Molecular Cancer

REVIEW

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Cellular senescence and SASP in tumor progression and therapeutic opportunities

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Abstract

Cellular senescence (CS), a permanent and irreversible arrest of the cell cycle and proliferation leading to the degeneration of cellular structure and function, has been implicated in various key physiological and pathological processes, particularly in cancer. Initially, CS was recognized as a barrier to tumorigenesis, serving as an intrinsic defense mechanism to protect cells from malignant transformation. However, increasing evidence suggests that senescent cells can promote tumor progression to overt malignancy, primarily through a set of factors known as senescence-associated secretory phenotypes (SASPs), including chemokines, growth factors, cytokines, and stromal metalloproteinases. These factors significantly reshape the tumor microenvironment (TME), enabling tumors to evade immune destruction. Interestingly, some studies have also suggested that SASPs may impede tumor development by enhancing immunosurveillance. These opposing roles highlight the complexity and heterogeneity of CS and SASPs in diverse cancers. Consequently, there has been growing interest in pharmacological interventions targeting CS or SASPs in cancer therapy, such as senolytics and senomorphics, to either promote the clearance of senescent cells or mitigate the harmful effects of SASPs. In this review, we will interpret the concept of CS, delve into the role of SASPs in reshaping the TME, and summarize recent advances in anti-tumor strategies targeting CS or SASPs.

Keywords Cellular senescence, SASP, Tumor, Tumor microenvironment, Therapy

Introduction

Cellular senescence (CS) was initially introduced in 1961 [1]. In 1965, it was further described as a manifestation of the finite replicative capacity of diploid cell lines in vivo, characterized by the Hayflick limit, which represents the maximum number of cell divisions achievable before cellular growth arrest [2]. This phenomenon was subsequently defined as replicative senescence, which was considered irreversible and permanent due to the cell's inability to physiologically reverse this cycle arrest [3]. Recent studies have shown that CS can result from exposure to various internal or external stressors, such as replication stress, telomere damage, metabolic disorders, and carcinogenic factors [4], leading to different types of senescence. In addition to arrested growth, another key feature of CS is the senescence-associated secretory phenotype (SASP), which includes a range of proinflammatory and proteolytic factors. SASP is generally diverse and dynamic, varying according to the type of senescent cells and the cellular environment [5]. However, SASP can also influence the surrounding environment, making CS and SASP not only cellular phenomena but also closely related to the development of various diseases, particularly tumors. For instance, SASP can either promote or inhibit tumor progression by remodeling the tumor microenvironment (TME), while the TME, in

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turn, affects SASP production. This intricate interaction significantly impacts tumor development. Although the mechanisms underlying this complex relationship are not yet fully understood, extensive preclinical studies have demonstrated that targeting senescence and/or SASP can benefit cancer patients.

In this review, we provide an overview of the characteristics and markers of CS, discuss the current mechanistic understanding of CS, and explore the impact of SASP components on the TME. Specifically, we highlight the "double-edged sword" role of SASP in cancer through its remodeling of the TME. Finally, we summarize recent advancements in anti-senescent therapies and propose their potential applications in future cancer treatments.

Types of CS

Replicative senescence

In addition to occurring under physiological conditions, CS can also be induced by various factors through different mechanisms (Fig. 1). Consequently, CS is categorized into different types based on its inducers. Replicative senescence (RS) was first proposed by Hayflick in 1961 and later defined as cell cycle arrest caused by continuous cell culture [1]. A hallmark of RS is the presence of short telomeres, which result from repeated cycles of DNA replication. Mechanistically, when telomeres reach a critical length, they are recognized as DNA double-strand breaks (DSB), which activate a DNA damage response (DDR). The earliest checkpoint kinases, ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad 3-related (ATR), are then activated to phosphorylate various proteins, including checkpoint kinase 2 (CHK2) [6]. CHK2 transmits DDR signals by phosphorylating the tumor suppressor protein p53, which is involved in cell cycle arrest, apoptosis, and DNA repair. Phosphorylated p53 subsequently activates the downstream protein p21 [7]. p21 inhibits the phosphorylation of retinoblastoma protein (RB) by restraining the function of cyclin-dependent kinase 2 (CDK2). Finally, the transcription of E2F, an essential protein in the S-phase of the cell cycle, is halted by the downregulation of RB phosphorylation, causing the cell cycle to arrest at the G1

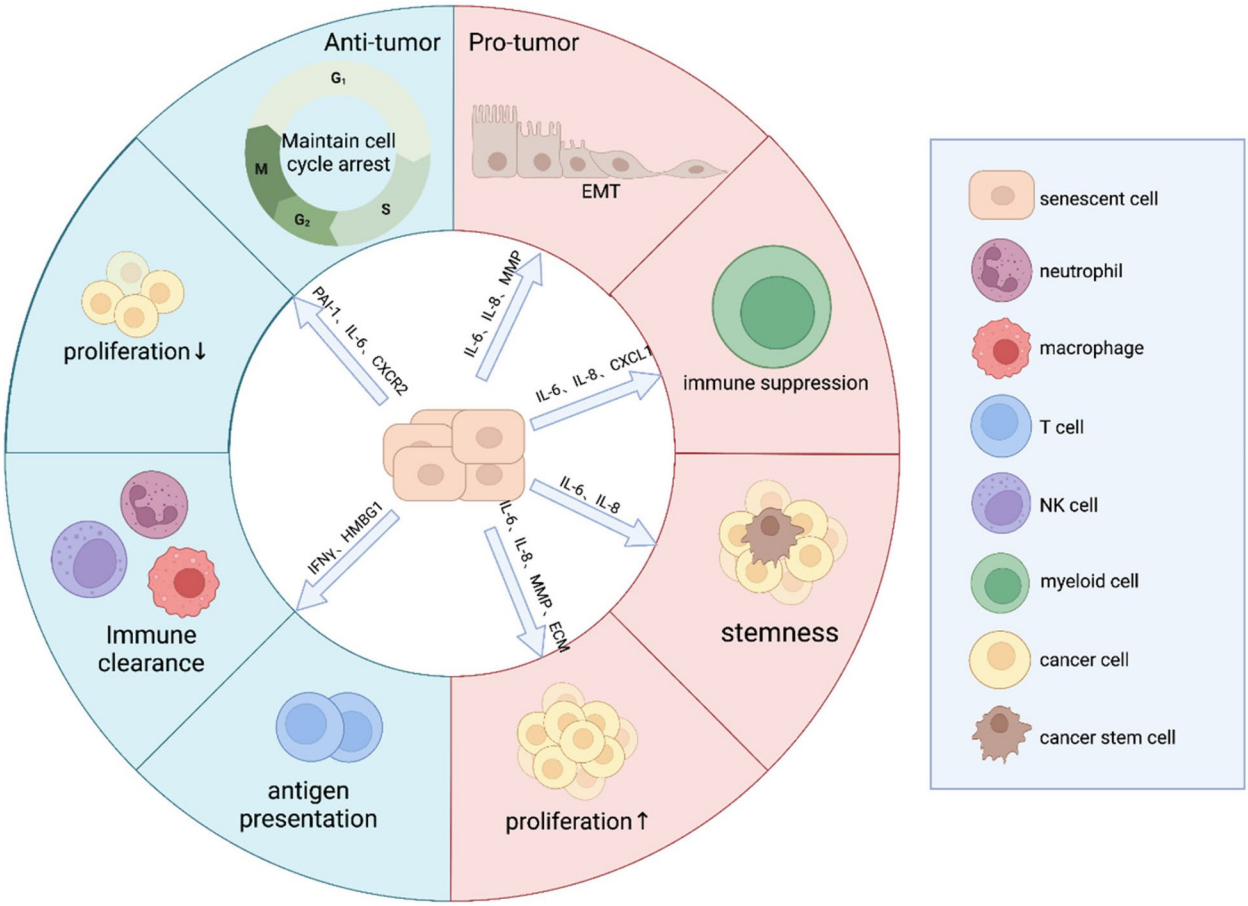

Fig. 1 Factors inducing cellular senescence (CS). CS can be triggered by various factors, including oncogenes, telomere shortening, mitochondrial dysfunction, DNA damage response (DDR), protein homeostasis disorders, and chemoradiotherapy

