence biomarkers may serve as predictors of treatment responsiveness, while SASP profiling can guide selection of senomorphic interventions. Temporal optimization of senolytic administration and careful consideration of the immune context are key for therapeutic success. Collectively, these strategies highlight the importance of mechanistic studies to elucidate adaptive responses of senescent cell populations, with the ultimate goal of developing targeted interventions that may potentially promote tumor suppression.

5. Biomarkers of senescent cells in the TME

Identification and characterization of senescent cells. The identification and characterization of senescent cells within the TME rely on established biomarkers, including upregulation of cell cycle inhibitors p21WAF1 and p16INK4a, increased SA- β -gal activity and the formation of SAHF (65,66). These markers not only enable the detection and monitoring of senescent cells but also provide insights into their roles in cancer progression and therapeutic response (Fig. 4). Quantitative assessment of these biomarkers allows evaluation of the prevalence, spatial distribution and functional impact of senescent cells within the TME, which supports detailed studies on their contributions to tumor biology and treatment resistance (67-69).

SASP and its dual roles. A hallmark of senescent cells is the SASP, a complex and dynamic ensemble of secreted cytokines, chemokines and matrix-remodeling proteases. SASP has complex, context-dependent effects. Although SASP can activate antitumor immune responses, it could promote tumorigenesis by altering the microenvironment and impairing immune surveillance as well (70). Epigenetic regulation-such as histone acetylation of SASP-related genes further modulates SASP activity, which influences whether senescent cells function as tumor suppressors or facilitators of malignancy. Epigenetic regulation further modulates SASP activity, which influences whether senescent cells function as tumor suppressors or facilitators of malignancy. Dysregulation of tumor-suppressor pathways including p53-p21, p16INK4a-Rb, PTEN-PI3K-AKT, p27Kip1 and TGF- β -Smad that often undergo dysregulation, which disrupts their ability to regulate the cell cycle and enforce senescence-induced growth arrest, ultimately enabling cancer progression, which can bypass senescence-induced growth arrest, enabling cancer progression (1,5,15,25,33,64). Understanding these mechanisms is essential to develop therapies that selectively mitigate pro-tumorigenic SASP functions while preserving beneficial anticancer effects.

Therapeutic implications and future directions. Recent advances in senotherapy have expanded potential intervention strategies. Immune-based strategies represent a breakthrough, with uPAR-targeted CAR-T cells eliminating 67-90% of senescent cells in aged mouse tissues, improving glucose tolerance and exercise capacity for over 12 months through specific

