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REVIEW

Immunoregulatory mechanisms in the aging microenvironment: Targeting the senescence-associated secretory phenotype for cancer immunotherapy

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Abstract The aging microenvironment, as a key driver of tumorigenesis and progression, plays a critical role in tumor immune regulation through one of its core features—the senescence-associated secretory phenotype (SASP). SASP consists of a variety of interleukins, chemokines, proteases, and growth factors. It initially induces surrounding cells to enter a state of senescence through paracrine mechanisms, thereby creating a sustained inflammatory stimulus and signal amplification effect within the tissue microenvironment. Furthermore, these secreted factors activate key signaling pathways such as NF-κB, cGAS–STING, and mTOR, which regulate the expression of immune-related molecules (such as PD-L1) and promote the recruitment of immunosuppressive cells, including regulatory T cells and myeloid-derived suppressor cells. This process ultimately contributes to the formation of an immunosuppressive tumor microenvironment. Furthermore, the article explores potential anti-tumor immunotherapy

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Anti-tumor immunotherapy

strategies targeting SASP and its associated molecular mechanisms, including approaches to inhibit SASP secretion or eliminate senescent cells. Although these strategies have shown promise in certain tumor models, the high heterogeneity among tumor types may result in varied responses to SASP-targeted therapies. This highlights the need for further research into adaptive stratification and personalized treatment approaches. Targeting immune regulatory mechanisms in the aging microenvironment—particularly SASP—holds great potential for advancing future anti-tumor therapies.

1. Introduction

The tumor microenvironment (TME) plays a pivotal role in tumorigenesis, progression, and immune evasion, comprising diverse cell types and secretory factors[1]. This complex network not only facilitates tumor cell growth and proliferation but also suppresses anti-tumor immune responses through intricate immunoregulatory mechanisms. With the progressive aging of TME, the aging microenvironment, characterized by the predominance of senescent cells, has emerged as a focal point of research due to its distinctive immunomodulatory functions[2,3]. The senescence-associated secretory phenotype (SASP), serving as a crucial mediator of cellular communication between senescent cells and their surrounding environment, plays an indispensable role in the immunoregulatory processes within the aging microenvironment, thereby contributing significantly to our understanding of TME-related pathological mechanisms. SASP exerts anti-cancer effects in the early stages by inducing cellular senescence, activating the immune system, and promoting tissue repair, serving as an intrinsic defense mechanism to protect cells from malignant transformation[4,5]. However, if senescent cells are not cleared, their continued expression can trigger chronic inflammation, alter cellular communication, and allow tumor cells to gradually adapt to immune pressure, thereby promoting tumor progression. On the other hand, the persistent activation of inflammatory pathways such as NF-κB and cGAS−STING can sustain and enhance SASP expression, shifting the immune response from activation to suppression, and increasing the TME's tolerance to immune attacks. Therefore, the continuation of inflammatory signaling not only maintains SASP but also reshapes its biological characteristics, transforming it from an anti-tumor to a pro-tumor factor. The interplay between time and environmental changes drives the shift of SASP function from "defense" to "attack," and this dynamic regulatory process offers important insights for the design of tumor immunotherapy strategies.

In some cases, SASP can suppress anti-tumor immune responses, promoting cancer progression and recurrence, especially after cancer treatment[6-8]. Moreover, research on SASP provides both macro and micro perspectives for exploring immune regulatory mechanisms in the aging microenvironment. From a macroscopic standpoint, the immune system undergoes functional decline with aging, accompanied by chronic low-grade inflammation, a phenomenon collectively referred to as immunosenescence[9]. At the cellular level, persistent inflammatory responses may directly drive tissue cells into a senescent state by inducing oxidative stress and DNA damage, further exacerbating SASP secretion. Integrating these global and local perspectives not only helps elucidate the complex mechanisms of SASP in the aging microenvironment but also deepens our understanding of its dual regulatory functions in immune modulation[10,11]. Specifically, SASP promotes the infiltration of myeloid-derived suppressor cells (MDSCs) and other myeloid cells that suppress natural killer (NK) and T cell functions, significantly enhancing the immunosuppressive properties of the TME. Consequently, targeting SASP has emerged as a potential strategy to enhance anti-tumor immunity. For instance, in prostate cancer models, inhibitors of CSF-1R, CCR2, and CXCR2 have been employed to block the recruitment and infiltration of senescent-induced suppressive myeloid cell populations[12-14]. Additionally, another approach involves neutralizing immune-related SASP factors (such as IL-6 and CCL2) using antibodies, as these factors have been shown to attract and activate MDSCs, further promoting tumor immune evasion[15]. Notably, certain SASP factors may exhibit dual roles in different TMEs, simultaneously driving tumor growth pathways that are closely linked to immune system mechanisms[6,16]. The direction of these effects depends on the state of tumor cells and the specific characteristics of the microenvironment. In other words, precise regulation of SASP factor release not only holds promise for inhibiting tumor progression but may also rebalance the microenvironment by restoring or enhancing immune surveillance, offering a novel strategy for anti-tumor immunotherapy.

