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REVIEW

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The controversial role of senescence-associated secretory phenotype (SASP) in cancer therapy

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Abstract

Cellular senescence, characterized by partially irreversible cell cycle arrest, has a dual role in cancer progression via the senescence-associated secretory phenotype (SASP). SASP encompasses a wide range of bioactive chemicals, including cytokines, chemokines, growth factors, and proteases, all of which can have a significant impact on the tumor microenvironment (TME). Initially, SASP can enhance tumor suppression by attracting immune cells and inhibiting cancer cell proliferation, but its long-term presence at TME can promote tumor growth, metastasis, and treatment resistance. Moreover, therapy-induced senescence, a common side effect of cancer treatments, can result in an increase of senescent cells and pro-tumorigenic SASP. Therefore, recent research has highlighted the potential of targeting SASP to improve cancer therapy. Among the therapeutic strategies, senolytic therapies selectively eliminate senescent cells, whereas senomorphic drugs decrease SASP without cytotoxicity, and there is also combined therapy targeting SASP for oncotherapy. Therefore, it is of crucial importance to develop more specific senotherapeutics and investigate the clinical applications of SASP modulation, such as using SASP components as biomarkers for therapy monitoring and personalized medicine. Taken together, understanding the molecular processes of SASP induction and their function in TME, including its heterogeneity across cell types and tissues, and designing personalized treatment are critical for optimizing cancer therapy and improving patient outcomes.

Keywords Cellular senescence, Senescence-associated secretory phenotype (SASP), Tumor microenvironment, Cancer therapy, Senolytic therapies

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Introduction

Telomere shortening [1], DNA damage [2], oxidative stress [3], and oncogene activation [4] are some of the stresses that can result in cellular senescence, a state of partially persistent cell cycle arrest [5] that contributes intricately to the formation and progression of cancer [6]. In some instances, cellular senescence leads to cell cycle arrest [7, 8]. However, under particular circumstances, such as oncogene activation or prolonged senescent state, these cells may re-enter the cell cycle, leading to tumor progression, which will be discussed in the subsequent sections [9–11]. No matter under what condition, the senescent cell presents a senescence-associated secretory phenotype (SASP), which is the group of bioactive substances secreted by these cells, including cytokines [12, 13], chemokines, proteases, and growth factors. SASP is one of the most important characteristics of senescent cells (Fig. 1) [14, 15]. Of note, SASP markers are not sufficient to verify the senescence phenotype alone and should be implemented as part of a multi-marker guideline approach, including the guideline from the International Cell Senescence Association (ICSA) [16], a two-phase algorithmic assessment to quantify various senescence-associated parameters [17], and other novel ways to track senescent cells [18–20].

In cancer biology, the SASP has a dual perspective. In the initial stage of tumor formation, SASP can function as a strong tumor-suppressive regulator by recruiting the immune cells to eliminate the stressed or injured cells, and thereby inhibiting cancer development. This is particularly relevant in the early stages of cancer, when the SASP can act as a barrier to prevent carcinogenesis by causing premalignant cells to undergo cell cycle arrest and death. However, the SASP may additionally promote tumor growth, metastasis, and treatment resistance when tumor cells undergo chronic inflammation. Senescent cells' bioactive substances can alter the TME, creating an environment that promotes tumor growth, immunological evasion, and resistance to anticancer therapies. In detail, SASP can stimulate angiogenesis, improve the epithelial-mesenchymal transition (EMT), and cause chronic inflammation (Fig. 2).

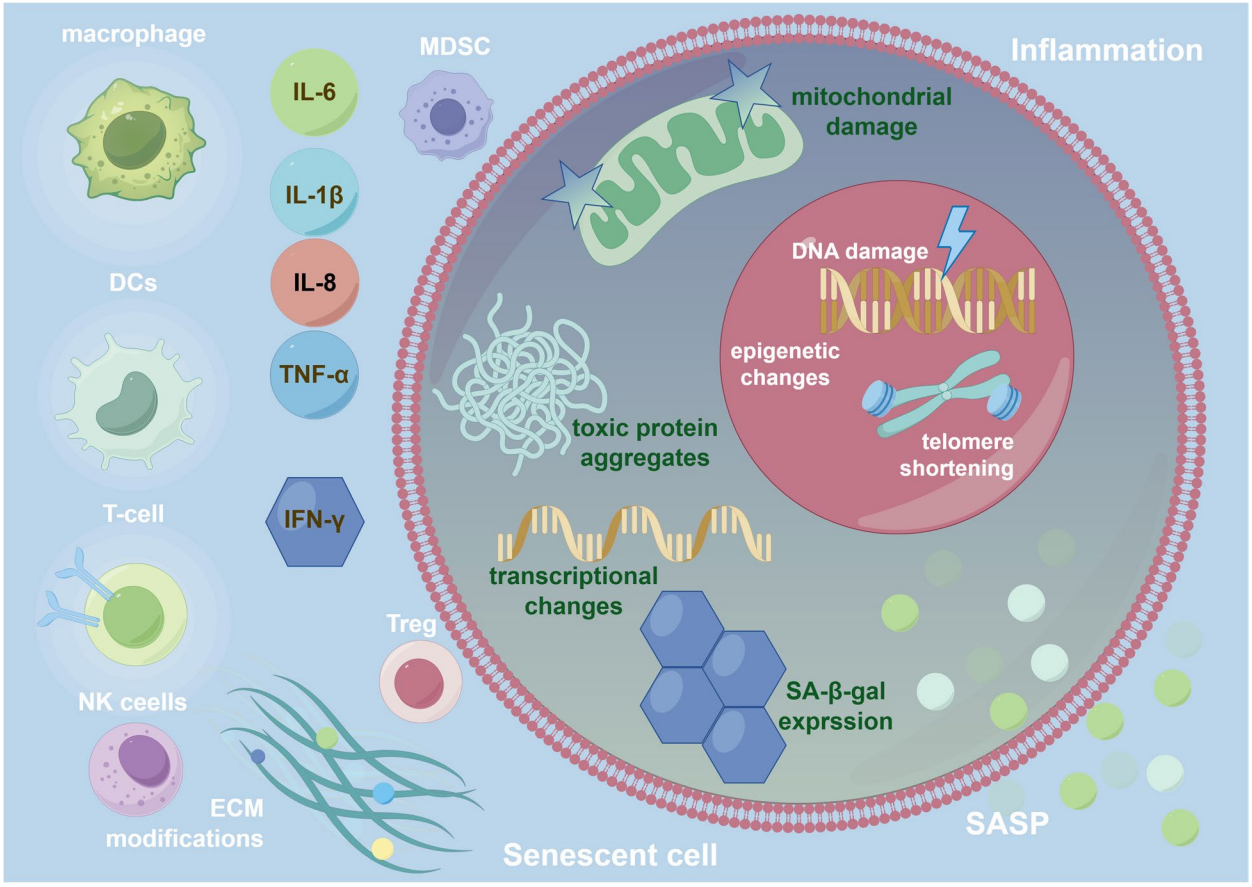

Fig. 1 SASP in cellular senescence. Senescent cells show signs of mitochondrial damage, DNA damage, epigenetic changes, toxic protein aggregation, transcriptional changes, and telomere shortening. Cellular alterations can release pro-inflammatory cytokines such as IL-6, IL-1β, IL-8, TNF-α, and IFN-γ, causing inflammation and affecting nearby cells such as macrophages, MDSCs, DCs, T-cells, B-cells, and Tregs. Furthermore, ECM modifications are induced, which have an additional impact on the cellular environment

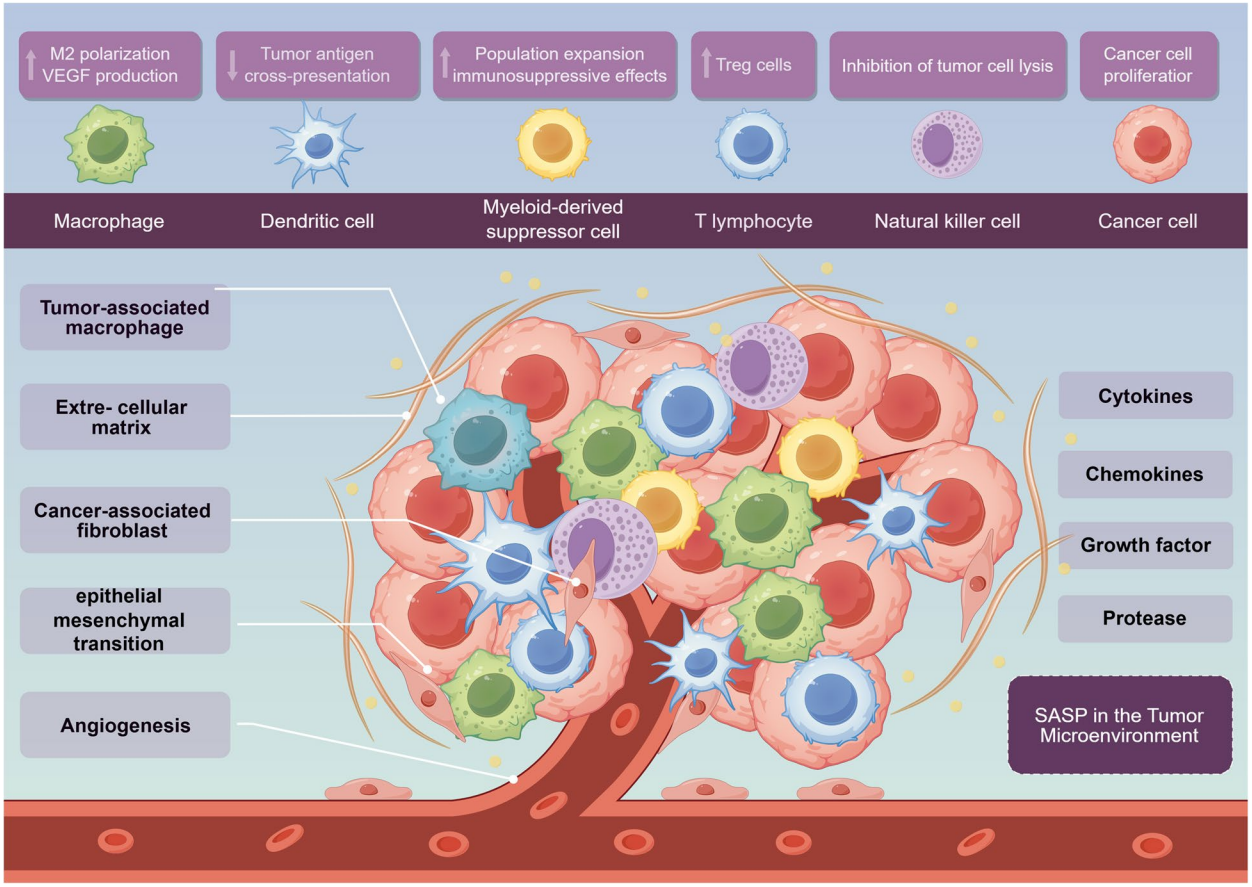

Fig. 2 SASP in tumor microenvironment (TME). This figure demonstrates how SASP impacts a range of immune cells, including cancer cells, T cells, natural killer cells (NKs), dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and macrophages. M2 polarization, VEGF production, tumor antigen cross-presentation, population growth, immunosuppressive effects, an increase in Treg cells, inhibition of tumor cell lysis, and cancer cell proliferation are among the cytokines, chemokines, growth factors, and proteases that are produced and contribute to the progression of tumors. It also illustrates how angiogenesis, cancer-associated fibroblasts (CAFs), extracellular matrix, tumor-associated macrophages (TAMs), and epithelial-mesenchymal transition (EMT) contribute to the development of an environment that is conducive to tumor growth and metastasis