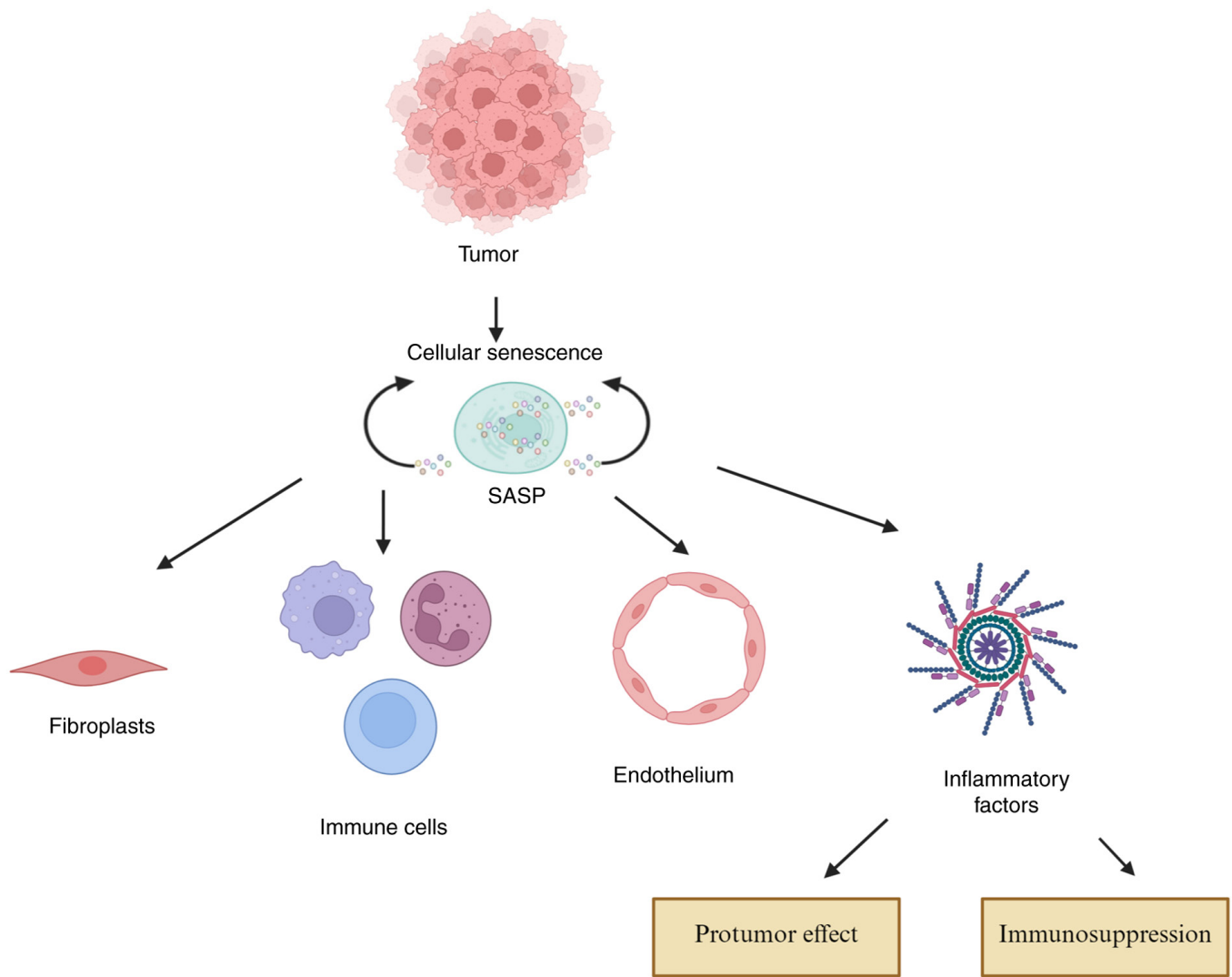


Figure 3. Interaction between senescent cells and the TME. The schematic illustrates the complex crosstalk between senescent cells and multiple components within the TME, highlighting how senescent cells modulate immune responses, stromal cells, and inflammatory signaling. The black arrows visualize bidirectional crosstalk initiated by senescent cells via SASP: i) Arrows for immune cell recruitment point from senescent cells to distinct immune populations. ii) Arrows for immune response suppression point from senescent cells to pathways that impair anti-tumor immunity, aligning with the review's discussion on senescence-mediated immunosuppression. Additionally, SASP signals to fibroblasts, endothelial cells and inflammatory factors with further driving pro-tumor effects and immunosuppression. SASP, senescence-associated secretory phenotype; TME, tumor microenvironment.

recognition of the senescence marker uPAR (80). For SASP modulation, JAK inhibitor ruxolitinib and mTOR inhibitor rapamycin showed dual efficacy in silencing pro-tumor inflammation while preserving regenerative functions, validated in myelofibrosis trials and preclinical studies on age-related pathologies (81). These advancements collectively highlight the shift from single-agent senolysis to precision strategies combining targeted delivery, immune engineering, and SASP regulation, with clinical trials and guideline endorsements solidifying their translational value. Senolytic drugs, such as navitoclax and fisetin, selectively eliminate senescent cells, thereby reducing SASP-mediated tumor promotion. Senomorphic agents, by contrast, modulate SASP activity without inducing cell death, providing refined control over downstream effects (19). The interplay between senescent cells and immune regulation offers additional therapeutic opportunities. The interplay between senescent cells and immune regulation offers additional therapeutic opportunities

specifically for enhancing cancer treatment efficacy, such as reversing SASP-mediated immunosuppression, developing senescence-targeted immunotherapies and preventing therapy-induced recurrence by blocking senescence-driven immune escape; these opportunities also extend to alleviating age-related diseases by targeting their dysregulated crosstalk. By shaping immune responses through secreted factors, senescent cells can influence the efficacy of immunotherapies. Combining senolytics with checkpoint inhibitors or adoptive cell therapies may enhance antitumor immunity while counteracting SASP-mediated immune evasion (13).