Pharmacological interventions targeting the SASP are gaining increasing attention. These interventions aim to selectively eliminate senescent cells or mitigate the harmful effects of the SASP, thereby optimizing the TME. Although several reviews have reported on the immune regulatory functions of SASP, there is still a lack of comprehensive reviews systematically summarizing potential therapeutic strategies and evaluating their clinical translational value. This review focuses on the multiple mechanisms of SASP in remodeling the TME, with particular emphasis on several widely researched therapeutic approaches, including: precise regulation of SASP expression through gene editing technologies, targeted delivery using nanocarriers, molecular interventions to inhibit SASP secretion pathways, drug strategies for clearing senescent cells, and combination therapies with immune checkpoint inhibitors. We not only summarize the latest research progress of these strategies but also assess the challenges and prospects they face in clinical translation, aiming to provide theoretical support and strategic insights for the development of efficient and feasible SASP-targeted immunotherapy approaches.

2. SASP in tumor progression

The production of SASP is regulated by a complex network of signaling pathways and molecules (as shown in Fig. 1), primarily involving the activation of DNA damage response (DDR)

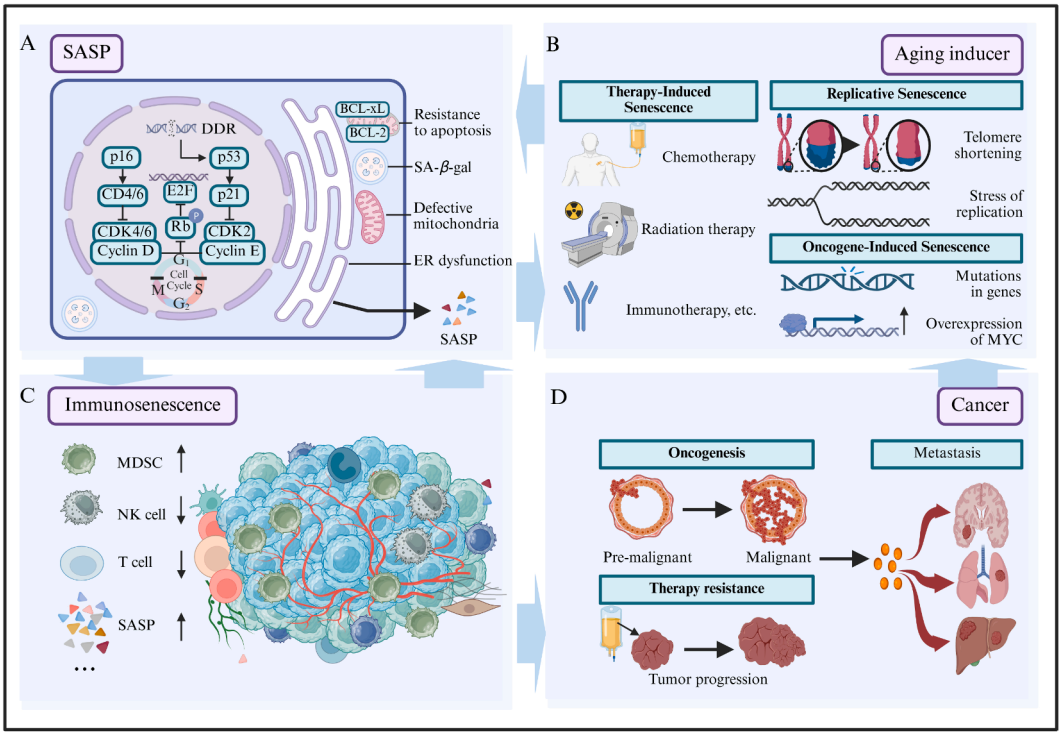

Figure 1 Interaction between the generation of the senescence-associated secretory phenotype (SASP), immunosenescence, and cancer progression. The production of SASP is regulated by various signaling pathways and molecules, including the activation of DNA damage response pathways that trigger the p53 and p16 signaling cascades. Upon DNA damage response activation, p53 upregulates the expression of p21, which inhibits the binding of CDK2 to Cyclin E, blocking the G1/S transition in the cell cycle. Meanwhile, p16 inhibits the activity of CDK4/6 and Cyclin D, preventing the phosphorylation of Rb, maintaining the inactivation of E2F transcription factors, leading to cell cycle arrest and promoting SASP secretion. The generation of SASP is closely linked to various senescence-inducing factors, including replicative senescence (triggered by telomere shortening and replication stress), therapy-induced senescence (such as chemotherapy, radiotherapy, and immunotherapy), and oncogene-induced senescence (such as gene mutations and MYC overexpression). Immunosenescence further exacerbates SASP production, for instance, by recruiting myeloid-derived suppressor cells and suppressing T cell functions, creating a self-reinforcing feedback loop. At the same time, SASP not only amplifies senescence-inducing factors such as RS, TIS, and OIS, but also leads to more severe cellular damage and changes in the microenvironment. In cancer, SASP promotes tumor initiation, treatment resistance, and metastasis formation by remodeling the tumor microenvironment. Moreover, cancer itself further aggravates senescence-inducing factors by worsening the microenvironment and increasing cellular damage, creating a malignant cycle that promotes disease progression and amplifies the association between SASP, senescence, and cancer.