The significance of understanding the SASP in cancer treatment has been emphasized by recent research. Many anticancer treatments, such as chemotherapy, radiation, and targeted therapies, frequently result in therapy-induced senescence (TIS) [21]. Although TIS can temporarily lessen the tumor burdens, therapeutic failure and disease recurrence may result from the eventual generation of senescent cells and associated SASP. As a result, there is an increasing interest in creating therapeutic approaches that either target senescent cells or alter the SASP in order to improve the effectiveness of cancer treatments. Senolytic medications, which specifically eliminate senescent cells, and SASP inhibitors are being investigated as possible adjuvant treatments to enhance patient outcomes [22, 23]. Furthermore, the content and consequences of the SASP might differ based on the primary cellular stressor and the genetic background of the cells, and it is not consistent across various cell types and tissues [24, 25]. This variation emphasizes the necessity of a sophisticated, comprehensive understanding/quantification of the SASP in various cancers [25]. The molecular processes governing the SASP and its influence on cancer biology are being better understood because of developments in single-cell analysis and high-throughput screening methods. Potential biomarkers and therapeutic targets are being identified by these investigations, which may be used to modify the SASP and enhance cancer treatment [26].

Overall, the SASP is a complex and situation-specific phenomenon that presents both opportunities and difficulties for the treatment of cancer. Properly utilizing the tumor-suppressive effects of the SASP while reducing its tumor-promoting activities by deciphering the intricate interactions among senescent cells, the SASP, and the tumor microenvironment could result in better patient outcomes [27]. Therefore, we summarized the specific role of SASP in cancer, current therapy, and potential future directions.

Components of SASP

Senescent cells release a complex and dynamic collection of bioactive chemicals, known as the SASP [28]. These chemicals modulate the TME and influence different aspects of cancer biology, such as tumor development, immune response, and therapeutic resistance.

Cytokines

Senescent cells release many cytokines, which contribute to an inflammatory and pro-tumorigenic environment. Key cytokines include Interleukin-6 (IL-6), Interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and Interleukin-1 beta (IL-1β).

IL-6 is a multifunctional cytokine that stimulates inflammation and immune cell recruitment. It has been proven to improve the development and survival of cancer cells and is frequently increased in several malignancies, including lung cancer, breast cancer, and colorectal cancer [21, 29–31]. The chemokine IL-8 recruits neutrophils and other immune cells to the site of inflammation [32]. It promotes tumor development, angiogenesis, and metastasis [33–35]. TNF-α is a pro-inflammatory cytokine that triggers apoptosis, inflammation, and immune cell activation. It is frequently high in the TME, which leads to tumor growth [36]. Both IL-1α and IL-1β are pro-inflammatory cytokines that can promote tumor development and immune evasion. They are released by senescent cells and can affect the TME to promote tumor formation [37].

Chemokines

Chemokines are a family of small cytokines that primarily function to attract immune cells to sites of inflammation. Key chemokines include Chemokines, such as CXCL1, CXCL2 (C-X-C motif chemokine ligand 1), CXCL5 (C-X-C motif chemokine ligand 2), CXCL8 (C-X-C motif chemokine ligand 5, also named as IL8), CXCL12 (C-X-C motif chemokine ligand 12), CXCL14, CCL2 (C–C motif chemokine ligand 2, also named as MCP-1), CCL5 (C–C motif chemokine ligand 5, also named as RANTES), CCL20 (C–C motif chemokine ligand 20) and CX3CL1 (C-X3-C motif chemokine ligand 1). These chemokines are responsible for the recruitment of neutrophils and other immune cells to the TME, contributing to inflammation and tumor progression [38–45].

Growth factors

Growth factors are proteins that stimulate cell growth, proliferation, and differentiation. The growth factors include HGF (hepatocyte growth factor) [41],TGF-β (transforming growth factor-beta) [46], GM-CSF (granulocyte–macrophage colony-stimulating factor) [47], IGFBP (insulin-like growth factor binding proteins, including IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6, IGFBP-7) [42, 48, 49], AREG (amphiregulin) [43, 50], epiregulin [44, 51], EGF (epidermal growth factor) [52, 53], and GDF15 (growth differentiation factor 15) [45]. Of note, IGFBP-3 regulates cell proliferation and death. It can affect the bioavailability of insulin-like growth factors (IGFs) and tumor cell behavior [54, 55]. Among these, VEGF (vascular endothelial growth factor) [56, 57] and FGF (fibroblast growth factor) [58] are essential for angiogenesis. It is frequently increased in the TME and promotes tumor growth and metastasis by promoting the development of new blood vessels that give nutrients and oxygen to the tumor [56, 59]. Growth factors in SASP collaborate to create a pro-tumorigenic environment that promotes tumor growth and angiogenesis. These growth factors may influence cell proliferation and differentiation [60–63].

Proteases

Proteases are enzymes that digest proteins and peptides. Proteases can modify the ECM, promoting tumor invasion and metastasis in SASP [64, 65]. The MMP family of proteases is important because it degrades ECM components. MMP2 and MMP9 play a critical role in cancer progression because they degrade the ECM, allowing tumor invasion and metastasis [60, 66, 67].

Other factors

In addition to cytokines, chemokines, growth factors, and proteases, SASP contains various bioactive compounds that help to modify the TME. TIMP2 (tissue inhibitor of metalloproteinases 2) inhibits MMPs and regulates ECM remodeling [68]. It may disrupt the balance between ECM breakdown and synthesis, which affects tumor growth [69]. PAI-1 (plasminogen activator inhibitor-1) regulates fibrinolysis and ECM remodeling by inhibiting the degradation of ECM components, potentially contributing to tumor growth [70–72].

Mechanisms of SASP induction

Numerous cellular stresses and signaling pathways can cause SASP, a dynamic and intricate process [73, 74]. Outlining SASP's function in cancer development and treatment resistance requires an understanding of the mechanisms underlying its induction. Here, our focus is on the main processes, including DNA damage response [5, 75], oncogene activation [27, 76], TIS [37, 77], and epigenetic regulation [78], which underlie the induction of SASP (Fig. 3).

DNA damage response

Cellular senescence and the ensuing development of SASP are largely caused by persistent DNA damage [79, 80]. In order to prevent injured cells from proliferating, cells that sustain DNA damage that cannot be effectively

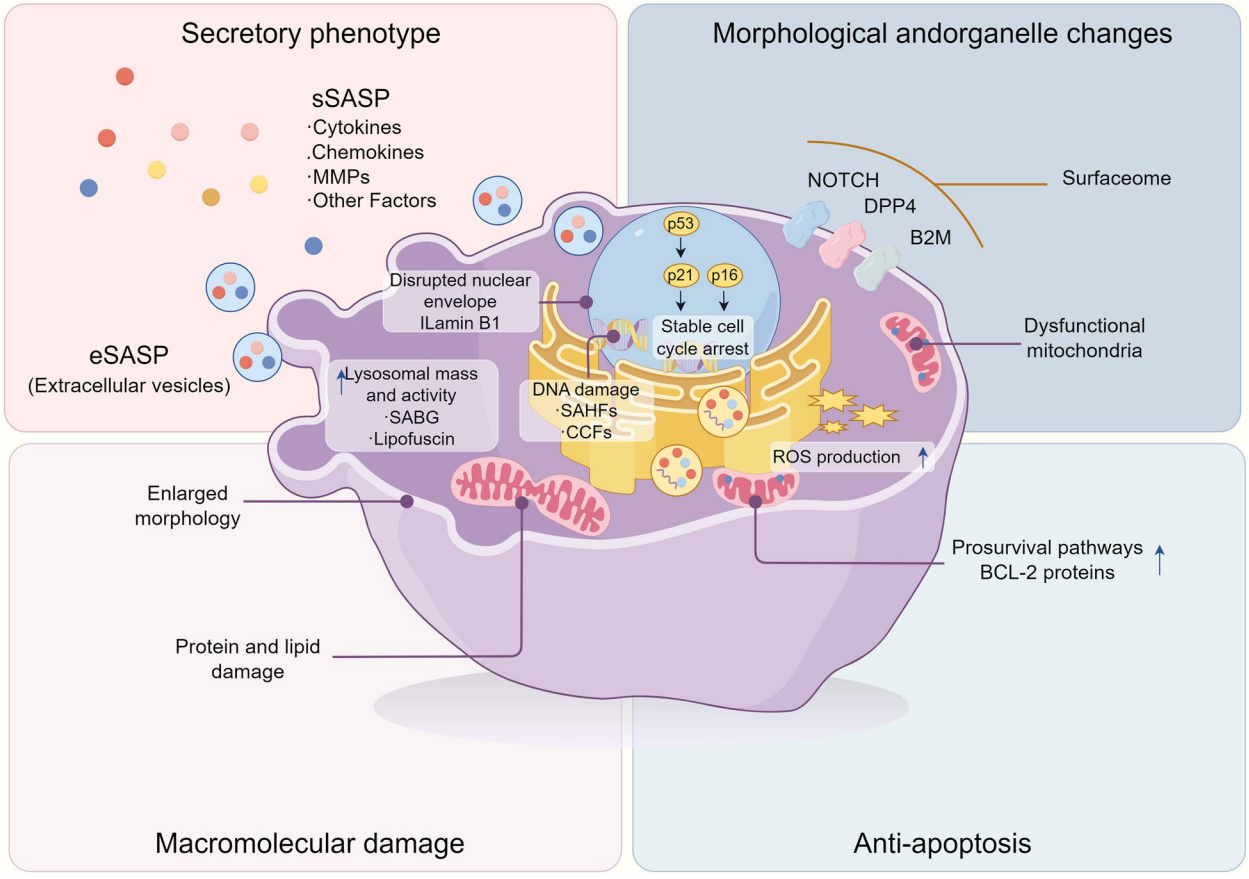

Fig. 3 The induction and outcomes of SASP. The cells undergo stable cell cycle arrest (by p53, p21, and p16), DNA damage, disrupted nuclear envelope, increased lysosomal mass and activity, and ROS from dysfunctional mitochondria. Therefore, the cytokines, chemokines, matrix metalloproteinases (MMPs), and other elements that contribute to the SASP are secreted initially by extracellular vesicles (eSASP), and then to the microenvironment as part of the secretion phenotype (sSASP). With the secretion of SASP, cells were characterized by enlarged morphology, protein damage, and increased prosurvival to obtain anti-apoptosis features