Future research aims to refine these strategies using single-cell omics, spatial transcriptomics and artificial intelligence (AI)-driven modeling to resolve the heterogeneity of tumor-associated senescence. Identification of predictive biomarkers will enable patient stratification, optimizing treatment timing and combination regimens to maximize therapeutic benefit. The ultimate goal is precision senotherapy,

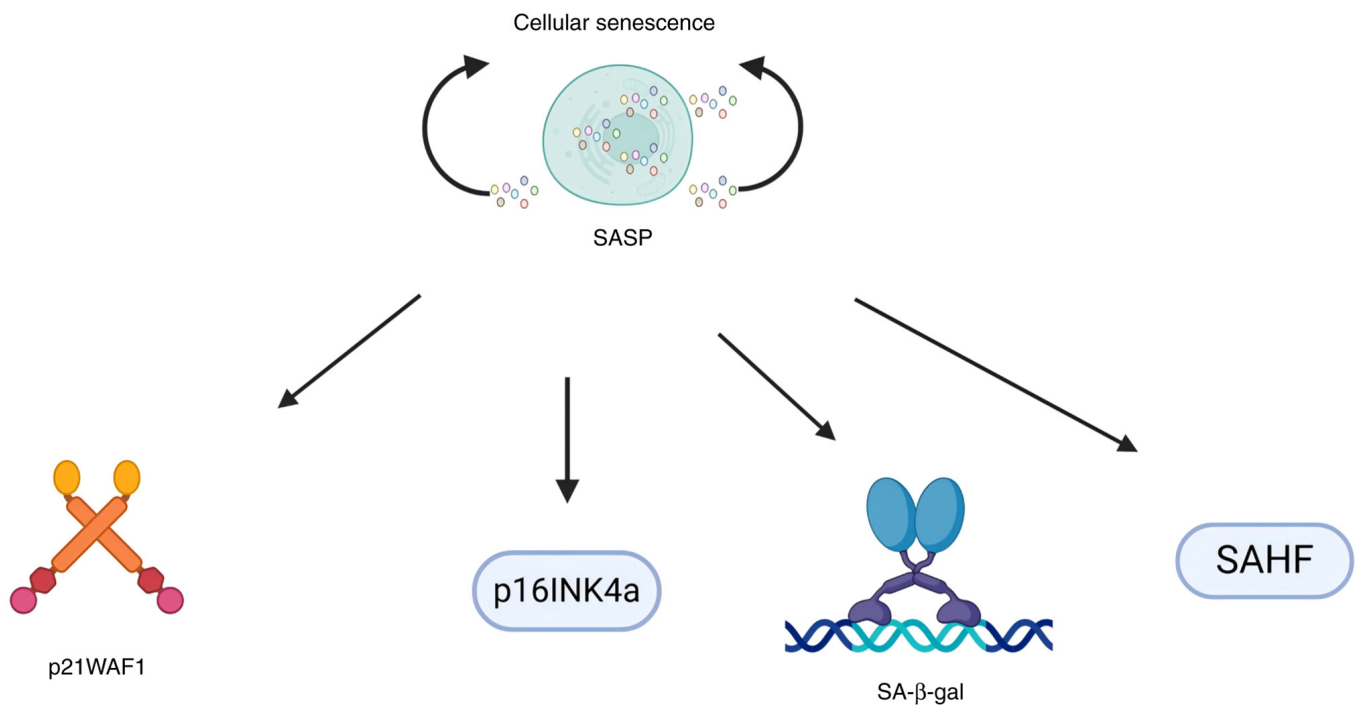


Figure 4. Biomarkers of cellular senescence. The schematic summarizes the key biomarkers used to identify and monitor senescent cells, including cell cycle inhibitors (p16INK4a, p21WAF1), SA- β -gal and SAHF. For consistency with the text, the 'INK4a' in p16INK4a and 'WAF1' in p21WAF1 in this figure correspond to the gene subtype (INK4a) or protein alias (WAF1) described in the main text, with the same functional meaning. The black arrows in this figure visually connect senescent cells to their key biomarkers, as detailed in the review: i) Arrows for intracellular biomarkers point from senescent cells to cell cycle inhibitors, SA- β -gal and SAHF. These markers reflect cell-autonomous senescence features and are critical for 'tracking senescent cell populations'. ii) An arrow for the secretory biomarker SASP points from senescent cells to SASP, highlighting its origin from senescent cells and aligning with the document's definition of SASP as a 'dynamic secreted phenotype' that also mediates TME interactions. SA- β -gal, senescence-associated β -galactosidase activity; SAHF, senescence-associated heterochromatin foci; SASP, senescence-associated secretory phenotype.

where interventions are tailored to individual senescence profiles, harmonizing tumor suppression with microenvironmental homeostasis. Such advances may transform cancer care, moving from broadly cytotoxic treatments to mechanism-driven, immune-compatible therapies that improve outcomes while minimizing toxicity (82,83).

Emerging strategies exploit context-specific senescence mechanisms, as summarized in Table I. These include targeting lncRNAs in HCC or combining senescence induction with chemotherapy in glioma, demonstrating how context-specific interventions can potentially promote tumor suppression (36,84,85).

6. Clearance of senescent cells and tumor treatment

Senescence as a tumor-suppressive mechanism and pro-senescence therapy. Clinical evidence increasingly demonstrates that chemotherapy-induced accumulation of senescent cells within tumors is often associated with improved patient outcomes (86,87). Preclinical studies corroborated these observations, which demonstrates that defects in p53-dependent senescence pathways can promote tumorigenesis and confer chemotherapy resistance (18,88,89). These findings position cellular senescence as a natural tumor-suppressive mechanism, notably restraining cancer progression. The recent Food and Drug Administration approvals of CDK4/6 inhibitors, including abemaciclib and palbociclib, which possess senolytic properties, further support 'pro-senescence