stage and enter senescence [8, 9]. Notably, cancer cells can also induce p21 through retroviral-mediated CHK2 activation without the involvement of p53 [10]. In addition to the p53/p21^{CIP1} mechanism associated with cell cycle arrest, the p16^{INK4a}/RB pathway can also induce CS. p16, also known as cyclin-dependent kinase inhibitor 2A (CDK2A), binds to the kinases CDK4 and CDK6, forming complexes that block RB phosphorylation, resulting in CS [11]. Currently, an increasing number of factors have been found to play important roles in the p53/p21^{CIP1} and p16^{INK4a}/RB pathways. For example, a complex has been identified that regulates the cell cycle through the p53/p16-RB-E2F-DREAM pathway [12], and the knockout of YPEL2 reduces cell proliferation in S-phase and promotes endothelial cell senescence by activating the p53/p21 signaling pathway (Fig. 2) [13].

Premature Senescence

Various stressors can lead to premature senescence, which can be categorized into different types depending on the stimulus. Below are several types of cancer-related premature senescence:

Oncogene-induced senescence (OIS)

OIS is primarily triggered by the expression of certain oncogenes. It was initially observed as a result of the

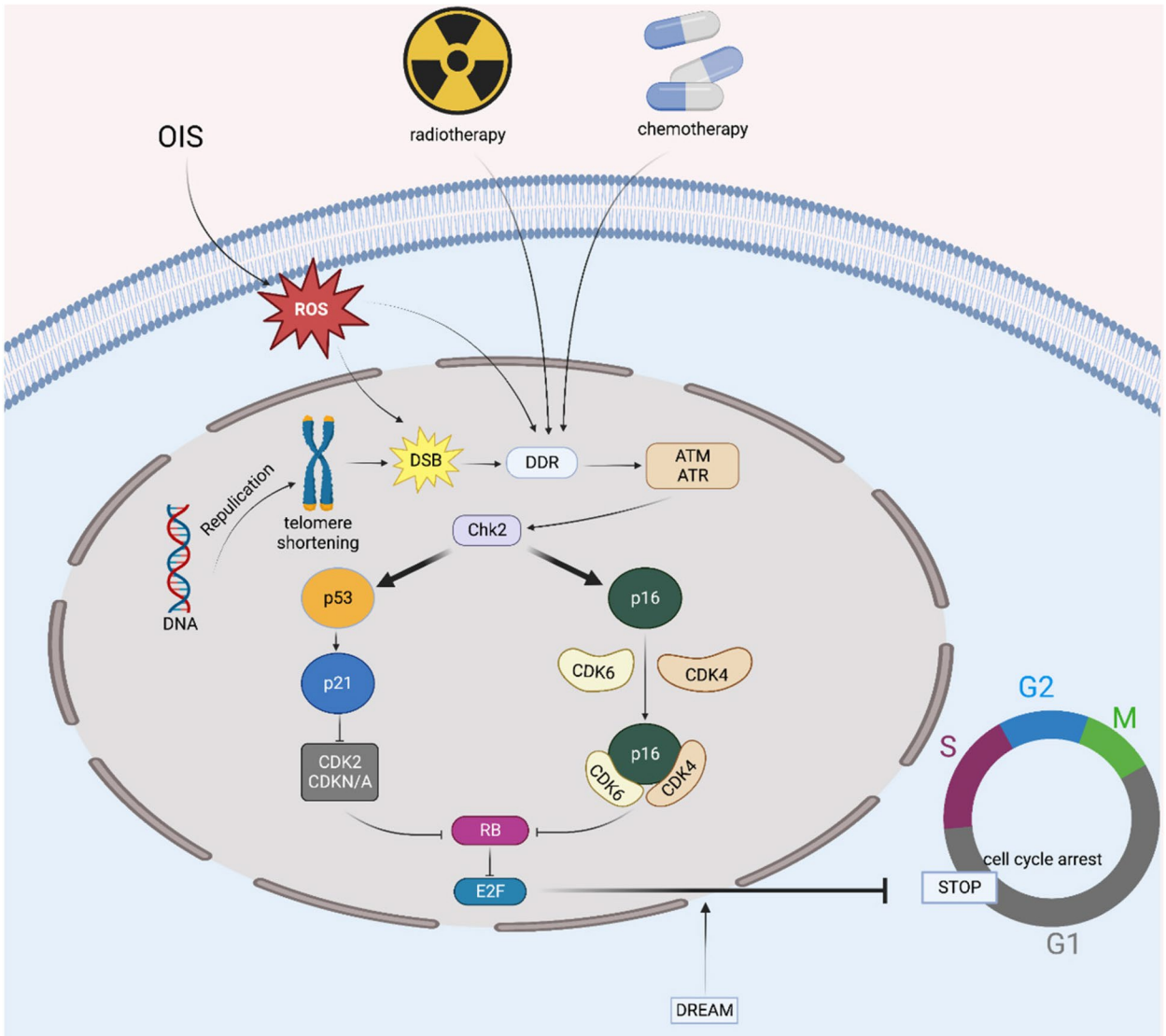

Fig. 2 Signaling pathways involved in CS. During DNA replication, telomeres progressively shorten, triggering a DDR and DSB, which activate ATM and ATR, leading to the activation of CHK2. This activation blocks E2F transcription through the p53/p21 and p16/RB pathways, causing the cell cycle to arrest in the G1 phase. Additionally, OIS and TIS can also initiate DDR and DSB, ultimately leading to cell cycle arrest

heterotopic expression of HrasV12, an oncogenic form of Ras, in human lung fibroblasts [14]. The mechanisms underlying OIS have since been elucidated: oncogene activation induces the production of reactive oxygen species (ROS), which leads to DSBs and DDR, thereby initiating CS [15]. The TP53/CDKN1A and p16/RB pathways are also involved in OIS. TP53 acts to inhibit cancer cell growth, and its loss can lead to increased invasiveness [16]. Meanwhile, RB plays an important role in maintaining OIS by inhibiting the expression of the DNA transcription factor E2F [17]. OIS is also associated with signs of DNA replication stress, which can cause DSBs and genomic instability in human precancerous lesions [18, 19]. Bartkova et al. demonstrated that CS acts as a barrier to tumor formation in precancerous lesions by activating DNA damage checkpoints in response to DNA replication stress [18]. Furthermore, research has shown that oncogene expression alone does not trigger DDR in the absence of DNA replication. Thus, OIS arises from DDR activation driven by oncogene-induced DNA hyper-replication [20].

Therapy-induced senescence (TIS)

TIS occurs when senescence is induced by various types of chemotherapy or radiation therapy, which cause DSBs and activate DDR [21]. Chemotherapeutic agents such as cisplatin, paclitaxel, bleomycin, and cyclophosphamide are more likely to induce TIS than radiation therapy [22]. The mechanisms by which different chemotherapeutics induce TIS vary. For instance, busulfan induces CS through the p38 pathway, while cisplatin primarily triggers senescence via the p53 pathway [23]. TIS is an effective strategy for suppressing cancer growth and has been shown to benefit cancer patients [24].

SARS-CoV-2 (viral)—induced senescence

The coronavirus disease 2019 (COVID-19) pandemic has brought severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the spotlight [25]. Recent studies have revealed that SARS-CoV-2 is closely linked to CS. For example, Yang et al. found that SARS-CoV-2 infection can induce senescence in dopaminergic neurons [26]. Similarly, Meyer et al. reported that SARS-CoV-2 infection triggers epithelial cell senescence and increases the levels of SASPs [27]. Moreover, recent research by Gioia et al. discovered that SARS-CoV-2 infection can cause DNA damage and disrupt the DDR due to the depletion of CHK1. Additionally, the SARS-CoV-2 N protein can bind to damage-induced long non-coding RNAs (lncRNAs), impairing the recruitment of 53BP1 and thereby hindering DNA repair [28].