repaired go into irreversible cell cycle arrest. The DNA damage response (DDR) pathway coordinates this reaction by initiating a series of signaling events involving important proteins like p53, ATM, and ATR [81, 82]. In detail, the p53 tumor suppressor protein is a key player in the initiation of senescence and a critical regulator of the DNA damage response (DDR) [83]. The DDR is triggered in response to DNA damage, which causes p53 to become phosphorylated and stabilized [84]. The ATM/CHK2 and ATR/CHK1 pathways, which detect DNA damage and send signals to activate p53, are principally responsible for this [85]. The CDK inhibitor p21 (also known as $p21^{Cip1}$), which is encoded by the CDKN1A gene, is transcriptionally promoted by p53 once it is activated. By suppressing the activity of cyclin-dependent kinases (CDKs), especially CDK2, p21 stops the cell cycle from progressing, which activates the retinoblastoma protein (Rb) and causes cell cycle arrest [86–90].

The $p16^{INK4a}$/Rb pathway is also important in DNA damage-induced senescence, in addition to the p53/p21 pathway [91, 92]. The expression of p16, p14, and p15 (encoding the CDKN2A locus) is increased in response to several stresses, including DNA damage. p16, also referred to as p16Ink4a, suppresses CDK4 and CDK6 activity, which is necessary for the cell cycle to proceed. Rb becomes hypophosphorylated as a result of this inhibition, which stops it from releasing the E2F transcription factors necessary for cell cycle advancement [92]. Senescence results from the cell cycle ceasing in the G1 phase.

The p53/p21 and $p16^{INK4a}$/Rb pathways are not isolated, and they interact and influence each other [93]. For instance, the activation of p53 can indirectly affect the expression of p16 through various mechanisms [83, 94]. Additionally, other pathways and factors contribute to the induction of senescence. For example, oxidative stress, which often accompanies DNA damage, can activate the p38 MAPK pathway, further reinforcing the senescence process [95, 96]. Moreover, the PARP1/NAD+/SIRT1 signaling pathway, which is involved in the crosstalk between the nucleus and mitochondria, also plays a role in DNA damage-induced senescence

[97]. Activation of PARP1 due to DNA damage can lead to NAD^+ depletion, reducing the activity of sirtuins and ultimately causing mitochondrial dysfunction, which can contribute to cellular aging (Fig. 4) [98, 99].

Reactive oxygen species (ROS)

The complicated process of ROS-induced senescence involves several signaling networks that control how cells react to oxidative stress [3]. The important regulator of ROS-induced senescence is the NF-κB pathway [100]. Oxidative stress activates NF-κB, which in turn stimulates the expression of SASP components, such as growth factors and inflammatory cytokines (e.g., IL-6, IL-8). By activating the DDR in bystander cells, the SASP can further spread senescence in nearby cells. Furthermore, ROS-induced senescence is mediated by the mTOR (mammalian target of rapamycin) pathway via both DDR-dependent and DDR-independent pathways. By suppressing autophagy, which is essential for preserving cellular homeostasis and limiting the buildup of damaged organelles and proteins, mTOR can cause senescence. Rapamycin inhibits mTOR, which inhibits NF-κB transcriptional activity and SASP component expression [101–104]. The senescent state is maintained via a feedback loop that is created by the persistent activation of DDR signaling and the ongoing generation of ROS. By keeping the cell in a persistent growth arrest, this feedback loop inhibits oxidatively damaged cells from proliferating [100, 105].

The p53/p21 pathway is also involved [87]. The DDR, which is triggered by ROS-induced DNA damage, stabilizes and activates the p53 protein [106]. The cyclin-dependent kinase inhibitor p21, which suppresses CDK2 activity and stops cell cycle progression, is expressed more when p53 is activated. Generating the initial cell cycle arrest that defines senescence depends on this process [107, 108]. Apart from the p53/p21 pathway, ROS-induced senescence is also significantly influenced by the $p16^{INK4a}$/Rb pathway [109]. By blocking CDK4 and CDK6 activity, p16 prevents the retinoblastoma protein (Rb)

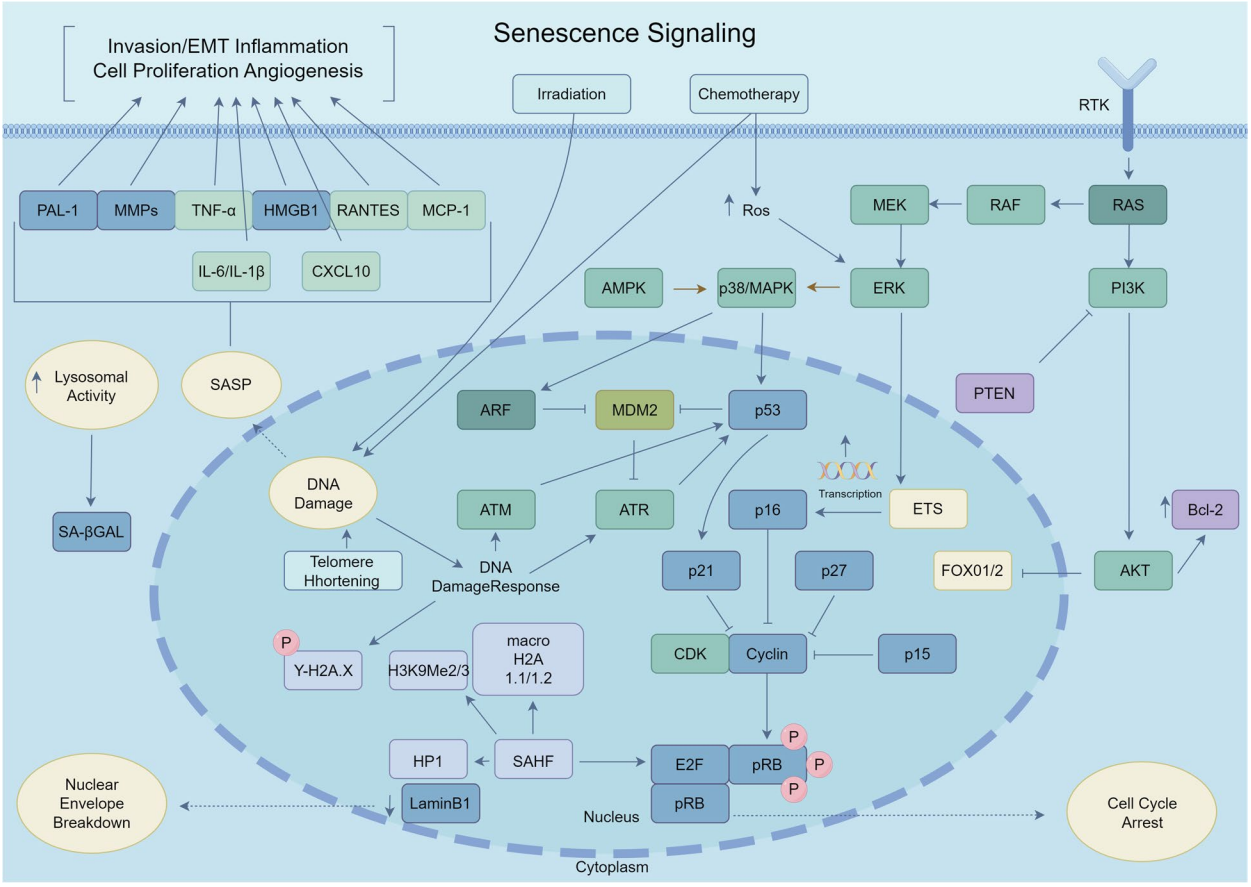

Fig. 4 The senescence signaling pathway in cancer cell. Upon irradiation or chemotherapy, cancer cell DNA is damaged with the activation of DNA Damage Response (DDR), by activating ATM/p53, ATR/p53 signaling. Further activated senescence markers as p21, p16, p27 cause cell cycle arrest with the inhibition of checkpoint proteins as cyclins and phosphor-Rb/E2F. Moreover, RAS/MEK/ERK signaling could activate downstream of p38/MAPK signaling, which further stimulate the activation of p53 and ARF to inhibit MDM2 activation (MDM2 inhibits ATR activity). PTEN could inhibit PI3K/AKT signaling pathway to activate Bcl-2 with anti-apoptosis function. With these activated or inhibited signaling pathway networks, SASP, including IL-6, IL-1β, CXCL10 and etc., is secreted to induce tumor invasion, EMT, inflammation, cell proliferation, and angiogenesis

from being phosphorylated and rendered inactive. By blocking the release of E2F transcription factors, which are necessary for cell cycle advancement, active Rb maintains cell cycle arrest [75, 110].

Moreover, the SAPK/JNK and p38 MAPK pathways are ROS-responsive stress-activated protein kinase cascades [111]. These pathways, which are triggered by oxidative stress, control the expression of genes that promote senescence, including TNFα, $p16^{INK4a}$, and $p14^{ARF}p19^{ARF}$. The activation of the p38 MAPK and JNK pathways is linked to mitochondrial ROS by the ROS-sensing complex known as the ASK1-signalosome [112, 113]. By increasing inflammation and oxidative stress, these pathways not only cause senescence but also age-related illnesses.