therapy' as a viable anticancer strategy, particularly in breast cancer and non-small cell lung cancer (90).

Senolytic therapy: Targeting senescent cells to remodel the TME. Senolytic therapy, which selectively eliminates senescent cells, is emerging as a promising strategy to remodel the TME and enhance therapeutic efficacy (91,92). By inducing apoptosis in senescent cells, senolytics such as navitoclax and fisetin reduce their abundance, thereby mitigating deleterious SASP effects including angiogenesis, invasion and metastasis (93). This approach addresses the accumulation of age-associated senescent cells, which contributes to cancer susceptibility and represents a notable advance in oncology (94,95). Depletion of senescent cells suppresses pro-inflammatory and tumorigenic SASP factors, creating a TME more conducive to effective anticancer therapies (96). Numerous preclinical compounds including BH3 mimetics, PROTAC degraders, dual-mechanism small molecules, and epigenetic modulators which exhibit potential by selectively eliminating senescent cells, reversing SASP-mediated immunosuppression, or synergizing with other therapies; as mechanistic understanding of their targeting of senescence-associated pathways increases, senescence-targeted interventions are poised to become a central component of cancer treatment.

However, the dual role of senescent cells complicates therapeutic implementation. While their clearance can counteract pro-tumorigenic effects, residual SASP factors may persist and influence neighboring cells, potentially maintaining a

tumor-permissive environment (97). Premature removal of senescent cells during specific treatment phases such as the early stage after chemotherapy or radiotherapy, when SASP still secretes antitumor factors to recruit cytotoxic CD8⁺T cells could also disrupt SASP-mediated immune responses that support antitumor activity (98); therefore, optimizing the timing and context of senolytic interventions is key. Future studies can refine senolytic mechanisms and elucidate dynamic crosstalk among senescent cells, immune populations and stromal components within the TME. Balancing senescence induction with selective elimination will be essential to maximize therapeutic benefit while minimizing tumor-promoting risks (99). Addressing senescence-driven therapeutic resistance remains a key challenge, which requires strategies to counteract immune evasion and treatment failure (100) (Fig. 5).