Rare types of senescence

Rare forms of senescence that do not depend on DNA damage include sodium butyrate- and nuclear barrier-induced senescence, as well as senescence caused by mitochondrial dysfunction, aberrant epigenetic modifications, protein homeostasis disorders, and paracrine signaling [29]. Although these types of senescence are uncommon, further exploration of these different forms and their underlying mechanisms will provide a deeper understanding of age-related diseases and may ultimately benefit anti-senescence strategies for cancer treatment.

Biomarkers of CS

The biological markers of CS vary among different types of senescent cells. For example, lapatinib induces p15- and p27-dependent senescence without detectable upregulation of p16 and p21 in HER2-positive breast cancer cells [30]. Similarly, in prostate cancer cells, androgen primarily upregulates p15 to induce CS [31]. Notably, the expression of these markers can vary even within the same senescent cells. For example, senescence induced by glyoxal is initially mediated predominantly by the protein kinase B/FOXO3a/$p27^{KIP1}$ signaling pathway but gradually shifts to being driven by the $p16^{INK4}$/Rb pathway [32]. Furthermore, nonsenescent cells can also express some of these markers, which complicates the identification of CS, particularly in early cultures where a mix of nonsenescent and senescent cells may be present. This complexity may be due to the premature senescence of some primary cells. Additionally, prematurely senescent cells can influence surrounding nonsenescent cells to elevate the levels of certain markers, a phenomenon known as paracrine senescence [33].

SASP components, which include proteins conserved across cell types, are valuable phenotypic markers. However, SASP alone is insufficient to definitively identify senescent cells because several SASP components are also involved in inflammatory processes. Given the complexity of CS markers, a systematic, multiparameter approach has been employed to identify senescence. Recently, a method known as senescence-associated morphological profiles was developed, which uses multidimensional, phenotype-driven assessments to define senescence [34].

Although many markers have been identified (Table 1), none are specific for CS. Typically, a combination of factors, such as cellular morphology and nuclear characteristics, is used to determine whether cells are in a senescent state. The discovery of a specific marker would greatly enhance our understanding of the underlying mechanisms and unique pathology of CS. Since no single marker is currently sufficient to identify senescence, a combination of

Table 1 Markers of CS

Testing targets	Features of senescent cells	Reference
Cellular morphology	cellular enlargement	[36, 37]
	Irregular cellular shape	
Organelle and metabolic dysfunction	SA-β-gal↑	[38, 39]
	SA-α-Fuc↑	[40]
Cyclic arrest protein	$p16^{INK4A}$↑, p53↑, $p21^{CIP1}$↑, $p27^{KIP1}$↑, $p15^{IKK4b}$↑,	[30, 31, 41–44]
	Cdkn1a transcript variant 2↑	[45]
	EGR2↑	[46]
Other proteins	DPP4, SCAMP4↑	[47]
	uPAR↑	[48]
	ACKR3↑	[49]
	UPR↑	[50]
	ATP6V0D1, RTN4↑	[51]
	c-Met↑	[52]
	Angptl2↑	[53]
	RRAD↑	[54]
	Lipofuscin↑	[55, 56]
Nucleus related factors	large nuclei, lobulated, enlarged/fragmented nucleolus, Nucleocytoplasmic trafficking↓, Senescence-associated heterochromatin foci (SAHF)	[57–59]
	nc866↓	[60]
	Lamin-B1↓	[61]
	Nuclear transcription factors TFEB/TEB3↑	[62]
Secretory factors	Production of SASP: contains cytokines, chemokines, matrix metalloproteinases, hormones, etc	[5, 63]
Others detection	Autofluorescence	[64]
	ecto-5′-nucleotidase	[65]
	Cascade region-based convolution neural network	[66]
	Micro Magnetic Resonance Relaxometry	[67]
	CD26↑	[68]
	Multiparameter flow cytometric detection and quantification	[69]
	A dynamical systems model for senescence	[70]

SA-β-gal Senescence-associated β galactosidase, *SA-α-Fuc* Senescence-associated α fucosidase, *EGR2* Early growth response protein 2, *DPP4* Dipeptidyl peptidase-4, *SCAMP4* Secretory carrier-associated membrane protein 4, *uPAR* Urokinase-Type Plasminogen Activator Receptor, *ACKR3* Atypical chemokine receptor 3, *UPR* Unfold protein reaction, *ATP6V0D1* V-type proton ATPase subunit d 1, *RTN4* Recombinant Reticulon 4, *Angptl2* Recombinant Angiopoietin Like Protein 2, *RRAD* Ras-related associated with diabetes entrez, *TFEB/TEB3* Transcription factor EB/ transcription factor E3

multiple cellular senescence markers should be considered. For example, Estela et al. proposed a detailed multifactorial guide for evaluating senescence both in vitro and in vivo [35]. As such, this review will not further elaborate on these markers.

Senescence-associated secretory phenotype (SASP)

SASP is a key pathological feature of CS. Despite the arrest in cell cycle and proliferation, senescent cells maintain an active metabolic state and secrete a wide range of factors that influence both themselves and their surrounding environment. These secretory factors collectively form what is known as the SASP. The concept of SASP was first introduced in 2008 as a phenotype in which genotoxic stress-induced aging in human cells results in the secretion of substances associated with inflammation and malignancy [5]. SASP is now recognized as a complex secretory process composed of hundreds of different proteins and nonprotein signaling molecules, including pro-inflammatory factors, proteases, and growth factors. While numerous studies have

attempted to characterize the composition of SASP, its exact composition remains unknown [71]. The components and levels of SASP can vary significantly depending on the stimuli that drive senescence, the types of senescent cells involved, and the duration of senescence [5, 72].

Several studies have demonstrated that SASP plays an important role in cancer, with its diverse cytokines exerting differential effects on tumor cells and the TME, as summarized in Table 2. Below, we introduce several key SASP components:

Table 2 The components of SASP and their function

Type	SASP factor	Effects on TME	Reference
interleukin	IL-1α	Induces SASP factor transcription Signaling activation of SASP via IL-1R	[73–75]
	IL-1β	necessary for SASP expression Promote neovascularization	[73, 76]
	IL-6 IL-8	Maintain cell cycle arrest Promote tumor migration and invasion Enlarge SASP effect	[77, 78]
chemokine	CXCR2	Induce CS Promote tumor migration and invasion Promote EMT Involvement in angiogenesis	[79, 80]
	CCL2	Promote tumor migration and invasion Promote tumorigenesis	[81]
	CXCL1	Promote tumorigenesis	[82]
	CXCL11	Promote tumor migration and invasion	[83]
growth factor	IGFBP7	Induce CS	[84]
	AREG	Promote tumorigenesis	[85]
	IGFBP4	Induce CS	[86]
	IGFBP3	Induce premature CS	[87]
	MIC-1	Promote tumor migration and invasion	[88]
	TGF-β	Induce ROS production Inhibit tumor cell growth	[89]
Others	PAI-1	Induce CS Induce SASP secretion	[90]
	HMBG1	Activate SASP secretion Activate innate immunity	[16, 91]
	STC1	Inhibit inflammation	[92]
	MMP3	Promote tumor migration and invasion Promote neovascularization Promote EMT	[93–95]
	MMP1	Synergistic TGF-β1 induced CS Promote tumor migration and invasion Promote neovascularization Promote EMT	[93, 96, 97]
	B-cell activating factor (BAFF)	Promote SASP in monocytes Promote NF-κB activation in senescent cells of early monocytic leukemia Promote p53 level in senescent fibroblasts	[98]
	NAMPT	Increase NAD expression Promote M1 polarization of macrophages	[99]
	ANGPTL2	Induce SASP secretion Maintain cell cycle arrest Boosting cancer cell viability Promote tumor cell drug resistance	[53]
	complement factor D	Promote expression of MMP1	[100]