Oncogene activation

It has been well documented that oncogene-induced senescence (OIS) is an antitumor barrier mediated by DNA damage repair (DDR) [79, 80, 114, 115]. The activated oncogenes, including p53 [8] and BRAF(V600E) [116], could induce senescence and subsequent cancer development. Activation of oncogenes like RAS or MYC can result in DNA damage and genotoxic stress, which can trigger OIS [117, 118]. The DDR [79], p53/p21 [8], p16/Rb [119], and MAPK [120, 121] pathways are among the several signaling pathways involved in OIS, a strong and long-lasting antiproliferative response. One important regulator of OIS is the tumor suppressor protein p53 [8, 122]. The cyclin-dependent kinase inhibitor p21 is expressed more when p53 is activated by the DDR. p21 suppresses CDK2 activity, inhibiting cell cycle progression from G1 to S phase. This pathway is critical for inducing the initial cell cycle arrest that characterizes senescence. In addition to the p53/p21 pathway, the $p16^{INK4a}$/Rb pathway also contributes significantly to OIS, and this signaling pathway has been addressed in the previous section [119]. However, a recent study on p21 revealed that it could be oncogenic. The upregulation of p21 is correlated with cancer progression, metastasis, and chemoresistance independent of p53 [9]. Additionally, p53-mediated senescent cells maintain cancer stem cell characteristics by aggressive proliferation, an uncontrolled cell cycle, and cancer recurrence [10].

The MAPK (mitogen-activated protein kinase) pathway is another important mechanism in OIS. Oncogenic RasV12 activation causes continuous stimulation of the MAPK pathway, which can induce senescence. This pathway can also activate p38 MAPK, which helps to induce p53 and senescence [120, 121]. Under a prolonged senescence cycle arrest, cells could escape this state by activation of oncogene as cell division cycle 6 (CDC6) [11], H-Ras, and B-Raf [123], to re-initiate proliferation. Importantly, when these senescent cells re-enter the cell cycle, cancer progression, relapse, and chemoresistance occur [9, 10, 123, 124].

During this process, the production of SASP components by senescent cells can stimulate tumor growth in surrounding cells. SASP factors, such as IL-6 and IL-8, can trigger epithelial-mesenchymal transition (EMT), increasing cancer cells' invasive and metastatic potential [125]. Recent research has underlined the importance of OIS in oncotherapy. For example, targeted gene therapy that precisely disrupts oncogenic pathways might cause senescence in cancer cells, limiting their proliferative ability [126]. Yet, the associated SASP can establish a tumor-promoting environment, resulting in treatment resistance and tumor recurrence. Understanding the relationship between oncogene activity, senescence, and SASP is critical for creating successful cancer therapeutics.

Therapy-Induced Senescence (TIS)

Therapy-induced senescence (TIS) is a common side effect of various cancer treatments, including chemotherapy, radiation, and targeted therapies. While TIS can lower tumor burden by inhibiting cancer cell proliferation, the consequent buildup of senescent cells and associated SASP can result in treatment failure and disease recurrence [127]. For example, chemotherapy medicines like doxorubicin and radiation therapy can cause senescence in both cancer cells and stromal cells in the tumor microenvironment [128, 129]. The ensuing SASP may induce persistent inflammation, immunological suppression, and tumor growth [34]. Therapeutic therapies frequently cause DNA damage, hence activating the DDR process. This pathway is facilitated by ATM/CHK2 and ATR/CHK1, which phosphorylate and stabilize p53. The p53/p21 and p16/Rb pathways are also involved in TIS [27]. During senescence, mTOR activity causes 4EBP1 phosphorylation and MAPKAPK2 translation, resulting in the stability of SASP-related genes [130]. Rapamycin, a medication that inhibits mTOR, can reduce inflammation by reducing IL-1α translation and NF-κB activity.

The cGAS-STING pathway is another key regulator of the SASP. cGAS detects cytoplasmic DNA and produces cGAMP, which activates the adaptor protein STING. STING recruits TBK1 and IκB kinase, activating IRF3 and NF-κB, resulting in the release of type I interferons and inflammatory cytokines as IL-6. This pathway can be turned off to limit SASP synthesis and associated functions in senescent cells [12, 131–133]. Furthermore, the inflammasome pathway regulates SASP secretion. GSDMD (Gasdermin D), a downstream effector of inflammasome signaling, creates holes that facilitate the release of SASP components. Knocking down inflammasome components, such as NLRP1, can drastically reduce SASP in irradiation-induced senescence cells [134].

Several investigations have shown that TIS plays a dual role in cancer therapy [77]. On the one hand, TIS can improve the efficacy of cancer treatments by permanently stopping the proliferation of cancer cells. Senescent cells, on the other hand, release SASP, which can create a protumorigenic milieu, leading to therapy resistance and disease recurrence. As a result, efforts to reduce the negative effects of SASP, such as the use of senolytic medicines or SASP inhibitors, are being investigated as potential adjuvant therapy to improve treatment outcomes [129].

Epigenetic regulation

DNA hypermethylation

SASP regulation is profoundly affected by epigenetic changes. During senescence, global DNA methylation patterns shift, frequently leading to hypermethylation of certain gene promoters, which can mute tumor suppressor and other regulatory genes [74]. DNA methylation typically involves the addition of a methyl group to the cytosine base in CpG dinucleotides, which can lead to gene silencing [135]. Some senescent cells, for example, show hypermethylation of the *CDKN2A* promoter by SIRT7 and cell cycle arrest [136, 137]. DNA methyltransferase inhibitors can influence the expression of SASP-related genes, demonstrating the potential for epigenetic therapeutics to target senescence and SASP in cancer treatment [74, 138].

Histone modifications

Histone modifications, including both methylation and acetylation, have a substantial impact on chromatin structure and gene expression during senescence [139]. Histone methylation markers, such as H3K27me3 (trimethylation of lysine 27 on histone H3), are linked to gene regulation. During senescence, H3K27me3 levels rise at the promoters of senescence-associated genes, suppressing their expression. In contrast, the demethylase enzyme UTX can erase H3K27me3 marks, which promotes the expression of senescence-related genes [140, 141]. Histone acetylation generally increases gene expression by loosening chromatin structure. Histone deacetylases (HDACs) and histone acetyltransferases (HATs) have conflicting effects on histone acetylation. For example, HDAC1 and HDAC2 are implicated in the suppression of senescence-associated genes, whereas HATs such as CBP/p300 enhance their expression [142–144]. Besides, the sirtuins (SIRT1, SIRT6) are NAD^+-dependent deacetylases that control histone acetylation and are involved in metabolic sensing and genomic stability [145–147].

Chromatin remodeling

Chromatin remodeling complexes, including the SWI/SNF complex, are critical for regulating chromatin shape and accessibility. These complexes can compress chromatin to suppress gene expression or decompact it to stimulate transcription [148, 149]. During senescence, chromatin remodeling contributes to the creation of SAHF (senescence-associated heterochromatin foci), which assist in maintaining the cell cycle arrested [150–152].

RNA epigenetic regulation

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play important roles in epigenetic control during senescence. For example, the miR-34 family is increased during senescence and regulates genes involved in cell cycle progression and DNA repair [153–155]. lncRNAs interact with chromatin-modifying complexes, influencing chromatin structure and gene expression. For example, the lncRNA HOTAIR can direct PRC2 (polycomb repressive complex 2) to specific genomic regions, resulting in histone methylation and gene silencing [156].

Other signaling networks with epigenetic regulation

Signaling networks, including the p53/p21 and $p16^{INK4a}$/Rb pathways [87, 92, 157], the mTOR pathway [158], the insulin/IGF-1 pathway [159, 160], and the cGAS-STING pathway [161–163], interact with epigenetic mechanisms to regulate senescence. Firstly, epigenetic changes affect the p53/p21 and p16/Rb pathways. For example, DNA methylation and histone changes tightly downregulate the transcription of *CDKN2A* to prevent senescence, and once this regulation is loosened, cells will undergo senescence [164]. Secondly, mTOR can also influence histone acetylation and DNA methylation, which modulate gene expression [165, 166]. Thirdly, the insulin/IGF-1 pathway influences chromatin states via regulating transcription factors such as FOXOs. FOXOs can recruit chromatin-modifying enzymes, which affect gene expression and cellular metabolism [167]. Furthermore, the buildup of DNA fragments in the cytoplasm of senescent cells can activate the cGAS-STING pathway, resulting in the release of inflammatory cytokines and chemokines [161–163]. This pathway is especially important in the circumstances of aging and cancer, when persistent DNA damage and genomic instability are prevalent. The cGAS-STING pathway increases SASP while also increasing the immunogenicity of senescent cells, thereby connecting senescence to immune surveillance systems [12, 168]. Lastly, BRD4 (bromodomain containing 4) and super-enhancer mediate the regulation of SASP-gene expression [169]. BRD4, which belongs to the bromodomain and extra-terminal domain (BET) family, is a typical chromatin-reader protein that can recognize acetylated histones and bind to acetylated histones [170]. It regulates gene expression through binding to transcription

factors and other proteins associated with chromatin. During senescence, BRD4 physically associates with the promoters and super-enhancers of the SASP genes and enhances their transcription [170]. Super-enhancers are large clusters of regulatory elements abundant in transcription factors and co-activators, and they are essential to induce the expression of their target genes [143]. Super-enhancers develop near critical SASP genes in cellular senescence. These super-enhancers are marked with high levels of H3K27ac and recruit Brd4, leading to an increased transcription of SASP genes [143].

Dynamics of SASP

SASP synthesis is dynamic and changes in response to various cellular contexts and stresses. Understanding the SASP's role in tumor growth and suppression requires the background information of its dynamic evolution, a complex process marked by temporal shifts, the influence of microenvironmental stresses, and cell type plasticity.

Plasticity across cell types and tissues

Numerous studies demonstrate SASP's adaptability to diverse cell types [28, 171]. For example, under irradiation-induced senescence conditions, fibroblasts and renal epithelial cells share only 58 SASP components, according to a comprehensive proteomic investigation [171]. The number of shared SASP factors decreases to 19 when other cell types and senescence inducers are taken into account, such as UVA-induced senescent keratinocytes [172] and mesenchymal stem cells [68]. This emphasizes the cell-type-specific nature of SASP by indicating that only a small number of proteins are shared by all senescent cell types.