Combining senolytics with immunotherapy and emerging therapeutic strategies. SASP-mediated immunosuppression enables tumor cells to evade immune surveillance and resist therapy (101), highlighting the potential of combining senolytics with immunotherapy, particularly immune checkpoint inhibitors, such as PD-1 blockers, PD-L1 inhibitors, CTLA-4 antibodies and novel LAG-3 inhibitors. Such combinations can concurrently eliminate immunosuppressive senescent cells and enhance antitumor immunity, potentially overcoming SASP-mediated therapy resistance (102). Targeting specific SASP factors, including IL-6 and TGF- β , may further reprogram the TME from immunosuppressive to immune-active, opening opportunities for synergy with adoptive cell therapies or cancer vaccines (103).

Implementing these strategies requires a precision medicine framework, incorporating biomarker-driven patient stratification to identify optimal candidates for senolytic-immunotherapy combinations. Advanced approaches, such as single-cell profiling and AI-based predictive modeling, can help resolve tumor-associated senescence heterogeneity and guide personalized regimens (104). Translating these innovations will necessitate multidisciplinary collaboration among oncologists, immunologists and computational biologists to ensure safe and effective application across diverse patient populations.

The dualistic nature of senescent cells, both restraining and promoting cancer, presents a complex yet promising therapeutic frontier. While pro-senescence therapies can inhibit tumor growth, senolytic strategies offer a means to counterbalance their detrimental effects. Optimizing combination approaches that integrate senescence modulation with immunotherapy, chemotherapy and targeted agents will be pivotal specifically for balancing the tumor-suppressive and pro-tumorigenic effects of senescence, overcoming therapy-induced senescence-related resistance, remodeling the immunosuppressive TME which can reduce MDSC recruitment via IL-6 inhibition and reinvigorating CD8⁺T cells with PD-1 blockers in HCC, enabling precision senotherapy tailored to cancer heterogeneity and minimizing treatment toxicity. By systematically dissecting the role of senescence in cancer, next-generation therapies can exploit its protective mechanisms while neutralizing pro-tumorigenic potential, ultimately improving survival and quality of life for patients.

Beyond established senolytics such as dasatinib and quercetin, emerging agents such as exisulind have demonstrated efficacy in GC by inducing apoptosis in senescent cells and synergizing with palbociclib to enhance senescence clearance (83). In breast cancer, inhibition of the flap endonuclease 1-pre-B cell leukemia factor 1 axis triggers senescence via reactive oxygen species accumulation and activation of p53/p21 pathways, which suppresses tumor growth (84). These findings support the expansion of senolytic and senescence-inducing strategies beyond conventional regimens.

7. Dual nature of senescent cells in tumor immune evasion and therapeutic opportunities

Paradoxical roles of senescence and SASP in tumor immunity. Cellular senescence exerts a key yet paradoxical influence in cancer, simultaneously constraining tumor initiation while promoting immune evasion and therapy resistance. The SASP is central to this duality, comprising a complex mixture of inflammatory cytokines (e.g., IL-6 and TNF- α), chemokines (e.g., CCL2 and CXCL12) and proteases that notably shape the TME (105,106). Initially, SASP factors recruit immune effector cells; however, chronic SASP activity drives immunosuppression through multiple mechanisms: Polarizing macrophages toward tumor-promoting M2 phenotypes (107), recruiting Tregs (107,108) and inducing T-cell dysfunction via p16INK4a-mediated senescence (108). Therefore, a permissive niche is established, enabling malignant cells to evade immune surveillance despite the tumor-suppressive growth arrest in senescent cells.

Oncogene-induced senescence and context-dependent tumorigenesis. The interplay between senescence and tumorigenesis is particularly evident in oncogene-induced senescence. Activation of oncogenes such as human Ras oncogene G12V, HER2, EGFR and PI3K triggers senescence as an intrinsic tumor-suppressive response (109), yet concurrent SASP secretion undermines this protection by promoting immunosuppression and remodeling tissue architecture. Conversely, oncogene inactivation (e.g., Myc) can induce senescence and tumor regression across various cancer types (110), like lymphoma, HCC, triple-negative breast cancer, highlighting the context-dependent nature of these processes. Senescent cells disrupt normal tissue structure and suppress antitumor immunity via their secretory profile, thereby facilitating immune evasion and disease progression (28).