CXCR2 CXC-chemokine receptor 2, *CCL* CC-chemokine ligand, *CXCL* CXC-chemokine ligand, *IGFBP* Insulin-like growth factor-binding protein, *AREG* Amphiregulin, *MIC-1* Macrophage inhibitory gytokine-1, *TGF-β* Transforming growth factor-β, *PAI-1* Plasminogen activator inhibitor-1, *HMGB1* High mobility group box 1, *STC1* Stanniocalcin 1, *MMP* Matrix metallopeptidase, *NAMPT* Nicotinamide Phosphoribosyl Transferase, *ANGPTL2* Angiopoietin-like Protein 2

Interleukin-1 (IL-1)

The IL-1 pathway is essential for the expression of most SASP factors, although it is not necessary for the induction of senescence itself. IL-1α can activate SASP through IL-1R signaling, while IL-1β, which shares the same signaling pathway as IL-1α, is also crucial for SASP expression. Both IL-1α and IL-1β can independently affect SASP without a hierarchical relationship between them [73]. Buhl et al. found in their study on hair cell astrocytoma that IL-1β can induce growth arrest and senescence in proliferating hair cell astrocytoma cells, as well as upregulate SASP factors [101]. The release of IL-1α depends on caspase-5 and caspase-11 [102]. Kelly et al. discovered that the expression of DOT1L is necessary for SASP gene expression, possibly through the upregulation of H3K79me2/3 at the IL-1A locus [103].

Interleukin-6 (IL-6)

Wang et al. found that atorvastatin can induce senescence in hepatocellular carcinoma (HCC) cells by inhibiting the IL-6/STAT pathway. Previous studies have shown that high levels of IL-6 are closely associated to HCC [104]. Interestingly, Shriki et al. found that IL-6 deficiency can lead to the deterioration of liver cancer in mice, which is related to severe damage and senescence of SASP [105]. The contradictory effects of IL-6 may be related to the specific environment; for example, in chronic liver injury, IL-6 can inhibit liver injury, fibrosis, and the occurrence of liver cancer, while inhibiting IL-6 in acute liver injury can reduce the risk of liver cancer [106].

Galectin-9

Tarallo et al. first reported that senescent cells secrete Galectin-9 in melanoma [107]. Previous studies have shown that Galectin-9 has immunosuppressive effects in the TME, promoting the apoptosis of T cells and monocytes, increasing the regulation of T cells, helper T cells, and M2 macrophages, and impairing anti-tumor immune responses [108]. On the other hand, some reports suggest that Galectin-9 can inhibit melanoma metastasis [109].

Extracellular vesicles (EVs)

Lehmann et al. were among the first to report an increase in senescence-associated exosome secretion [110]. Suppression of small extracellular vesicle release induces the accumulation of DNA damage and apoptosis-like death in senescent cells [111]. EVs have recently emerged as crucial intermediaries within SASP and have been shown to play various roles in senescence. Similar to the more conventional "soluble" SASP, this vesicular secretome also induces a diverse array of effects that can be beneficial or detrimental depending on the specific cellular environment. These effects are driven by a varied set of EV cargos, including proteins, nucleic acids, and lipids, which support the functional roles of EVs in senescence [112]. Misawa et al. found that senescent cell-derived EVs function as SASP factors by regulating cancer growth. Since numerous EVs are found in all bodily fluids, including blood, saliva, and urine, they are considered valuable targets for liquid biopsy, which is simpler and less invasive than traditional diagnostic techniques. Therefore, EV release might be a potential target for the treatment or prevention of age-related diseases.

CS and SASP on the TME

The impact of SASP on the TME varies significantly depending on the type of cells undergoing senescence and the specific triggers of senescence. For example, SASP can promote the neuroendocrine transdifferentiation of breast cancer cells through the NF-κB pathway [113]. In melanoma, treatment with SASP-associated cytokines supports the immune system's self-sustained surveillance of senescent cells [114]. Furthermore, senescent cells can enhance melanoma metastasis by increasing the production of soluble E-cadherin [115]. In HCC, hepatic SASP facilitates HCC progression by polarizing macrophages, a process closely linked to Bcl3 expression in hepatocytes [116]. SASP components such as Coactosin-like protein 1, Alpha-enolase, and Peroxiredoxin 2 contribute to the proliferation and behavioral changes of HCC cells [117]. Additionally, acute SASP derived from mesenchymal stromal cells induce senescence in immortal prostate cells, but not in prostate cancer cells, suggesting that SASPs from acutely senescent cells may be more effective at preventing cancer initiation within the TME rather than eradicating established cancer cells [118]. Senescent fibroblasts secrete growth differentiation factor 15 (GDF15), a component of the TME that not only promotes the formation of colon cancer but also induces the proliferation, migration, and invasion of colon cancer cells [88]. SASP also has the capacity to recruit various cell types to the tumor periphery. For example, CXCR2 can attract and enhance the protumor properties of tumor-associated macrophages, facilitating epithelial-mesenchymal transition (EMT) [80]. The knockout of BTG1 has been shown to induce senescence and create a microenvironment conducive to angiogenesis and tumor growth, thereby promoting tumor metastasis [119]. Moreover, senescent cells interact with platelets through SASP, increasing platelet aggregation and promoting platelet activation. In vivo, senescent cells

recruit platelets to sites of senescence-induced inflammation, altering the TME and leading to endothelial dysfunction, proliferation of premalignant cells, and enhanced tumor invasion and metastasis [120].

Deng et al. discovered that SASP factor IL-6, secreted by senescent tumor cells, elevates adenosine levels in the TME, which, in turn, promotes CD73 expression in macrophages via the JAK/STAT3 signaling pathway, leading to further adenosine accumulation. Their research also showed that even after the clearance of senescent cells, the infiltration of T cells in the TME was impaired. Targeted inhibition of CD73 not only suppresses tumors but also enhances the efficacy of anti-PD-1 monoclonal antibody immunotherapy. They proposed that early remodeling of the TME by senescent macrophages may play a crucial anti-tumor role, which is significant for cancer patient prognosis [121]. Additionally, adenosine has been shown to upregulate PD-L1 expression in human macrophages, further influencing the immune landscape of the TME [122].

Double roles of SASP in tumors

The SASP plays a dual role in tumor biology due to its heterogeneity. SASP can act as both a tumor suppressor and a promoter of tumor initiation and progression. On one hand, SASP is known to enforce cell cycle arrest and recruit immune cells to eliminate damaged or oncogene-expressing cells, acting as a protective mechanism against tumorigenesis. On the other hand, SASP can create an immunosuppressive environment that supports tumor progression and recurrence.

In this review, we summarize the key biological functions of SASP, focusing on the cytokines and intercellular interactions that shape the TME and influence the response to immunotherapy in geriatric oncology. We also discuss current clinical strategies targeting TME components and explore potential therapeutic targets within the senescent TME. Here, we highlight recent advances that underscore the conflicting roles for SASP in tumor development and treatment response (Fig. 3).