Furthermore, the composition of SASP varies greatly depending on the tissue. For instance, the SASP profiles of cutaneous fibroblasts (27 proteins involved in metabolism) [173] and hepatic stellate cells (higher in MMP1, MMP3, IL-8, IL-1β, and CXCL1) [174] varied greatly, depending on their microenvironment and biological origin [175]. Therefore, tissue-targeted therapeutics have become feasible based on the tissue diversity and heterogeneity of SASP.

Moreover, due to tissue specificity, different cells within the tumor microenvironment secrete distinct SASP components, which can lead to tumor progression or suppression. For example, epithelial cells may secrete IL-33, a family member of IL-1, which could limit tumor growth [176], whereas tumor cells may secrete IL-6 [177], IL-8 [13], and VEGF to promote cell proliferation, angiogenesis, and EMT transition [178, 179].

Influence of microenvironmental stressors

SASP composition alters significantly under different microenvironmental stresses. These stressors encompass a broad spectrum of conditions, including substrate stiffness [180, 181], co-culture with other cell types [182], and distinct biochemical (eg., chemotherapy) and physical induction (eg, irradiation) [183, 184].

A complex network of proteins and carbohydrates, the extracellular matrix (ECM) gives cells structural and biochemical support. ECM stiffness variations can change signaling cascades and cell behavior [185]. For example, changes in the ECM components and stiffness induce the malignancy, cancer invasion, and metastasis [186, 187]. Drugs, such as hyaluronic acid, could inhibit the fibroblast senescence by regulating the SASP component and ECM stiffness [188]. Another example is that the NF-κB phosphorylation status in UV-induced fibroblast senescence is influenced by substrate stiffness, indicating that the composition of the ECM may influence the composition of SASP [189].

When co-culturing the squamous cell carcinoma and replicative senescent (RS) fibroblasts, the RS cells could stimulate the senescence of cancer cells by upregulating certain key SASP gene expression, including IL-8, IL-1β, or CCL2 [182]. This cell–cell interaction underscores how nearby cells affect the SASP profile and lead to surrounding cells becoming senescent. Moreover, it has been demonstrated that senescent cells release bioactive substances into the bloodstream that change hemostasis and promote blood coagulation [190].

SASP can also be modulated by additional biochemical and mechanical stress [184], in addition to ECM stiffness and co-culture effects. For instance, ultraviolet-induced photoaging could induce the expression of specific SASP components, including IL-6, CCL5, CCL7, CXCL12 and etc., which lead to cellular senescence [191]. Low-intensity pulse ultrasound and radiotherapy could also stimulate senescent cells to secrete SASP, whereas the SASP component varied [184, 192–194]. For TIS, it is deliberately addressed in the previous section. Taken together, SASP components are dynamically changed under environmental stress, and could affect both the microenvironment and the whole body through blood circulation.

Temporal changes

Another important characteristic of SASP's plasticity is its temporal dynamics. Firstly, epigenetic alterations play a significant role in SASP expression dynamically [74]. Secondly, a transcriptomics study reveals that SASP components changed at different time periods. Early senescence was marked by p53 signaling and a DNA damage response, which may have been the initial reaction to the radiation-induced damage. The citric acid cycle, respiratory electron transport, p53-associated pathways, and signaling mediated by

p38-γ and p38-δ, two isoforms of p38-MAPK, were the hallmarks of intermediate senescence [120]. Cell-cycle arrest and chromatin remodeling were the most important differentially regulated pathways, outperforming other pathways only in late senescence. It's interesting to note that genes encoding SASP factors exhibited prominent variability that depended on time [195]. Thirdly, this differential expression of all the SASP genes for melanocytes and keratinocytes was observed on day 10, but for fibroblasts, at day 10, many SASP genes were not expressed, highlighting that the temporal change is different in cell type [195]. Using irradiated mesenchymal stromal cells from early to late senescence as an example, it is more significant to note that dynamic changes in SASP components cause not only aging but also other diseases like cancer [196].

Tumor suppressive function in the initiation stage of tumor formation

The SASP has a complex impact on cancer, affecting both tumor-suppressive and tumor-promoting processes (Fig. 5). In the initiation of tumor formation, SASP contributes to the suppression of tumors by recruiting immune cells for immune surveillance and preventing cancer cell proliferation [40, 73].

Improve immune surveillance

Pro-inflammatory cytokines, chemokines, and other SASP factors recruit NK and T cells to the TME. The recruitment of these immune cells promotes the removal of senescent cells, reducing the buildup of cells that would otherwise promote tumor formation [24]. However, even immune cells undergo senescence and secrete SASP, resulting in aberrant immune responses [197, 198].

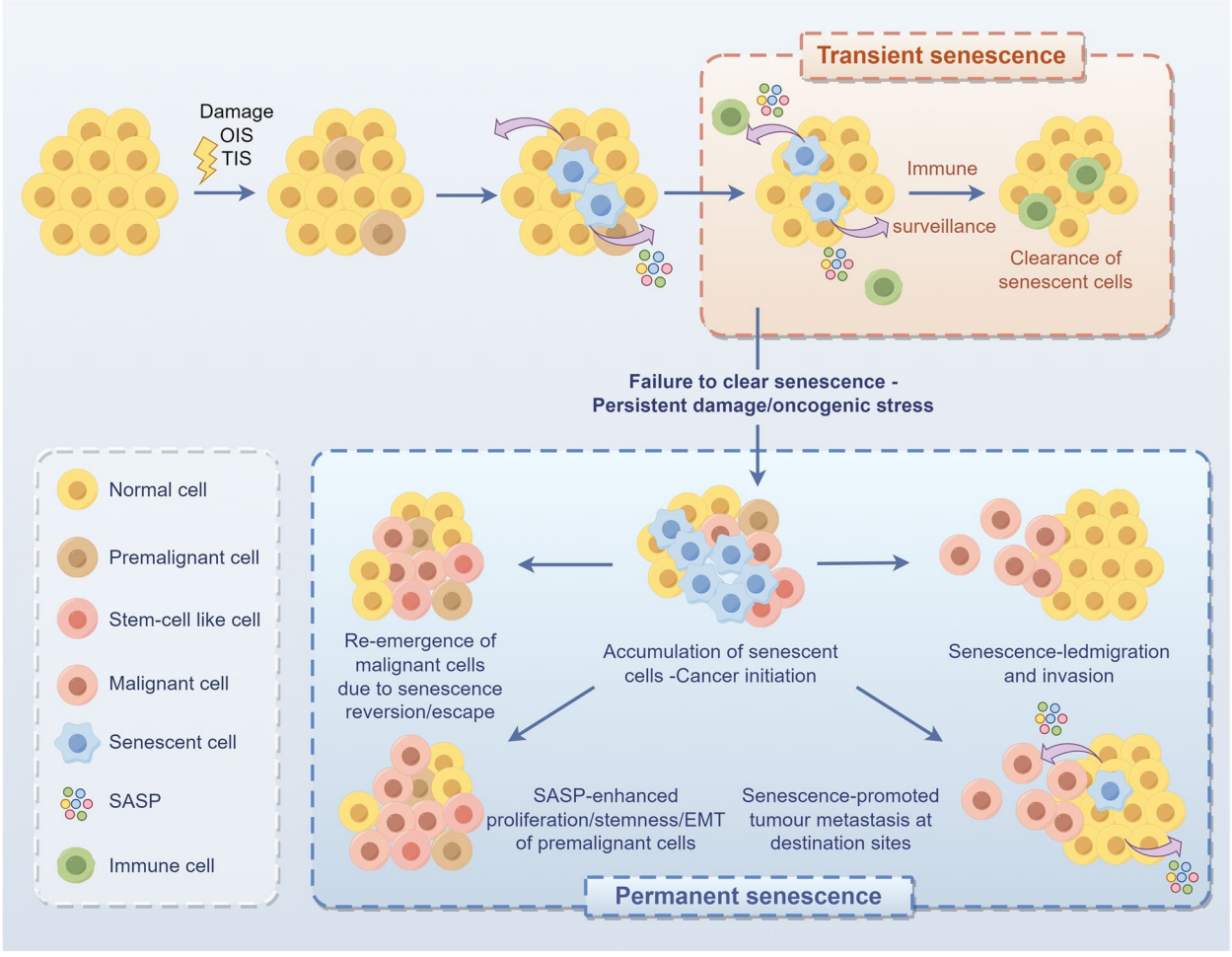

Fig. 5 The dual function of SASP in cancer. Upon damage or oncogenic stress as OIS or TIS, SASP recruits immune surveillance to eliminate the senescent cells, which is the transient senescence stage. Later on, with the failure to clear senescent cells, there exists persistent damage or oncogenic stress, which initiates the accumulation of senescent cancer cells. These senescent cells will migrate and invade the normal cells and cause them to become senescent cancer cells, thereby promoting tumor metastasis. In another aspect, SASP could enhance the cancer cell proliferation, stemness and EMT transition to maintain permanent senescence

NK cells play an important role in immune surveillance of the innate immune system, and can directly kill tumor cells [199]. By boosting IFN-γ production, IL-33, a cytokine of the IL-1 family of SASP, supports the activity of NK cells and tumor antigen-specific CD8 + T cells. Consequently, NK and CD8 + T cells are both necessary for IL-33's antitumor impact [176]. Furthermore, another member of the IL-1 family, IL1α, has been proven to activate the NK cells and $CD8^+$ T cells to inhibit liver cancer progression [200]. Chemokines (IL-15, IL-18, and CXCL10) released by the SASP recruit and activate them at the tumor site. NK cells are largely activated via the JAK/STAT pathway, which is triggered by IL-15 and IL-18 [201, 202]. Furthermore, CXCL10 interacts with the CXCR3 receptor on NK cells, promoting their migration to the tumor site [203, 204].

T cells, specifically $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells, play an important role in tumor immune surveillance by identifying and destroying tumor cells. IL-6, one of the SASP components, has been shown to enhance $CD8^+$ T cell cytolytic activity and TCR-independent proliferation [205]. Meanwhile, IL-6, by upregulating c-Maf, stimulates the differentiation of $CD4^+$ T cells to Th2 cells [206, 207]. Moreover, $CD4^+$ helper T cells are strongly stimulated by IL-8 [208]. Besides, TNF-α and IFN-γ trigger cell death and activate T lymphocytes via the NF-κB pathway [209, 210]. IL-1 has also been reported to inhibit tumor growth by activation of $CD4^+$ Th1 cells [211]. Therefore, taking pancreatic cancer as an example, senescent cells can attract NK and T cells by secreting chemokines such as CCL2 and CXCL9/10, resulting in improved immune surveillance [212, 213].