Therapeutic strategies targeting senescence and SASP in cancer. This biological paradox presents both challenges and opportunities for intervention. While senescence induction halts tumor growth, SASP activity may drive therapeutic resistance and immune escape (111). Current strategies focus on three complementary approaches: i) Senolytic agents that selectively eliminate senescent cells to abrogate pro-tumorigenic effects; ii) SASP-modulating therapies that inhibit deleterious factors while preserving beneficial functions; and iii) rational combinations with immunotherapy to overcome SASP-mediated immunosuppression (112). Research

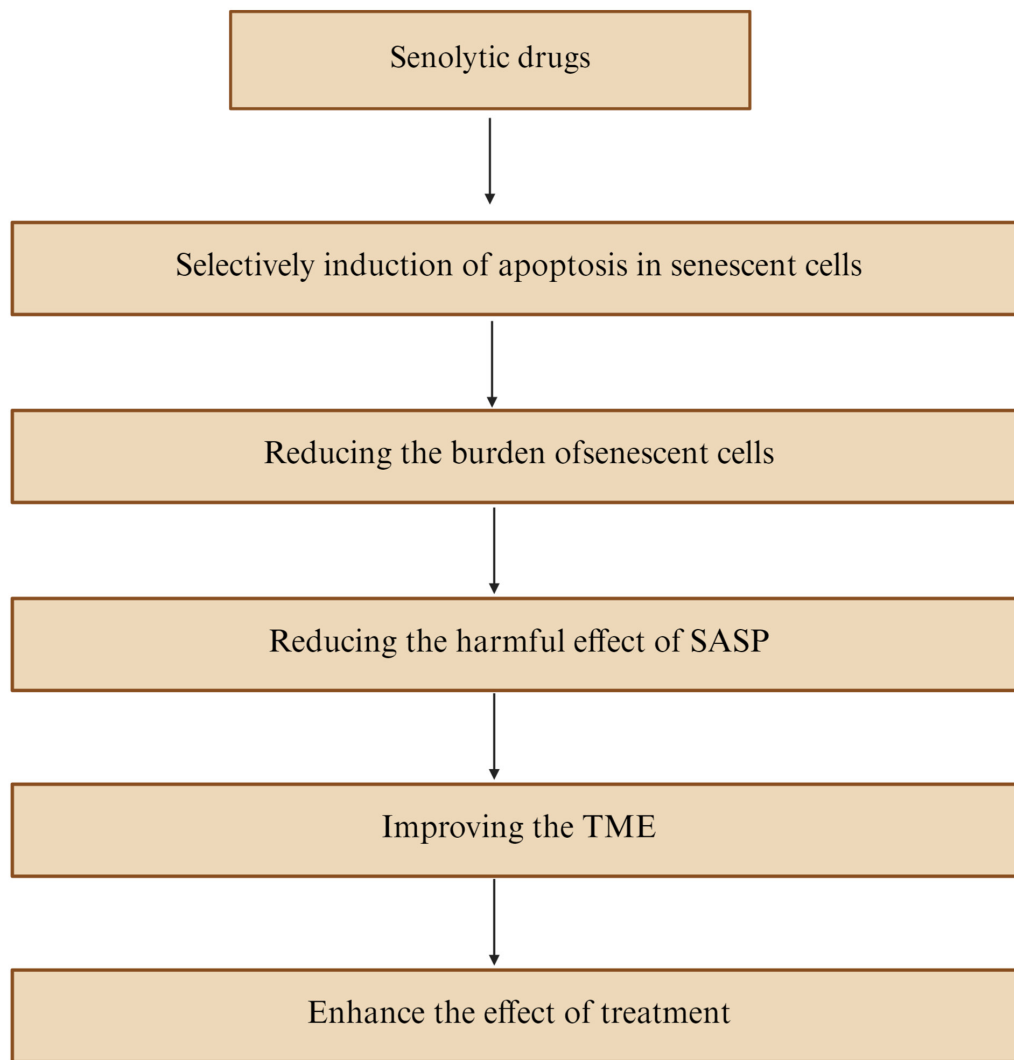


Figure 5. Mechanism of senolytic therapy. The figure illustrates the mechanism of action of senolytic therapies, demonstrating how these agents selectively target and eliminate senescent cells to mitigate SASP-driven effects and remodel the TME. The black arrows visually map the key steps of senolytic therapy's mechanism, consistent with the review: i) Arrows for 'selective targeting' point from senolytic agents to senescent cells, reflecting the agents' ability to specifically recognize senescent cells. ii) Arrows for 'cell elimination' correspond to Selective induction of apoptosis in senescent cells, which drives the reduction of the burden of senescent cells-a core function of senolytics as identified in the document. iii) Arrows for 'therapeutic effects' branch to two outcomes: Reduction of SASP-driven harm and Improvement of the TME, ultimately leading to enhancement of treatment efficacy-aligning with the review's view that senolytics alleviate SASP-mediated tumor promotion. SASP, senescence-associated secretory phenotype; TME, tumor microenvironment.

suggests that precisely timed senolytic interventions can enhance immune checkpoint blockades by remodeling the TME and reinvigorating antitumor T-cell responses (3,113). These findings align with the document's emphasis on temporal precision in senolytic-immunotherapy combinations to avoid late-stage immunosuppressive SASP while preserving early IFN-driven antitumor immunity (5,93) (Table II).

Future cancer therapies are likely to integrate advanced approaches leveraging the current growing understanding of senescence biology. These include biomarker-driven patient stratification, temporally controlled senolytic delivery and senomorphic agents designed to reprogram rather than eliminate senescent cells (113). By simultaneously targeting malignant cells and reshaping the immunosuppressive microenvironment, such strategies have the potential to overcome treatment limitations, reduce recurrence and improve long-term outcomes.