pathways that trigger the p53 and p16 signaling cascades. In this process, the activation of DDR leads to the upregulation of p53 expression, which in turn promotes the production of p21. p21 inhibits the binding of CDK2 to Cyclin E, blocking the transition from the G1 phase to the S phase of the cell cycle. Meanwhile, p16 inhibits the activity of CDK4/6 and Cyclin D, preventing the phosphorylation of Rb and keeping it in an active dephosphorylated state, thereby continuously inactivating the E2F transcription factor, which leads to cell cycle arrest and eventually promotes SASP secretion[17]. Additionally, one of the typical markers of cellular senescence is enhanced senescence-associated β-galactosidase activity, which is used as a key biomarker for detecting senescent cells[18]. At the same time, mitochondrial dysfunction and endoplasmic reticulum stress in senescent cells are also considered important drivers of SASP secretion. These damages play a crucial role in promoting the generation of reactive oxygen species (ROS)[19], activating inflammatory responses, and maintaining SASP secretion. These molecular mechanisms indicate that the formation of SASP is a critical response of cells to damage signals. More importantly, SASP production is closely associated with various senescence-inducing factors. These factors mainly include replicative senescence (RS, triggered by telomere shortening and replication stress)[20], therapy-induced senescence (TIS, *e.g.*, chemotherapy, radiotherapy, and immunotherapy)[21], and oncogene-induced senescence (OIS, such as gene mutations and MYC overexpression)[22]. Moreover, the involvement of immunosenescence further exacerbates SASP secretion[23], such as through the recruitment of MDSCs and the inhibition of T cell functions, creating a self-reinforcing feedback loop. Therefore, through these pathways, SASP not only amplifies senescence-inducing factors such as RS, TIS, and OIS but also leads to more severe cellular damage and significant changes in the TME[24]. In tumorigenesis and progression, SASP plays a key role by remodeling the TME[25], promoting tumor initiation, treatment resistance, and metastasis formation. Conversely, cancer itself further aggravates the effects of senescence-inducing factors, for instance, by worsening the tissue microenvironment and increasing cellular damage, thus creating a malignant cycle that promotes disease progression. This cycle further amplifies the complex interplay and association between SASP, senescence, and cancer, highlighting the central role of SASP in cellular dysfunction and tumor progression.