Macrophages can be classified as M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes. M1 macrophages participate in tumor suppression, whereas M2 macrophages stimulate tumor development. M1 macrophage exosomes or nanovesicles have been documented to inhibit tumor growth [214, 215]. Of the SASP components, IFN-γ could modulate the M2/M1 ratio by increasing M1 macrophage and thereby limiting lung tumor growth [216]. Moreover, IL-12 stimulates the M1 polarization and thereby enhances immune responses in various tumors [217, 218]. A recent study revealed that naïve macrophages possess anti-tumor function via the TNF-α secretion in pancreatic ductal adenocarcinoma (PDAC) [219]. Therefore, SASP components may inhibit tumor growth via the regulation of macrophage polarization.

DCs are crucial for antigen presentation and T cell activation. The SASP can help DCs to increase anti-tumor immunity, and as a positive feedback loop, cytokines released by DCs could recruit cytotoxic T cells to eradicate tumors. For example, under anticancer drug treatment, the dying tumor cells secrete IL-1β, which was primed by DCs, and then DCs recruit IFN-γ-producing T cells to eliminate these dying cells [220]. Moreover, a member of the IL-1 family, IL-33, could restore the anticancer function of NK cells [221]. Another study revealed that following IFN-β stimulation, TRAIL (TNF-α-related apoptosis-inducing ligand) expression on immature DCs is significantly up-regulated to eliminate TRAIL-sensitive tumor cells [222]. Meanwhile, cytokines released by DCs contribute to the killing of cancer cells. The cytokine-induced killer (CIK) cells, activated by DCs secreting cytokines such as IFN-γ, TNF-α, and TNF-β, have been shown to increase the anti-tumor efficacy of chemotherapy [223]. Additionally, co-culturing of DCs and CIK cells could inhibit liver cancer stem cell growth [224]. Another piece of research suggested that one of the SASP components, IL-18, would cause the DC to release IFN-γ, which would then limit the tumor's growth [225].

MDSCs and Tregs are two types of immune-suppressive cells. MDSCs are immunosuppressive cells that suppress the function of T and NK cells, whereas Tregs are immunosuppressive T cells that decrease the activity of effector T (Teff) cells. Senescent fibroblasts are known to secrete IL-33, a member of the IL-1 family [226]. And IL-33 could inhibit the immunosuppressive ability of MDSCs. Moreover, IL-33 treatment significantly reduced the number of Treg cells in the TME [227]. Another SASP component, IL-12, can convert MDSC into APC and restore macrophage activity to enhance the anti-tumor effects [228]. Meanwhile, IL-12 treatment could reduce the number of MDSCs within the TME and thereby increase the $CD8^+$ T cells, which ultimately lead to prolonged survival and decreased metastasis [229]. Moreover, IL-12 inhibits Treg differentiation and proliferation, and therefore improves tumor clearance [230, 231].

Inhibition of cancer cell proliferation

SASP factors can cause surrounding cancer cells to undergo senescence (Fig. 5) [232]. This impact is accomplished by paracrine signaling, in which senescent cells' secreted substances alter the behavior of neighboring cells [233]. Cytokines such as IL-6 and IL-8, for example, can induce senescence in surrounding cancer cells, restricting their ability to proliferate [13]. In lung cancer, SASP factors activate NF-κB, causing senescence in adjacent cancer cells and limiting tumor growth [234]. In another work, SASP from mesenchymal stromal cells was shown to promote senescence in immortalized prostate cells but not in metastatic prostate cancer cells [235]. This shows that SASP can help inhibit pre-tumorigenesis progression. Additionally, the SASP has a paracrine effect on neighboring normal cells, causing stable cell cycle arrest [37].

Tumor promotion function by persistent SASP

Chronic inflammation

Persistent SASP can cause a pro-inflammatory microenvironment that promotes tumor growth. NF-κB regulates SASP and produces pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α [102]. The DDR pathway components ATM and ATR phosphorylate IκB, activating NF-κB and transcription of SASP factors (IL-1β, IL-6, and TNF-α). These factors have an important role in the initiation and maintenance of chronic inflammation [102, 236]. p38 MAPK stimulates downstream pathways, including MSK1 and MSK2, which phosphorylate the p65 subunit of NF-κB, increasing transcription of SASP factors [121, 237]. As a result, under conditions of cellular stress and DNA damage, p38 MAPK regulates the cytokines, chemokines, and MMPs that make up SASP. Cytokines, such as IL-6 and IL-8 promote JAK-STAT signaling, which leads to the transcription of SASP components and the promotion of chronic inflammation. As a positive feedback loop, the JAK-STAT pathway regulates a subset of immunosuppressive SASP cytokines, including IL-6 and IL-8 [177, 238, 239]. cGAS detects cytosolic DNA fragments and activates STING, resulting in the generation of type I interferons and the activation of SASP components to sustain chronic inflammation [163, 240].

SASP can potentially affect TME and tumor metabolism [37]. In lung cancer, SASP factors can cause persistent inflammation, which promotes tumor growth by increasing glycolysis and oxidative phosphorylation (OXPHOS) via mTOR signaling [234, 241]. Moreover, chronic inflammation caused by SASP can lead to immunosuppression and promote tumor growth by altering the tumor microenvironment [27, 242] (Fig. 2).

Epithelial-Mesenchymal Transition (EMT)

SASP factors can induce EMT, a process where epithelial cells lose their cell–cell adhesion and acquire mesenchymal characteristics, promoting cancer cell migration and metastasis [77, 125, 243]. This transition is driven by the secretion of cytokines and growth factors that alter the cellular phenotype. SASP factors, particularly cytokines like IL-6 and IL-8, can induce EMT in neighboring epithelial cells. This is observed in non-aggressive human breast cancer cell lines, where treatment with conditioned medium from senescent cells leads to decreased E-cadherin and increased vimentin expression, hallmarks of EMT [13]. In lung cancer, SASP factors can induce EMT, leading to increased migration and metastatic potential [234]. Moreover, senescent cancer-associated fibroblasts (CAFs) can promote EMT in breast cancer cells through the secretion of SASP factors, thereby enhancing metastasis [244]. EMT can also influence SASP. For instance, the expression of EMT transcription factors such as Snail and Slug can modulate the secretion of SASP components, creating a feedback loop that enhances both processes [245] (Fig. 2).

Immune evasion

SASP can manipulate the immunological microenvironment to avoid immune surveillance. Senescent CAFs release CCL2 to attract MDSCs and Tregs, both of which contribute to immune suppression, resulting in an immunosuppressive environment [246–248]. Moreover, it has been documented that CAFs limit NK cell-mediated killing, thereby contributing to breast cancer progression [248]. Another study found that senescent CAFs in pancreatic ductal adenocarcinomas (PDAC) release SASP factors, which abolish the activity of $CD8^+$ T cells and promote immune evasion [249]. Similarly, senescent epithelial cells contribute to SASP by secreting IL-6 and IL-8, which can stimulate JAK/STAT3 signaling and increase the expression of PD-L1 on tumor and dendritic cells [250, 251].

Furthermore, SASP components, such as IL-6, IL-8, and TNF-α, contribute to the dysfunction of T cells. The IL-6/JAK/STAT3 pathway promotes tumor cell proliferation and metastasis while inhibiting anti-tumor immune responses by inhibiting tumor antigen expression [252–254]. This mechanism causes $CD8^+$ T cell depletion, which impairs antitumor immunity [255]. By suppressing cytotoxic T lymphocytes in a STAT3-dependent manner, the chemokine CXCL9 accelerates the development of human pancreatic adenocarcinoma [256]. Furthermore, SASP factors might cause immune evasion by suppressing the expression of MHC class I molecules on cancer cells, limiting their visibility to $CD8^+$ T cells [257, 258].

Senescent cells release IL-10 and TGF-β, which polarize tumor-associated macrophages (TAMs) towards the M2 phenotype, limiting their ability to phagocytose tumor cells [259, 260]. IL-1β secreted by senescent cell could also stimulate M2 polarization and thereby lead to the progression, migration and EMT transition of esophageal squamous cell carcinoma [261]. Although controversial, M1 macrophages has also been reported to have pro-tumor function by stimulating metastasis of ovarian cancer via NF-κB activation [262]. IL-6 inhibits DC development via the JAK/STAT3 pathway, limiting their ability to sense antigens and activate T lymphocytes [252, 253, 263, 264].

Additionally, senescent cells release CCL2, which attracts MDSCs to the tumor site, and TGF-β, which stimulates Treg proliferation and function. MDSCs then suppress the activity of $CD8^+$ T and NK cells, resulting in an immunosuppressive environment. Besides, CXCL1 and CXCL2 attract MDSCs to the tumor site, where they inhibit T and NK cell function [265–267]. Another subtype of important immune evasion cells are Tregs. It has

been reported that IL-10 enhances Treg-mediated immunosuppression [268, 269]. Treg cells could also limit the function of Teff cells, allowing malignancies to evade the immune system [270, 271].

Stromal remodeling

SASP can modify the extracellular matrix (ECM), making the environment more conducive to tumor growth [65, 272]. Senescent cells secrete proteases and other substances that break down and modify the extracellular matrix, allowing cancer cells to invade and metastasize. SASP factors can modify the ECM composition, causing greater fibrosis and inflammation in the TME [65]. Senescent CAFs, for example, release pro-tumorigenic factors such as IL-6, IL-8, and osteopontin, all of which have been related to stroma-mediated therapy resistance [24]. Meanwhile, changes in the composition of the ECM can have an effect on senescence cells. For example, alterations in the ECM's composition can influence the senescence-associated secretory phenotype [65, 273].

SASP in the TME

Cancer-Associated Fibroblasts (CAFs)

CAFs, a major component of the tumor stroma, can undergo senescence in response to various stimuli, including DNA damage, oxidative stress, and therapeutic interventions. Senescent CAFs secrete a range of SASP factors, including cytokines, chemokines, and growth factors, which can significantly influence the tumor microenvironment. Senescent CAFs can promote cancer cell proliferation, migration, and resistance to therapy through the secretion of SASP factors [243, 274, 275]. For example, SASP factors such as IL-6 and IL-8 can stimulate cancer cell growth. Factors like CXCL12 can enhance cancer cell migration and invasion. Moreover, SASP can induce a pro-inflammatory microenvironment that supports cancer cell survival and resistance to chemotherapy and radiation. In pancreatic cancer, senescent CAFs in pancreatic cancer can promote tumor progression through the secretion of SASP factors, including IL-6 and IL-8 [274, 276] (Fig. 2).