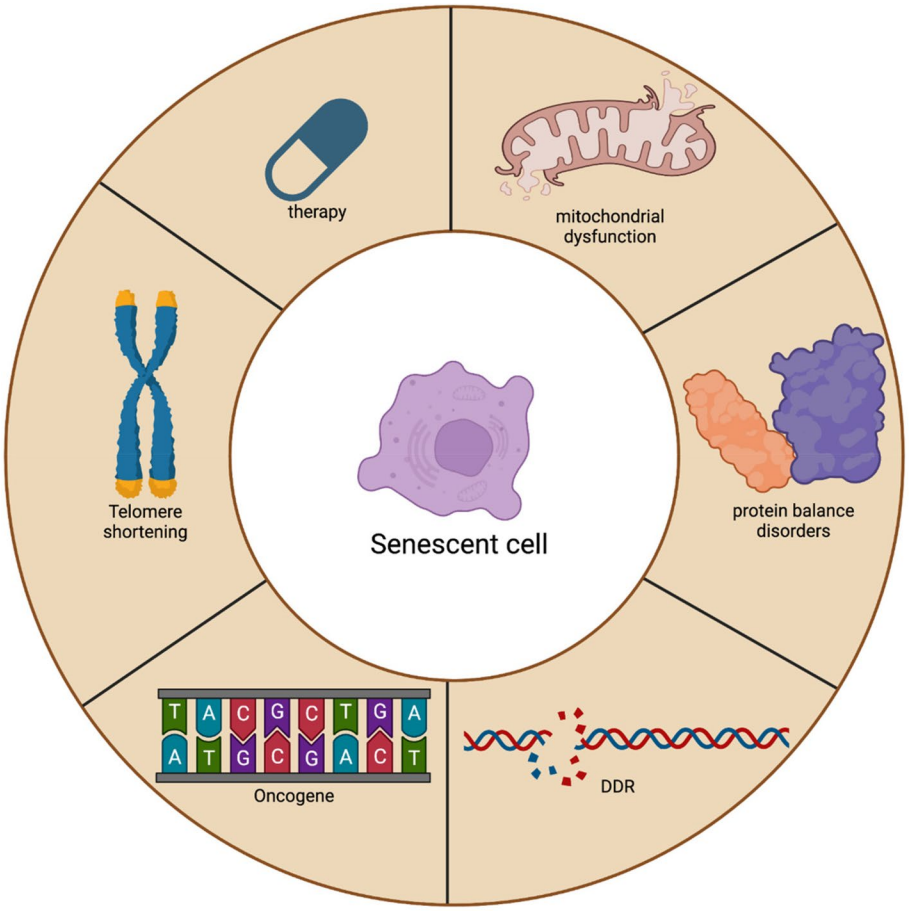

Fig. 3 The double-edged sword effect of SASP in tumors. The SASP exhibits dual roles in tumor dynamics. On one side, it enforces cell cycle arrest, thereby inhibiting tumor cell proliferation. Additionally, SASP recruits immune cells to clear senescent cells, bolstering immunosurveillance and enhancing antigen presentation. On the opposite side, SASP can promote tumor cell proliferation, facilitate the emergence of cancer stem cells and EMT, and suppress immune responses, contributing to tumor progression and immune evasion

Antitumor effects of SASP

Preserving cell cycle arrest

One of the critical antitumor mechanisms of the SASP is its role in maintaining cell cycle arrest. For example, RNAi inhibition of PAI-1, a p53 target gene, can induce fibroblasts from primary embryonic mice, as well as primary human BJ fibroblasts, to exit from replicative senescence. Conversely, p53 knockout and PAI-1 overexpression induce CS [123]. SASP factors such as IL-6 and CXCR2 maintain cell cycle arrest via p53, thereby inhibiting tumor cell growth and proliferation [124–126]. Although the precise mechanism by which SASP maintains cell cycle arrest is not fully understood, it is generally agreed that SASP does not directly cause cell cycle arrest but makes the arrest irreversible once the cell enters this state. Interestingly, rapamycin has been found to inhibit SASP factor expression and reduce SASP-induced inflammation in human fibroblasts without reversing CS, suggesting that targeting SASP does not disrupt age-related cell cycle arrest [127]. This finding implies that cell cycle re-entry might be possible by inhibiting specific SASP factors or targeting downstream molecules.

Immunosurveillance

Although the full mechanisms by which SASP affects immune cells are not completely understood, SASP is theoretically capable of significantly impacting immune responses. In fact, senescent cells can generate a SASP that regulates the microenvironment of surrounding tissue, particularly affecting nearby normal endothelial cells, which in turn mediate NF-κB factors in the SASP. These factors activate $CD4^+$ T cells via STAT1 and inducible costimulator/its ligand signaling, recruiting neighboring T cells and driving immune-mediated senescence surveillance and clearance of senescent cells [128]. For instance, in a mouse model of pancreatic ductal adenocarcinoma, tumor cell senescence following MEK and CDK4/6 inhibition induces SASP, leading to T-cell infiltration [129]. Similarly, in a mouse model of hepatic fibrosis induced by CCl4, activated hepatic astrocytes induce hepatic CS, which is inhibited by the knockout of p53 and $p16^{INK4a}$ [130]. Moreove, senescent hematopoietic stem cells (HSCs) attract NK cells and other immune cells to fibrotic lesions, thereby limiting immune-mediated fibrosis [130]. In mouse liver cancer models, p53-induced CS suppresses macrophages, neutrophils, and NK cells [16], leading to the clearance of tumor cells through phagocytosis and NK cell activation [16]. Interestingly, tumor regression is not observed when p53 is activated in mice lacking both B and T lymphocytes, suggesting that adaptive immunity may not needed for the clearance of senescent tumor cells within the SASP-recruited immune microenvironment [131]. Recent studies have also shown that tumor cell senescence can shift from immune evasion to immune surveillance, with IFN-γ synergizing with SASP to enhance antigen presentation and immune surveillance, ultimately leading to tumor cell rejection [132]. Thus, SASP effects can be leveraged for therapeutic purposes, such as forcing tumor cells into CS or exploiting SASP- mediated immune surveillance in cancer therapy. However, the dual nature of SASP in the TME— possessing both antitumor and tumor-promoting properties—complicates its use as an antitumor strategy.

Pro-tumor effects of SASP

Promotion of tumor cell proliferation

The initial protumor mechanism of SASP is its role in promoting tumor cell proliferation. For example, senescent human fibroblasts can stimulate hyperproliferation and progression of preneoplastic epithelial cells, accelerating tumorigenesis in neoplastic epithelial cells [133]. Compared to 'young' mesenchymal stem cells (MSCs), senescent human umbilical cord MSCs (s-UCMSCs) significantly accelerate the proliferation and migration of breast cancer cells via IL-6/STAT-3-dependent signaling [134]. Additionally, senescent breast luminal cells secrete SASP factors, including IL-6 and IL-8, which activate stromal fibroblasts through the STAT3 pathway, leading to tumor development in a paracrine manner [135]. Similarly, human senescent fibroblasts induced by bleomycin foster cancer cell proliferation and promote preneoplastic cells through the secretion of matrix metalloproteinases (MMPs) [136]. Senescent macrophages also contribute to tumor transformation by reshaping the TME [137], and eliminating these senescent macrophages has been shown to ameliorate KRAS-driven lung tumors [138]. Recently, small extracellular vesicles (sEVs) from senescent cells were identified as crucial mediators of protumor functions, with senescent cells increasing EphA2 in sEVs, thereby promoting cancer cell proliferation through activation of the MAPK pathway [139]. Furthermore, the extracellular matrix (ECM) secreted by SASP enhances tumor cells proliferation and provides a conducive environment for tumor progression [140]. For example, ECM production of senescent fibroblasts induced by irradiation boosts the proliferation of premalignant epidermal cells via PI3K and MAPK signaling [141]. Collectively, SASP not only induces CS but also directly promotes tumorigenesis and the proliferation of precancerous cells.