2.1. *Remodeling of the tumor microenvironment by SASP*

SASP plays a crucial role in the remodeling of the TME, particularly in weakening immune surveillance, driving immune evasion, and matrix remodeling. In terms of matrix remodeling, SASP factors influence tumor blood supply and invasiveness. Vascular remodeling supports tumor cell growth and metastasis while also providing support for immune evasion within the TME. This article focuses on the weakening of immune surveillance and driving immune evasion.

2.1.1. *Weakening immune surveillance*

The aging microenvironment profoundly influences immune system surveillance through SASP, significantly regulating cancer initiation and progression (as shown in Fig. 2)[26,27]. A deep understanding of these mechanisms is critical for developing precise clinical treatment strategies. SASP exacerbates immune senescence, further weakening immune surveillance, and this effect is particularly significant within the TME. Immune senescence leads to decreased function of effector immune cells and increased activity of immune-suppressive cells, thereby promoting tumor immune escape. Tumor-associated macrophages (TAMs) are the core of the immune-suppressive cell and cytokine network[28], and SASP can induce their polarization into either M1-like or M2-like phenotypes[29]. In aging mouse models, dysregulation of the mTOR kinase signaling pathway is closely associated with the secretion of IL-1α, IL-1β, and TNF by microglia, which interfere with normal megakaryocyte function. IL-6 promotes the conversion of macrophages to TAMs and stimulates the release of CCL20 in the TME, which acts chemotactically on CCR6, thereby driving the progression of colorectal cancer[26,30]. Additionally, SASP weakens NK cell cytotoxicity, making tumor cells more likely to evade immune surveillance[31-33]. SASP restricts NK cell activity through chemokines to block the recruitment and maturation of CCR2 myeloid cells, thereby escaping aging surveillance and accelerating the growth of fully developed liver cancer[34]. B cells induce interferon responses *via* the STING/IL-35 axis and secrete SASP factors that inhibit NK cell proliferation and function, significantly weakening anti-tumor effects[35]. Moreover, the presence of C−X−C motif chemokine ligand 13 in the TME increases the levels of $CD45^+/CD19^+/IL\text{-}10^+$ cells and weakens the ability of B cells to initiate anti-tumor immune responses, ultimately promoting melanoma metastasis[36]. However, the precise mechanisms by which SASP affects B cells remain to be elucidated. Meanwhile, SASP not only promotes the recruitment of MDSCs but also accelerates immune escape within the TME by enhancing their immunosuppressive functions[37,38]. MDSCs significantly suppress immune responses by stimulating regulatory T cells (Tregs) activity, upregulating amino acid catabolic enzymes, and secreting SASP factors like IL-10 and TGF-β[39,40]. Elevated levels of IL-22, IL-6, and tumor necrosis factor-α (TNF-α) further enhance the immunosuppressive function of MDSCs and are closely linked to the accelerated progression of gastric cancer, particularly in elderly patients[39,41]. The aging microenvironment promotes the release of CXCR4 and CD62, driving the transformation of neutrophils to TANs, which form a pre-metastatic niche in breast cancer metastasis, ultimately promoting tumor proliferation[42,43]. SASP factors significantly drive tumor immune escape by affecting T cell function and phenotype[44]. IL-6 and TGF-β induce T cell senescence and exhaustion, leading to the