Immune cells

NK cells play an important role in immune surveillance and can directly kill tumor cells. Chemokines (IL-15, IL-18, and CXCL10) produced by the SASP draw them to the tumor site [277–279]. Chronic SASP exposure, on the other hand, can cause T cell exhaustion, in which NK cells become less effective at eliminating cancer cells [277, 280]. This paradoxical impact emphasizes the dual character of SASP in immune modulation.

SASP can modulate T cell function in a context-dependent manner. Some SASP factors can enhance T cell activation and anti-tumor activity, while others can suppress T cell function and promote immune evasion. For example, certain cytokines like IL-12 can enhance T cell activation and cytotoxicity [281, 282]. Conversely, factors like TGF-β and IL-10 can suppress T cell function, leading to immune tolerance and tumor progression [271, 283–285].

Macrophages can differentiate into M1 or M2 phenotypes. M1 macrophages participate in tumor suppression, whereas M2 macrophages stimulate tumor development. SASP cytokines, including IL-6, TNF-α, and TGF-β, play a significant role in macrophage polarization [178, 179, 286, 287]. IL-1α and IL-1β trigger the NF-κB pathway to promote M2 polarization [179]. TGF-β promotes M2 polarization through the SMAD pathway [288, 289].

DCs are crucial for antigen presentation and T cell activation. SASP could weaken DCs' antitumor immunity. For example, IL-6 inhibits DC development via the JAK/STAT3 pathway, limiting their ability to present antigens and activate T cells [252, 253]. IL-10, a potent immunosuppressive cytokine, can also impair DC development and functionality [290].

MDSCs and Treg could be recruited and activated by SASP cytokines and chemokines (IL-6, IL-8, and CXCL1 for MDSCs; TGF-β and IL-10 for Treg) [291–293]. These cells could inhibit the function of T cells and NK cells, promoting tumor progression.

Therapeutic strategies targeting SASP

Senolytic drugs

Senolytic medicines preferentially destroy senescent cells, lowering the overall prevalence of SASP in the tumor microenvironment (Table 1). For example, Navitoclax, a Bcl-2 family inhibitor, can cause apoptosis in senescent cells [320]. Dasatinib, a tyrosine kinase inhibitor, when combined with quercetin, a natural flavonoid, was demonstrated to effectively eradicate senescent cells [298]. Furthermore, senolytic medicines have shown promise in preclinical studies, lowering tumor burden and increasing treatment results. Dasatinib and quercetin, for example, have been shown to lower the amount of senescent CAFs and improve therapeutic efficacy in cancer models (Table 2). Furthermore, the combination of dasatinib and quercetin could eliminate senescent cells stemming from patient-derived LKB1-deficient lung adenocarcinoma organoids following TIS, suggesting that this therapy has great promise for the treatment of dormant and/or relapse tumors [324]. However, these senolytic drugs have been reported with adverse effects as nausea, vomiting, diarrhea, fatigue, and, more importantly, even thrombocytopenia and neutropenia [332–334]. Therefore, in a recent study on TIS models, combining the senolytic drugs with the encapsulation of galacto-oligosaccharides could increase tumor xenograft regression [335]. Moreover, based on the concept that lipofuscin is

Table 1 Senolytic drugs in pre-clinical studies

Drug Name	Mechanisms	Cell Model	Dose	References
Dasatinib	Inhibits BCR-ABL, SRC family kinases, and EFNB-dependent receptor signaling	Non-small cell lung cancer, AGS cell, Human preadipocytes, murine embryonic fibroblasts (MEFs)	50 nM (human preadipocytes), 250 nM (MEFs)	[294–296]
Quercetin	Inhibits PI3K, serpins, and other kinases	Human umbilical vein endothelial cells (HUVECs), MEFs, primary (Colo-320) and metastatic (Colo-741) colon adenocarcinoma cell lines	10 μM (HUVECs), 50 μM (MEFs), 25 μg/ml fir colon cancer	[297]
Dasatinib + Quercetin	Combination therapy targeting multiple pathways (cell); decrease in senescence markers $p16^{INK4a}$, $p19^{ARF}$, and SASP molecules IL-6 and MMP13 (animal)	Human preadipocytes, HUVECs; 6-, 14-, and 18-months mice	Dasatinib 200 nM plus Quercetin 20 μM (cell); 5 mg/kg Dasatinib plus 50 mg/kg Quercetin (animal treated till 23 months)	[298–300]
Fisetin	Inhibits BCL-2 family proteins, PI3K/AKT pathway, increased levels of phosphorylated AMPK, decreased levels of AKT and HSP90, and impaired mitophagic response to eliminate drug-resistant senescent breast cancer cells	HUVECs, MEFs, HCC1500, CAMA-1, HCC1428, and ZR-75–30 cells (cell model); 27 months old mice	0.5 μM (caspase activity), 5 μM (cell viability), 10 μM (cell number); 100 mg/kg/day (mice)	[301–304]
Navitoclax (ABT263)	Inhibits BCL-2, BCL-xL	HUVECs, human preadipocytes, a panel of 12 senescent cells, and hematopoietic stem cells in mice	0.313 μM (HUVECs), 5 μM (preadipocytes), 1.25 μM (in vivo), 50 mg/kg/d (in mouse)	[305, 306]
Luteolin	Modulates SIRT1 and p53, alleviate oxidative stress and downregulate the expression levels of P21, P16, and IL-β	House Ear Institute-Organ of Corti 1 cells (HEI-OC1), UVA-induced fibroblast (NIH-3T3) senescence	2 μM—5 μM	[307, 308]
Curcumin	Targets NF-κB, MAP kinase, p53, NRF2, COX-2	Hepatic stellate cell, HUVEC, vascular smooth muscle cell senescence, etc	5 μM—10 μM	[309–311]
Curcumin Analog EF24	Induces apoptosis, ROS production, proteasome degradation of Bcl-2 family proteins, activation of PTEN	alveolar epithelial cell senescence, etc	EC50 of 1.62 μM (radiation-induced senescence), 4.69 μM (non-senescent cells)	[312, 313]
Geldanamycin, Tanespimycin, Alvespimycin	HSP90 inhibitors	Various cell types	1 μM (MEFs)	[314, 315]
Piperlongamine	Inducing apoptosis, decrease the expression of major senescence markers	Human WI-38 fibroblast senescence, chondrocyte senescence, etc	10 μM	[316, 317]
Aspirin	Decreases ROS, increases NO and cGMP (cell); reduced p53 and p21 accumulation	HUVEC, juvenile mice with doxorubicin	100 μM (cell); 0.02 g/100 ml in drinking water for 7–9 weeks (animal)	[318, 319]

accumulated in senescent cells, coupling dasatinib with a lipofuscin binding domain via an ester bond linker, and then encapsulating it in a poly(ethylene-oxide)-block-poly(ε-caprolactone) (PEO-*b*-PCL) micelle could efficiently eliminate the senescent cells with reduced adverse effects [336]. Besides, another study revealed that ferroptosis induction and ferrous iron-activatable prodrug could be a broad-spectrum senolytic strategy to eliminate primary and paracrine senescent cells induced by SASP [337]. Based on these up-to-date novel strategies for precisely targeting senescent cells, the senolytic therapy has more potential for clinical application.

Senomorphic drugs

Senomorphic medications suppress SASP without destroying senescent cells, reducing SASP's pro-inflammatory and pro-tumorigenic effects (Table 3). Rapamycin and metformin can target ROS and inhibit the translation of SASP factors like IL-1α [339]. For example, by reducing the TGF-β levels, rapamycin could inhibit renal cancer metastasis [345]. Several inhibitors, including NF-κB inhibitors, glucocorticoids (e.g., dexamethasone), resveratrol, and bepotastine, suppress the transcription of SASP-related genes [343, 344, 346]. Taking dexamethasone as an example, through the inhibition of TNF-α, it could limit the progression of squamous cell carcinoma [347]. Furthermore, targeting SASP cytokines with HDAC inhibitors may directly inhibit SASP [348]. Besides, BET inhibitors downregulate SASP factor expression in senescent cells as well [170]. However, because senomorphics drugs often lack specificity, they also have adverse effects. For instance, rapamycin has been documented to impair wound healing and induce immune suppression [349]. Moreover, based on a large population investigation, the mTOR inhibitor is correlated with high cardiovascular adverse effects, including arteriosclerosis, heart failure, hypotension, etc. [350]. Another example is that through the attenuation of the

Table 2 Senolytic drugs in cancer

Drug Name	Type of Cancer	Dose	Molecular Mechanisms	SASP Factors Involved	References
Navitoclax (ABT-263)	Myelofibrosis, Acute Myeloid Leukemia (AML), Solid Tumors	Varies by study, typically 100–400 mg daily	Inhibits BCL-2, BCL-xL, and BCL-W, promoting apoptosis in senescent cells	IL-6, IL-8, CCL2, CXCL1, MMPs	[321–323]
Dasatinib/Quercetin	patient-derived LKB1-deficient LUAD organoids following TIS, Ovarian cancer, melanoma, prostate cancer, etc	Dasatinib: 100–200 mg daily; Quercetin: 500–1000 mg daily	Dasatinib targets Src kinase and BCR/Abl; Quercetin targets Bcl-xL, regulates expressions of various proteins in WNT, PI3K, and MAPK pathways, leading to cell cycle arrest, apoptosis, and DNA damage. patient-derived LKB1-deficient lung adenocarcinoma (LUAD) organoids following TIS act as a potential source of tumor dormancy and cancer relapse, suggesting senolysis as a complementary approach to other anti-cancer treatments	IL-6, IL-8, TNF-α, MMPs	[324–326]
Fisetin	Acute Liver Injury, Skin Aging, Cancer	10–100 μM in vitro; 100–200 mg/kg in vivo	Selective BCL-XL inhibitor, reduces senescent cell viability	IL-6, IL-8, TNF-α	[327, 328]
Panobinostat	Multiple Myeloma, Lung Cancer	20–40 mg thrice weekly	Histone deacetylase inhibitor (HDACi), induces G2 block	IL-6, IL-8, CXCL1, MMPs	[329, 330]
BETd (BET Family Protein Degradation)	Hepatocellular Carcinoma (HCC)	10–100 μM	Degrades BET family proteins, inducing cell death by upregulating autophagic gene	IL-6, IL-8, TNF-α	[27, 232, 331]

CD28 co-stimulatory pathway, dexamethasone-mediated T cell suppression reduces the proliferation and differentiation of naïve T cells and thereby causes the immune suppression [351]. Based on the information above, combination therapies or targeting specific SASP components might provide a solution for better anti-cancer outcomes and fewer adverse effects.