Induce epithelial mesenchymal transition (EMT)

Increasing evidence indicates that SASP can induce EMT, thereby favoring tumor progression. In breast cancer, for example, senescent fibroblasts secrete IL-6 and IL-8, key components of SASP. These cytokines increase

vimentin expression, decrease E-cadherin levels, and reduce cytokeratin in noninvasive breast cancer cells [5]. Senescent fibroblasts can also inhibit the differentiation of epithelial cells and reduce the expression of differentiation markers by secreting MMP-3 [93]. Additionally, spindle cells have been observed in pancreatic epithelial cells exposed to senescence-conditioned media, which are poorly tumorigenic [142]. SASP can also induce EMT in nonsenescent cells; for instance, conditioned media from senescent malignant pleural mesothelioma cells trigger the emergence of EMT-like, clonogenic, and chemoresistant cell subpopulations [143]. In addition, senescent fibroblasts induce the morphological and functional differentiation of nonmalignant epithelial cells [93]. Through coculture systems and xenograft models, SASP, primarily from senescent fibroblasts, has been shown to induce EMT, promote angiogenesis, and enhance the progression of premalignant epithelial tumors [144]. Currently, it is well-established that SASP can induce EMT, influencing the differentiation status of tumor cells.

Induction of stemness in tumor cells

Initially, genotoxic-induced SASP was found to endow a subset of irradiated or doxorubicin-treated multiple myeloma cells with a stemness-like, highly tumorigenic state. CS induced by genotoxic stress produces SASP, leading to the release of IP-10 and RANTES in the TME, driving the formation of cancer stem cells (CSCs) [145]. In addition to promoting further differentiation of cells with unstable genomes, the senescent microenvironment grants premalignant cells a stem phenotype [146]. For instance, MCF-7 breast cancer cells in senescent conditioned medium were induced to express EMT programs, while treatment with IL-6 and IL-8 was also effective in inducing breast cancer cells to form mammosphere and exhibit stem-like properties, underscoring the crucial role of SASP in the induction of tumor cell stemness [77]. Currently, SASP is known to promote tumor cell stemness in both tumor and nontumor environment. For example, keratinocytes exposed to SASP upregulate stem cell markers [147], and injury-induced senescence enables in vivo reprogramming in skeletal muscle, suggesting a paracrine effect of senescence on cellular plasticity [148]. Overall, SASP plays a significant role in conferring a stemness-like, highly tumorigenic state to tumors, highlighting the potential of targeting senescent cells to combat tumors.

Immunosuppression and anti-inflammatory effects

Immune cells are a critical component of the TME, and SASP can recruit suppressor immune cells to prevent immune clearance of tumor cells while also inducing immune cell-mediated inflammatory responses that further promote tumor progression. For example, genetic knockout of Sin3B in the mouse genome inhibits pancreatic cancer progression by preventing CS induced by KRAS and reducing IL-1α in the SASP [149]. Notably, some SASP factors have been shown to both inhibit tumor initiation and promote tumor growth, depending on the tumor cell status. For example, chemokines secreted by senescent hepatic cells can inhibit HCC at an early stage but accelerate the growth of fully developed HCC cells, likely due to plasticity in myeloid CCR2 cells [150]. Elevated levels of MMPs in senescent fibroblast SASP from nonmelanoma skin cancer activate membrane PAR-1/thrombin receptors, leading to tumor escape following the senescence of tumor cells [151]. Additionally, Lau et al. found that IL-1 in SASP recruited macrophages in the mouse pancreas, with tissue-resident macrophages promoting pancreatic cancer progression, potentially explaining the role of SASP in promoting pancreatic cancer [122].

Beyond these protumor mechanisms, SASP also protects tumors in other ways. For example, in squamous cell carcinoma of the head and neck, early CS and SASP generation—where chemokine receptor ligands for CXCR2 play an important role— may lead to radioresistance [152]. Through these mechanisms, SASP creates a TME that not only fosters tumor progression but also shields tumors from immune system attacks and external drug elimination once fully developed, posing challenges for clinical anticancer strategies.

In summary, the impact of SASP on tumorigenesis and tumor development is a double-edged sword, with its effects depending largely on the composition of SASP. This duality presents opportunities for therapeutic interventions, such as enhancing immune system-mediated tumor cell killing, inducing tumor CS, and inhibiting tumor immune evasion. Therefore, it is crucial to identify which SASP factors have antitumor or pro-tumor properties to develop strategies that specifically inhibit tumors.

Therapy targeting CS and SASP in tumors

Although CS was once considered an irreversible state of cell cycle arrest, recent evidence suggests that senescent cells can occasionally escape and re-enter the cell cycle under certain conditions, potentially contributing to tumor recurrence [153]. For instance, Zampetides et al. discovered that oncogene-induced senescent cells can occasionally bypass the barrier of irreversible cell cycle arrest and resume proliferation [154]. Similarly, Yu et al. found that the loss of the H3K9me3 marker can enable cells to exit the senescent state and re-enter the cell cycle [155, 156]. Additionally, tumor cells may escape from senescence following anti-tumor treatments,

potentially due to accumulated genomic instability [157, 158]. These findings highlight the potential of targeting senescent cells as a promising strategy for treating cancer recurrence.

On the other hand, CS may contribute to the progression of senescence-related diseases, particularly cancer, through the SASP. Indeed, the removal of senescent cells has been shown to slow the progression of senescence-associated diseases [159]. Importantly, senescent cells possess unique defenses against apoptotic stimuli, known as senescent cell antiapoptotic pathways (SCAP), which include the BCL-2/BCL-X_L, PI3K/AKT, p53/p21/PAI-1&2, HIF-1α, and tyrosine kinase signaling pathways [160]. Therefore, the development of SCAP-targeting drugs may effectively eliminate senescent cells without harming normal cells. Currently, drugs that specifically target and kill senescent cells are collectively referred to as senolytics [160], and multiple reviews have already detailed their mechanisms and potential [161, 162]. Here, we summarize the current antitumor studies of senolytics, categorizing them according to their therapeutic mechanisms (Table 3).

Senolytics

To date, various senolytic drugs have been developed, including first-generation senolytics like dasatinib and quercetin (D + Q) [160], BCL-2 family inhibitors (such as ABT-263 and ABT-737) [163], and cardiac glycosides like ouabain and digitoxin [170]. Several of these senolytic agents have demonstrated efficacy in 'one-two punch' combination therapies against cancer. For instance, lung and breast cancer cells exposed to chemotherapy agents such as etoposide and doxorubicin typically enter a senescent state. Sequential treatment with ABT-263 can further suppress tumor progression by eliminating these senescent cells [180]. Beyond these drugs, other types of senolytics have emerged. For instance, the plant-derived compound piperlongumine (PL) has been found to selectively kill senescent cells by increasing reactive oxygen species (ROS) levels and inhibiting the PI3K/AKT/mTOR pathway. PL has also been shown to synergize with ABT-263 to enhance its senolytic effects [172, 181]. Additionally, a chimeric antigen receptor (CRT) -T cell targeting urokinase-type plasminogen activator receptor (uPAR) has been developed by Amor et al. for the treatment of

Table 3 Senolytics for tumor therapy

Types	drug	Function	Types of tumors	Reference
D + Q	D + Q	Reduce the spread of tumor Target SCAP	HCC	[160]
Bcl-2 inhibitor	ABT-737	Inhibit Bcl-2 family proteins	NSCLC Melanoma	[163]
	ABT-263		Glioma	
	735B		Leukemia	[164]
HSP90 inhibitor	17-DMAG	Inhibit the production of proteins required for tumors cells	HCC	[165, 166]
Targeting p53	FOXO4-DRI	Trigger p53 to intracellular Promote MDM2 ubiquitination Inhibit interaction between Bcl and BAK	NSCLC Liposarcoma	[167, 168]
	RG7112			[169]
cardiac glycoside	Ouabain	Inhibit sodium pumps Elimination of SASP and CS Raise BCL-2	adamantinomatous craniopharyngioma	[170]
	Digoxin	Inhibit sodium pumps Elimination of SASP and CS Raise BCL-2	Lung adenocarcinoma Melanoma	[171]
Natural chemical substances	Piperlongumine (PL)	Raise ROS Inhibit PI3K/AKT	Thyroid cancer	[172, 173]
	Procyanidin C1	Induce dysfunction of mitochondrion in CS Reduce chemoresistance in tumor cells	Prostate cancer	[174]
	The curcumin analog EF24	Raise ROS Induce ER stress Selective promotion of Bcl-2 protein degradation	stomach cancer	[175]
Others	S63845	Inhibit Mcl-1	Prostate cancer	[176]
	R406 (tamatinib)	Produce ROS Inhibit FAK and p38 MAPK	Leukemia	[177]
	ABV825	Reduce expression of xrcc4 Reduce BRD4	HCC	[178]
	Nintedanib	Inhibit JAK2/STAT3	Breast cancer	[179]