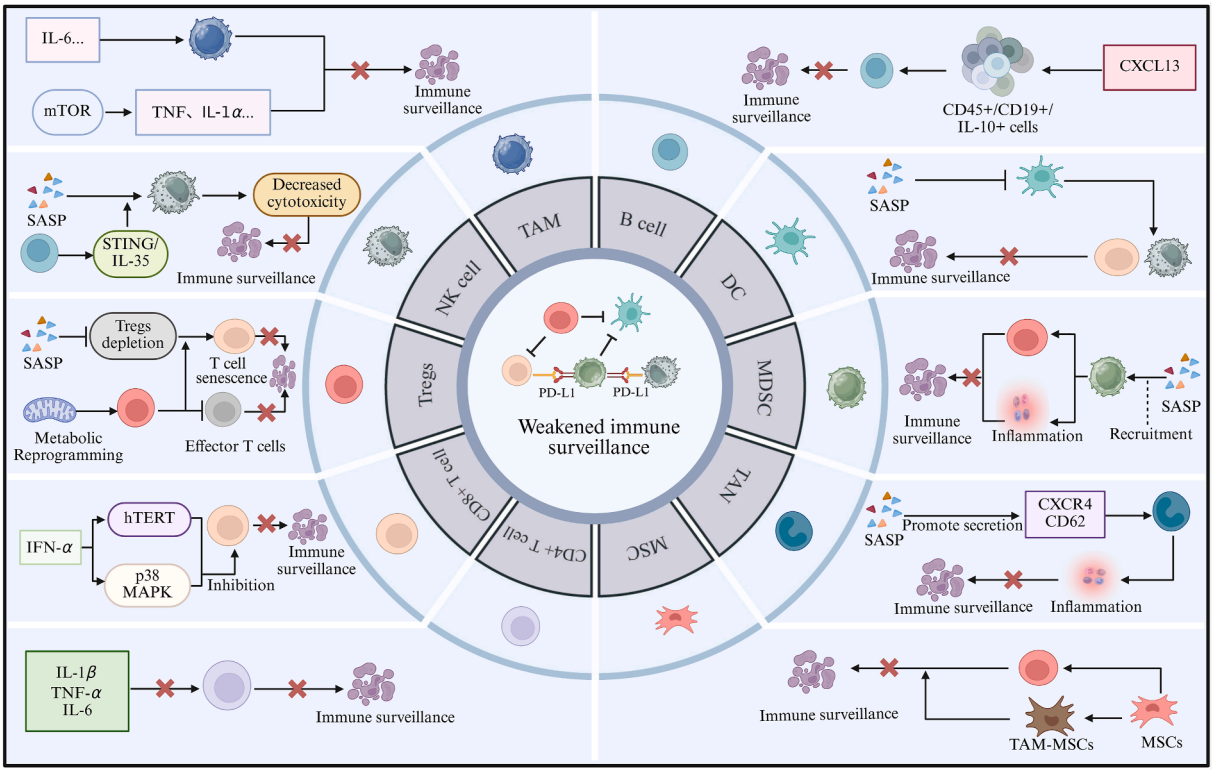

Figure 2 Mechanism diagram of the senescence-associated secretory phenotype (SASP) weakening immune surveillance. The aging microenvironment influences the tumor microenvironment through SASP, exacerbates immune senescence, weakens immune surveillance, and promotes tumor immune evasion.

loss of anti-tumor functions in effector T cells. Cytokines such as IL-1β, TNF-α, and IL-6 induce dysfunction in $CD4^+$ T cells, weakening anti-tumor immunity[45]. IFN-α suppresses $CD8^+$ T cell proliferation by downregulating human telomerase reverse transcriptase and activating the p38 MAPK pathway[46]. Immune senescence also leads to increased exhaustion and apoptosis of effector T cells, further weakening immune surveillance[47,48]. Some chemokines enhance the recruitment of Tregs by activating receptors such as CXCR3 and CXCR4, thereby suppressing anti-tumor immunity[49]. Additionally, IL-33 and IL-1β activate Tregs, promoting obesity-related liver cancer progression *via* immune suppression[50,51]. Tregs also drive T cell senescence by upregulating lipid metabolism enzymes (such as IVA phospholipase A2). Inhibition of this enzyme can reprogram effector T cell metabolism, restore their activity, and enhance the efficacy of immunotherapy in melanoma and breast cancer mouse models[52]. SASP also induces sustained senescence and functional exhaustion of effector T cells through paracrine and autocrine mechanisms, further reducing immune surveillance capacity[53-55]. The interaction between Tregs and effector T cells in the TME highlights the importance of metabolic competition. Senescence-mediated secretion of inflammatory mediators inhibits Tregs exhaustion, while surviving Tregs, in turn, induce effector T cell senescence, thereby enhancing the formation of an immunosuppressive TME through this dual action. In aging mice, Tregs outcompete effector T cells through metabolic competition and induce T cell senescence *via* ERK1/2 and STAT1/3 activation[56,57]. This competition limits anti-tumor responses and reinforces tumor progression. This competition not only promotes Tregs survival but also strengthens the immunosuppressive microenvironment by inducing T cell senescence[58]. SASP factors amplify the scope of immune senescence through pro-inflammatory exosomes, further weakening dendritic cell antigen-presentation ability[45]. Depletion or dysfunction of dendritic cells (DCs) also diminishes the anti-tumor capabilities of T cells and NK cells[59,60]. Moreover, interferon (IFN)-γ and TNF-α released by the aging microenvironment not only activate the immunosuppressive network but also promote tumor proliferation through chronic inflammation[26]. The complexity of the immune network further reveals the core role of mesenchymal stem cells (MSCs) in the immunosuppressive TME. MSC aging significantly induces Tregs activation while inhibiting effector T cell proliferation, weakening overall anti-tumor immune responses[61]. Notably, SASP can transform MSCs into tumor-associated MSCs, which promote tumor cell escape from aging effects and accelerate their invasion and metastasis by remodeling the TME[62].