Combination therapies

Combining senolytics or senomorphics with traditional cancer treatments (chemotherapy, radiotherapy, or immunotherapy) can improve treatment efficacy by targeting both cancer cells and senescent cells, which contribute to therapeutic resistance. For example, combining PARP inhibitors with senolytic medicines such as navitoclax has been demonstrated to improve treatment results in high-grade serous ovarian cancer models [352]. Furthermore, combining radiation therapy with senomorphic medicines such as metformin can boost anti-tumor activity by regulating SASP profiles [340]. Furthermore, combination medicines have shown substantial promise in preclinical tests, indicating that targeting senescent cells can improve the efficacy of current cancer treatments. For example, in colorectal cancer models, combining PARP inhibitors with CDK4/6 inhibitors and anti-PD-L1 treatment improved anti-tumor immunity and reduced tumor burden [353].

Targeting specific SASP components

Targeting specific SASP components can diminish SASP's pro-inflammatory and pro-tumorigenic effects while preserving the total senescent cell population. Drugs such as tocilizumab, an IL-6 receptor antagonist named tocilizumab, prevent cellular senescence related to other diseases, either by reducing IL-6-dependent STAT3 and γ-H2AX activation or via the inhibition of IL-6/GATA2/SERPINE1 pathway [354, 355]. Although there are reports that tocilizumab can diminish the pro-inflammatory effects in solid cancer [356–358], to date, no evidence on tocilizumab targeting SASP-related pro-inflammatory cytokines in cancer. Furthermore, MMP inhibitors can target the extracellular matrix remodeling caused by SASP [66]. Moreover, targeting certain SASP components can provide a more precise way to influence the tumor microenvironment. For example, specific inhibitors of IL-6 (Siltuximab) inhibited SASP's tumor-promoting actions in ovarian cancer models [356, 359]. Taken together, there is accumulating evidence that drugs targeting proinflammatory cytokines or other SASP components could inhibit the progression of cancer. However, to date, no reports have focused on these drugs targeting senescence-related cancer, although cellular senescence contributes greatly to the progression of cancer. Future study will be focused on tocilizumab/Siltuximab targeting SASP-related pro-inflammatory cytokines-induced senescence of cancer is still in great need (Table 4).

Clinical implications

The clinical implications of targeting the SASP are broad, with substantial potential for improving cancer detection, treatment, and patient outcomes. Here, we present the most important clinical applications, such as the use of SASP factors as predictive biomarkers, therapeutic

Table 3 Senomorphic drugs and molecular mechanisms

Drug Name	Cell/ Animal Model	Target	Mechanism	References
Rapamycin	Various animal models (e.g., Drosophila, mice)	mTORC1	Inhibits mTOR-mediated translation of SASP factors (e.g., IL-1α), reduces SASP, and extends lifespan	[338]
Metformin	Lung epithelial cells, mouse model	AMPK/NF-κB/mTOR	Decreases Ccl2 expression, targets AKT-p53/p21 signaling, reduces ROS accumulation, and protects epithelial cells by increasing autophagy activity	[339–341]
Ruxolitinib	Old mice	JAK1/2	Blocks JAK-STAT signaling, suppressing IL-6/IL-8 mediated SASP amplification	[342]
BET Inhibitors	mouse model	BRD4, chromatin modifiers	Represses transcription of SASP-related genes by reducing enhancer/promoter activity	[331]
Glucocorticoids (e.g., Dexamethasone)	Clinically approved	Glucocorticoid receptor/NF-κB	Represses SASP cytokine expression and suppresses general inflammation	[343]
Resveratrol	Nutraceutical; limited clinical trials	SIRT1/NF-κB	Activates SIRT1, inhibits NF-κB signaling, and oxidative stress	[344]
HDAC Inhibitors	Preclinical/repurposing from oncology	Histone deacetylases	Alters chromatin accessibility of inflammatory gene promoters	[330]

monitoring systems, and the potential for personalized therapy.

Prognostic biomarkers

Senescent cells release SASP factors, including IL-6 and IL-8, which can be detected in the bloodstream or tumor microenvironment. These characteristics can be used as biomarkers for illness progression and therapy response. Elevated serum levels of IL-6 have been linked to a poor prognosis in a variety of malignancies, including acute myeloid leukemia [371]. Higher levels of IL-6 after anti-cancer treatment, for example, were linked to shorter disease-free survival (DFS) in patients with locally advanced rectal cancer (LARC). Similarly, IL-8 levels have been linked to tumor growth and treatment resistance in various cancer types. As a result, monitoring SASP variables can provide early indicators of disease development and aid in patient stratification for more aggressive or alternative therapies [371].

Therapeutic monitoring

Changes in SASP throughout therapy can indicate the efficiency of therapeutic measures and the emergence of resistance mechanisms [37]. For example, a decrease in SASP factors could indicate that senescent cells have been effectively eliminated or that their secretory phenotype has been altered. Monitoring SASP variables in clinical trials with senolytic medications can assist in determining whether the treatment is effectively lowering the senescent cell burden. For example, dasatinib and quercetin lowered SASP factors in colon cancer models, indicating efficient senescent cell clearance [372]. Furthermore, monitoring SASP during combination therapies (e.g., chemotherapy and senolytics) can shed light on synergistic effects and potential resistance mechanisms. As a result, real-time SASP monitoring can assist in guiding treatment modifications and discovering resistance early on, allowing for faster intervention and better patient results [196].

Personalized therapy

Individual tumors' SASP profiles can change greatly, reflecting variations in the types and quantities of SASP components produced. Personalized therapy tailored to a patient's tumor's individual SASP profile can improve therapeutic efficacy while reducing negative effects. For example, if IL-6 is a strong SASP component, combining IL-6 inhibitors with other treatments could be especially successful [356, 359]. Furthermore, using senomorphic medicines that particularly target the SASP profile of a patient's tumor can improve TME modulation. Thus, personalized medicine approaches based on the SASP profile can result in more effective treatment plans and better outcomes.

Conclusion and perspective

The future of SASP research and clinical application is promising, with the potential to alter cancer treatment. In the future, if we could properly modulate the SASP in TME with novel technologies, the outcomes of oncotherapy could be greatly improved. Firstly, there exists some literature about tocilizumab and siltuximab on cancer therapy; however, there need for solid evidence focusing on the treatment for senescence-related cancer, for two reasons. One reason is that tocilizumab antagonizes

Table 4 Non-coding RNA targeting SASP for cancer treatment

RNA Type	Name	Type of Cancer	Targeted Gene	Molecular Mechanisms	SASP Factors Involved	References
miRNA	miR-21	Multiple Cancers (e.g., Lung, Breast, Colorectal)	MyD88, IRAK1	Targets the TLR signaling pathway, reduces replicative lifespan	IL-6, IL-8, TNF-α	[360–362]
miRNA	miR-34a	Osteosarcoma	Sirt1	Enhances the secretion of inflammatory cytokines and chemokines	IL-6, IL-10, IL-12, IL-13, GRO-α, MIG, I-309, PARC, MIP-1δ, IGFBP-3, PIGF, TIMP-2	[363, 364]
miRNA	miR-146a	Liver Cancer, colorectal cancer metastasis	IRF7	Inhibits aerobic glycolysis in liver cancer cells, promotes senescence	N/A	[365, 366]
lncRNA	GUARDIN	Non-small-cell Lung Carcinoma	LRP130/PGC1α-FOXO4 signaling axis	Negatively regulates cellular senescence	N/A	[367]
circRNA	foxo3	Embryonic Fibroblasts	ID-1, E2F1, FAK, HIF1α	Promotes cellular senescence	N/A	[368]
circRNA	PVT1	Fibroblasts	let-7, IGF2BP1, KRAS, HMGA2, miR-24-3p/CDK4/pRb axis	Inhibits cellular senescence	N/A	[369, 370]

the binding of IL-6 with its receptor and thereby reduces the function of IL-6. Because IL-6 is an important SASP component to stimulate cancer senescence, we assume that tocilizumab could alleviate senescent cancer growth by targeting the SASP component, as IL-6. Another one is tocilizumab, has been documented to prevent cellular senescence related to other diseases; it will work on cellular senescence-related cancer as well. Therefore, studies focusing on tocilizumab/siltuximab on senescent cancer should be explored. Secondly, the use of high-throughput sequencing and proteomics to identify major regulators and downstream effectors of SASP, and then screening neutralizing antibodies or compounds to inhibit the SASP and the corresponding downstream signaling proteins will greatly benefit cancer patients. Thirdly, by conduct genome-wide CRISPR/Cas9 screening to discover genes that influence SASP synthesis and its impact on the TME will change the TME in favor of eliminating cancer cells. Fourthly, using multi-omics technologies (genomics, proteomics, and metabolomics) to generate comprehensive biomarker panels to reflect SASP activity might generate a commercialized cancer diagnosis kit. Fifthly, by assessing cancer patients' SASP contents, we could make a personalized therapy plan. This personalized treatment targeting SASP will be in favor of the inhibition of cancer cell growth and metastasis. Lastly, by combining these emerging technologies, we could find novel biomarkers to identify patients who are more likely to benefit from SASP-targeting medicines. Moreover, noncoding RNAs might change the TME by targeting the SASP and thereby lead to cancer resistance or improve the outcome of cancer therapy. However, we still need to conduct long-term follow-up investigations to determine the durability of responses and the emergence of resistance mechanisms correlated with drugs targeting SASP.

Overall, mechanistic investigations will help us better understand SASP regulation, and clinical trials will confirm the efficacy of senolytic and senomorphic medicines. Exploring combination therapies and novel technologies to screen more drugs targeting SASP will improve treatment outcomes, while biomarker development will strengthen customized medicine approaches. By combining these efforts, we can create more effective and tailored medicines, hence improving patient outcomes and survival rates.

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Authors' contributions
L.H., Y.W., and Q.T. contributed to the conception of this review. L.C., Q.L., and K.L. drafted the main manuscript text, prepared the figures, and tables. L.H., Y.W., and Q.T. substantially revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors agree on the publication of this research article.

Competing interests
The authors declare no competing interests.

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