NSCLC Non-small cell lung cancer

liver cancer and hepatic fibrosis. Given that uPAR is less expressed in vital tissues, these CAR-T cells are more disease-specific and safer [182]. Another promising senolytic is the bromodomain and extraterminal domain (BET) family protein degrader (BETd). BETd has been shown to be effective in inhibiting HCC in mice [178]. The recently developed BETd ARV825 exhibits strong senolytic activity in vivo by reducing BRD4 levels, negatively regulating XRCC4 expression in senescent cells, exacerbating DSBs, and positively regulating autophagy gene expression. This results in the apoptosis of senescent cells by blocking nonhomologous end joining repair [178].

Given the lack of specificity of general senolytics, more targeted drugs have been developed in recent years. For example, Poblocka et al. are investigating the use of beta-2-microglobulin (B2M), a membrane protein marker on senescent cells, to deliver toxic drugs to these cells via antibody–drug coupling (ADC) [128]. Kento et al. developed an ADC drug that targets senescent dermal fibroblasts using apolipoprotein D (Apo D), which specifically kills senescent human dermal fibroblasts when combination with pyrrolobenzodiazepine, without significant side effects [183].

Additionally, galacto-oligosaccharide nanoparticle delivery systems have been explored for targeting senescent cells [184]. These nanoparticles release their encapsulated senolytics upon digestion by elevated SA-β-gal activity in senescent cells, effectively killing them [184]. Ana et al. developed a galactose-modified doxorubicin prodrug designed to target senescent cells with high SA-β-gal activity, providing a single-molecule approach for senescence-targeted antitumor therapies [185].

While senolytics hold great promise, they are not yet fully developed. The heterogeneity of senescent cells means that different senolytics have their own limitations in clinical practice. Therefore, it is crucial to optimize the clinical use of senolytics to maximize the clearance of senescent cells. Current thinking suggests that senolytics are best administered intermittently rather than continuously, as it takes time for senescent cells to form and generate SASPs. However, whether this approach might have detrimental effects on the organism remains to be explored. Further preclinical animal studies are needed to evaluate the potential adverse effects of intermittent drug administration. Additionally, experimental studies are required to determine the optimal timing, dosage, and other parameters for senolytic therapies. Moreover, senolytics may have side effects; for example, ABT-263 can lead to thrombocytopenia. Therefore, there is a need for more effective and safer senolytics that minimize damage to normal tissues. Alternatively, combining multiple senolytics, such as dasatinib with quercetin or PL with ABT-263, may improve efficacy while reducing adverse effects like hemotoxicity through combination therapy.

In conclusion, while senescent cell clearance is a promising therapeutic approach, it may also negatively impact normal tissue function. For instance, wounds healing may be impaired [41], and the blood-tissue barrier may be damaged, promoting fibrosis [186]. These findings suggest that targeting the detrimental aspects of senescence in the TME without killing senescent cells might be a more refined approach. This has led to the proposal of a novel therapy: senomorphics (Fig. 4).

Senomorphics

Senomorphics are drugs that modify the phenotype of senescent cells, restoring them to a more youthful state without inducing apoptosis. They achieve this by interfering with the inflammatory response of senescent cells and disrupting signaling pathways related to senescence and SASP expression [187]. Compared to senolytics, senomorphics may present fewer side effects since they do not directly kill senescent cells but instead inhibit the development of senescence. Senomorphics primarily target signaling pathways associated with SASP expression, such as NF-κB, JAK/STAT, C/EBPβ, and GATA4, offering promising targets for drug development. Another strategy involves targeting specific components of the SASP using antibodies, such as those against IL-6/8. However, this approach is limited by the heterogeneity of SASP expression across different stages and types of senescent cells, making precise targeting challenging. We have summarized the current research on senomorphics in cancer in the table below (Table 4):

Despite the development of numerous senomorphics, most studies have concentrated on a limited range of common SASP factors. As illustrated in the table above, many senomorphics primarily target IL-6, IL-8, and similar factors, without considering the comprehensive changes within the SASP profile. Consequently, we cannot dismiss the possibility that senomorphics may inadvertently increase the secretion of harmful substances. Thus, while senomorphics represent a promising cancer therapy, they may not offer a complete solution but rather serve as a more beneficial approach within the complex, double-edged nature of SASP. For this reason, future studies must explore the effects of senomorphics on a broader range of SASP components, beyond the commonly studied factors. This includes investigating their impact on ECM composition, microvesicles, and other elements of the TME. In other words, more extensive and detailed research is required to fully understand the role of senomorphics in modulating senescence and SASP in cancer.