Tumor-specific immune modulation by SASP illustrates the need for personalized approaches. In melanoma, senescence-associated gene expression is associated with increased CD8⁺ T-cell infiltration (36), whereas in HCC, high senescence scores are associated with immunosuppressive SASP and poor prognosis (38,39). Targeted interventions, such as enhancer of zeste homolog 2 inhibition to reactivate CDKN2A and enhance immune infiltration (85,86) or lncRNA NEAT1 knockdown to restore senescence (84), exemplify strategies to exploit senescence biology for precision oncology.

8. Interplay between senescent cells and telomerase pathways in cancer

Telomerase reactivation and senescence escape in tumor cells. Cellular senescence and telomerase activity are closely intertwined in cancer development and progression. Telomerase, which preserves telomere length, is largely

Table II. Therapeutic approaches and challenges.

Therapeutic approach	Mechanism	Potential benefit	Challenges
Senolytic therapy	Selective elimination of senescent cells	Reduces SASP-mediated immunosuppression	May disrupt tumor-suppressive senescence
SASP modulation	Targeted cytokine inhibition (e.g., IL-6 blockade)	Preserves senescence arrest while blocking harmful secretions	Complex cytokine network redundancy
Combination immunotherapy	Senolytics + checkpoint inhibitors	Enhances T cell reinvigoration	Timing/dosing optimization required

SASP, senescence-associated secretory phenotype.

Table III. Natural compounds targeting telomerase.

Compound	Source	Target cancer (cell line)	Key findings	(Refs.)
Icaritin	<i>Epimedium</i> extract	Leukemia (HL-60)	Notable telomerase suppression	(120)
Wogonin	<i>Scutellaria baicalensis</i>	Ovarian (SKOV3)	Dose-dependent inhibition <i>in vitro/in vivo</i>	(121)

inactive in normal somatic cells but reactivated in ~85-90% of human cancer types, enabling tumor cells to bypass replicative senescence and sustain ‘immortal’ proliferation (114). This observation supports the telomerase theory of cancer, in which telomerase activation is regarded as a near-universal hallmark of malignancy (115). Nevertheless, notable molecular distinctions exist between replicative senescence in normal cells, mediated by p53/p16-dependent G₀/G₁ arrest and telomere shortening, and senescence-like arrest in cancer cells, which frequently occurs independently of telomere attrition (116-118).