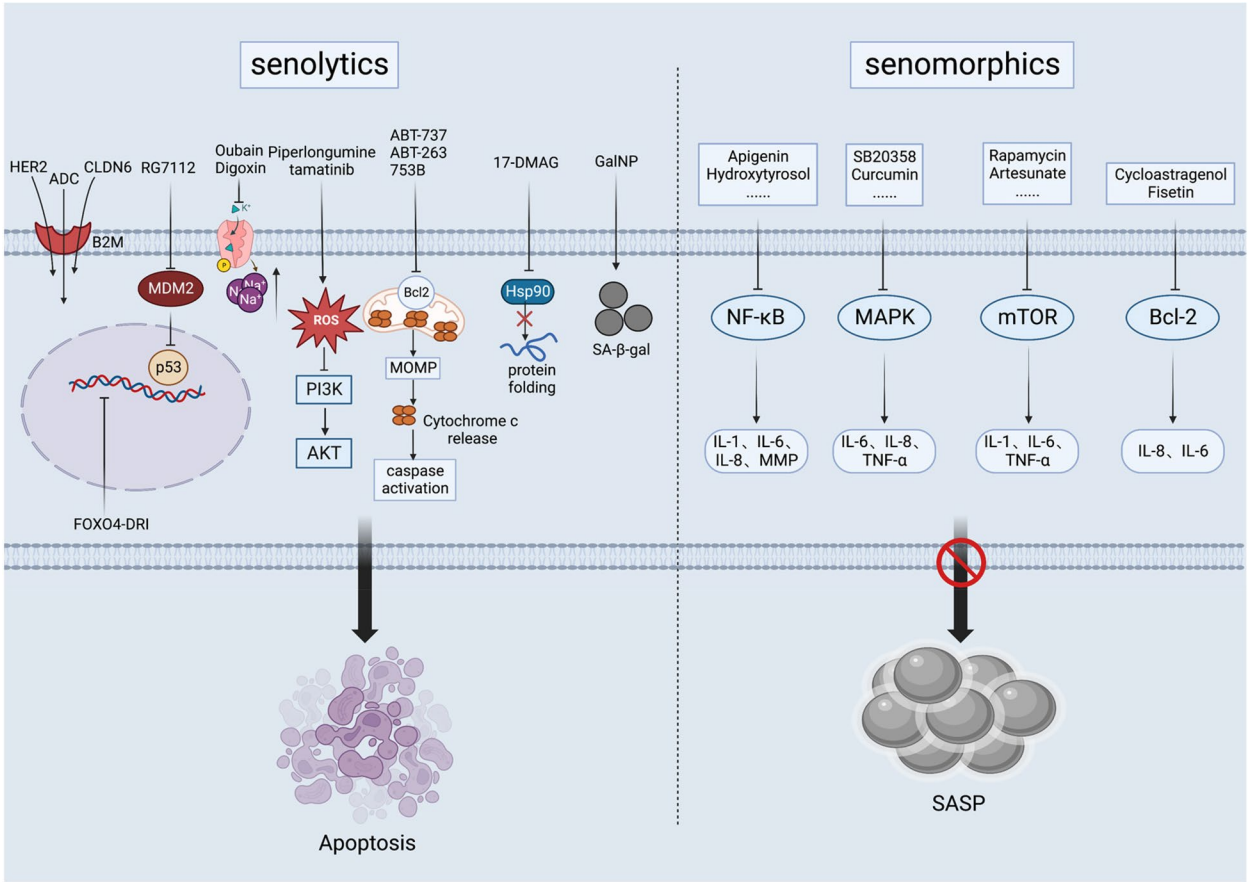

Fig. 4 Mechanism of senolytics and senomorphics. Senolytics induce apoptosis in cells undergoing CS by targeting various SCAPs. These pathways include MDM2, Bcl-2 family members, HSP90, SA-β-gal, PI3K/AKT, Na^+-K^+ pumps, FOXO4, and ADC. On the other hand, senomorphics inhibit pathways like NF-κB, MAPK, mTOR, and Bcl-2, thereby preventing senescent cells from releasing SASP factors such as IL-6, IL-8, MMP, and others

Future perspectives and conclusion

CS is a crucial process in growth, development, and cancer. Although significant progress has been made in understanding the mechanisms of CS and SASP, further studies are essential due to the heterogeneity of CS and SASP, which vary by cell type and stage. Additionally, the role of CS and SASP in vivo, particularly within the TME, requires more evidence. Such research could lead to the identification of simpler, more accurate, and more specific biomarkers. Furthermore, an in-depth exploration of the dual effects of SASP might provide new avenues for developing antitumor therapies. However, more specific drugs targeting CS are necessary to ensure their clinical efficacy. As our understanding of the roles and mechanisms of CS and SASP deepens, new tumor-targeting strategies are likely to emerge, ultimately improving clinical outcomes for cancer patients and advancing the field of precision medicine.

Despite the increasing number of studies on senescence characteristics and SASP, numerous challenges remain. Key issues include how to identify CS more simply and specifically, and how to determine the status of different senescent cells at various time points. Given that CS is dynamic in both space and time, early and late factors that activate and sustain CS may differ. While 'one-two punch' strategies hold promise for enhancing cancer therapies, several critical questions persist. For instance, determining the optimal timing for administering senolytics during anticancer regimens, identifying the best sequence of administration, and evaluating whether sequential treatment (initiating senescence followed by senolytics) offers the greatest benefits are crucial considerations. It is also important to recognize that when senescence is activated, it affects the surrounding microenvironment through SASP, creating a bidirectional communication between CS and the microenvironment. The heterogeneity of SASP means that different SASP profiles may contribute to either a favorable or detrimental microenvironment. This review aimed to highlight the dual nature of SASP in the microenvironment

Table 4 Senomorphics for tumor therapy

Type of senomorphics		Name	Type of senescent cells	Type of tumor	Impact on SASP	Reference
NF-κB inhibitors		Apigenin	BJ fibroblasts	NSCLC	IL-1, IL-8, IL-1β↓	[188]
		Hydroxytyrosol	Human fibroblasts	Breast cancer	IL-6; MMP-2; MMP-9 ↓	[189]
		Resveratrol, β-caryophyllene	HUVEC	Colorectal Lung cancer	IL-6, IL-1β, TNF-α↓	[190]
		Silybum marianum flower extract	Human neonatal dermal fibroblasts	Breast cancer	IL-6, MMP-1	[191]
		Oleuropein	Human fibroblasts	Breast cancer	IL-6, IL-8, MCP-1, RANTES↓	[192]
		Avenanthramice C	Human fibroblasts	——	IL-1, IL-8, THF-β↓	[193]
p38-MAPK inhibitors		SB203580	Human fibroblasts	NSCLC	IL-6, IL-8, IL-10, TGF-β, TNF-α	[194]
		BIRB796	Human fibroblasts	Glioblastoma	IL-6↓	[194]
		Curcumin	Human hepatocytes	Colorectal	IL-6, IL-8↓	[195]
mTOR inhibitors		Metformin	The human HNSCC cell line Cal27	head and neck squamous cell carcinoma	IL-6, IL-8, MCP-1, GRO↓	[196]
		Rapamycin	Mice fibroblasts	Nephroblastoma	IL-6, IL-8, TNF-α, IL-1α↓	[197]
		Artesunate	Human fibroblasts	Breast cancer	IL-1, IL-6, TNF-α	[198]
		Ginsenoside Rb2	human dermal fibroblasts	Breast cancer	SA-β-gal↓, DRAM2↑	[199]
Bcl-2 inhibitors PI3K/AKT inhibitors		Cycloastragenol	Human fibroblasts	Colorectal	MMP9, SDF1, IL-6↓ Senolytics Synergize with ABT263	[200]
		Fisetin	Human adipose-derived stem cells	Breast cancer	IL-6, IL-8↓	[201]
Others	HSP90 inhibitors	IPI-504	ARPE-19	NSCLC	IL-1β, IL-8↓	[202]
	NRTI	Lamivudine	Human fibroblasts	Breast cancer	IFN-1↓	[7]
	HMG-CoA inhibitors	Simvastatin	Human fibroblasts	Breast cancer	IL-6, CXCL-1↓	[203]
	JAK inhibitors	Ruxolitinib	senescent human preadipocytes	Squamous cell carcinoma of the skin	IL-6, IL-10, IL-1α、MCP-3, MCP-10, MMP-12, VEGF↓	[204]
	Nrf2 agonists	SR9009	Human fibroblasts	Prostate cancer	IL-1↓	[205]
	5-LO inhibitors	Zileuton	Human fibroblasts	Pancreatic cancer	IL-6↓	[206]
	Targeting pre -senescent osteoclasts	Zoledronic acid	Human lung fibroblasts	Breast cancer	CCL7, IL-1β, TGF-β	[207]
	Activate CD8 T cells	HCW9218	Diabetic db/db mouse model	Melanoma	IL-6, TNF-α, TGF-β↓	[208]
	Suppress ATM and HIF-1 α/ TRAF6 interaction	Rutin	Human prostate stromal cells	Prostate cancer	IL-6, IL-8, IL-1, CXCL3, MMP3↓	[209]
	TNF-αinhibitors	Adalimumab	HUVECs	Breast cancer	IL-6↓	[210]

MCP Monocyte Chemotactic Protein 3, *GRO* Growth-related oncogene, *DRAM2* Damage regulated autophagy modulator 2, *IFN-1* Interferon-1, *VEGF* Vasoactive Endothelial Growth Factor

and cancer, as SASP has been shown to have both positive and negative effects in cancer, influencing the induction and elimination of CS. A better understanding of the mechanisms underlying CS and SASP could lead to more effective cancer prevention and treatment strategies. In the case of senolytics, attention must be given to their long-term adverse effects, as the elimination of senescent cells could increase the body's burden and trigger dysfunction. For senomorphics, it is important to consider their broader therapeutic impacts. Identifying specific methods for CS detection, elucidating the mechanisms of CS and SASP, and developing more effective anti-senescence drugs will be critical steps forward in cancer therapy.

Abbreviations

CS	Cellular senescence
SASP	Senescence-associated secretory phenotype
TME	Tumor microenvironment
RS	Replicative senescence
DSB	DNA double-strand breaks
DDR	DNA damage response
RS	Replicative senescence
ATR	Ataxia telangiectasia and Rad3-related
ATM	Ataxia telangiectasia mutated
Rb	Retinoblastoma protein
CDK2	Cyclin dependent kinase 2
CDK2A	Cyclin dependent kinase inhibitor 2A
OIS	Oncogene-induced senescence

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