Therapeutic targeting of telomerase and challenges of alternative lengthening of telomeres (ALT) pathway. Targeting telomerase represents a promising anticancer strategy. Natural compounds, including icaritin (from *Epimedium*) and wogonin (from *Scutellaria baicalensis*), have demonstrated potent telomerase inhibition in leukemia (HL-60) and ovarian cancer (SKOV3) models, respectively (119-121). These agents selectively induce cytotoxicity in telomerase-positive tumors while sparing normal tissues. Clinical translation, however, requires optimization of pharmacokinetics and development of effective combination regimens (Table III).

Certain cancer types (10-15%) evade telomerase dependency by employing the ALT pathway, which maintains telomere length via homologous recombination rather than telomerase. ALT is particularly prevalent in osteosarcomas (~60%) and glioblastomas (~40%), which poses a notable therapeutic challenge due to resistance to conventional telomerase-targeted drugs, e.g. olaparib, RAD51 inhibitor, telomere homologous recombination inhibitor with oxadiazole scaffold, tazemetostat (122,123). Emerging strategies to overcome ALT-mediated resistance include ataxia telangiectasia and Rad3-related inhibitors, CRISPR-based disruption of ALT machinery

and synthetic lethality approaches that exploit ALT-specific vulnerabilities (124).

Future perspectives: Integrating telomere biology with senescence-targeted therapies. Future directions emphasize patient stratification according to telomere maintenance mechanisms and the development of combination therapies that integrate telomerase inhibitors with immunotherapy or epigenetic modulators. The creation of novel diagnostic tools will be key for real-time monitoring of telomerase activity. The crosstalk between senescence and telomere dynamics constitutes a pivotal frontier in cancer therapy, offering opportunities to enhance treatment efficacy, prevent relapse and overcome resistance in both telomerase-dependent and ALT-driven malignancies. By combining telomerase inhibition with senolytic strategies, it may be possible to simultaneously disrupt tumor cell immortality and remodel the immunosuppressive TME, establishing innovative therapeutic paradigms.

9. Conclusions

The present review highlights the central role of cellular senescence in cancer, emphasizing its paradoxical function as both a tumor-suppressive mechanism and a promoter of malignancy. The intricate interplay between senescent cells and the TME, largely mediated through SASP, presents novel avenues for therapeutic intervention. Future research can prioritize the elucidation of tumor-specific variations in SASP composition and their distinct contributions to cancer progression. The development of next-generation senotherapeutics, including innovative senolytics and senomorphics, holds notable promise in selectively targeting deleterious senescent cells while preserving their protective functions.

Integrating Traditional Chinese Medicine with contemporary therapeutic strategies offers additional opportunities to

enhance senescence modulation, advancing the field towards precision oncology. Cutting-edge technologies, such as single-cell omics, spatial transcriptomics and AI-driven modeling, are essential to dissect the spatiotemporal dynamics of senescent cells within the TME. Furthermore, novel approaches, including SASP-specific inhibitors and senescent cell vaccines, may provide targeted solutions to the complex interactions between senescence and tumorigenesis.

Clinical translation will require robust biomarkers for patient stratification and carefully designed trials, particularly for aging populations and refractory types of cancer. Future research can focus on balancing the protective functions of senescence, such as clearance of damaged cells, against potential detrimental effects, including chronic inflammation and immune suppression. Optimizing the timing and context of senolytic interventions is key to maximizing therapeutic benefit while minimizing adverse effects. Strategically targeting pathological senescence thus represents a transformative approach in oncology, which offers personalized, effective therapies that simultaneously disrupt tumor cell immortality and remodel the immunosuppressive TME.

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Authors' contributions

YL conceptualized the present review, validated the data and conducted the formal analysis, wrote the original draft, and edited and reviewed the manuscript. JG collected, screened and systematically organized key data from relevant literature and existing studies, wrote the original draft, and edited and reviewed the manuscript. PY conceptualized the present review, validated the data, obtained funding, and edited and reviewed the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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