2.1.2. *Driving immune evasion*

In the aging microenvironment, interleukins (ILs) and TNF-α are considered core stimulatory factors for PD-L1 expression[6]. They regulate the fine-tuned processes of PD-L1 transcription and translation through multiple signaling pathways (as shown in Fig. 3)[63,64]. Specifically, IFN-γ binds to type II interferon receptors and activates the JAK−STAT signaling pathway, with STAT1 serving as its key mediator[65,66]. STAT1 subsequently induces the expression of multiple downstream transcription factors, particularly IRF-1, which directly promotes PD-L1 transcription by binding to the IRE1 and IRE2 elements in the 5′ flanking region of the CD274 promoter[67-69]. Similarly, the ATM−ATR−Chk1−-STAT1/3−IRF1 pathway activated by DNA double-strand breaks also leads to downstream upregulation of PD-L1[70]. On the other hand, IL-6 activates the STAT3/c-MYC/miR-25-3p signaling axis,

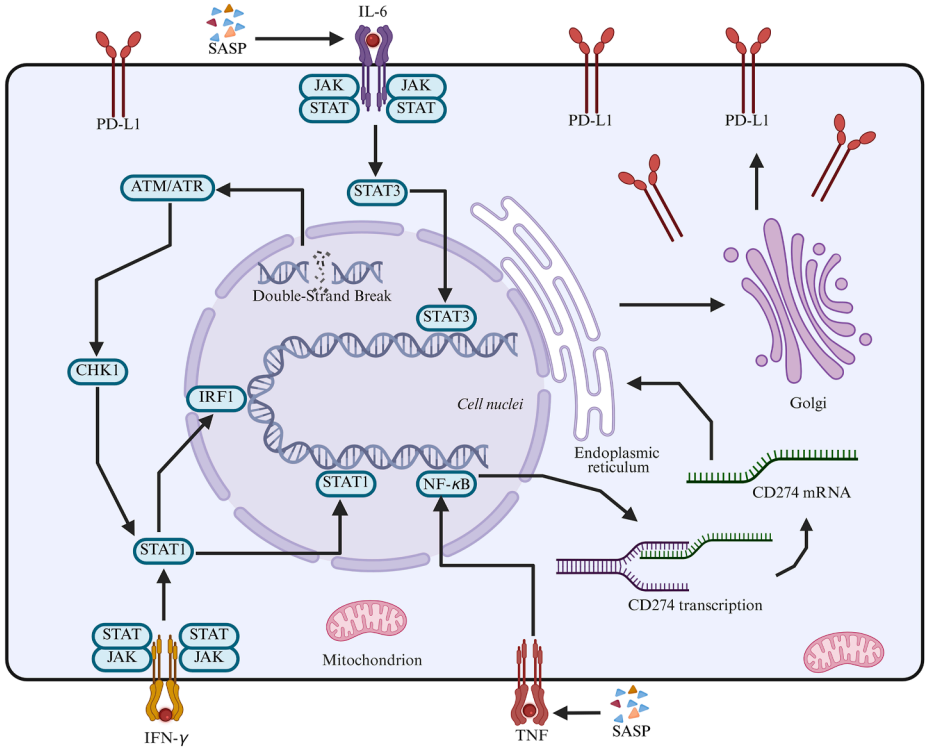

Figure 3 Mechanism underlying PD-L1 upregulation mediated by the senescence-associated secretory phenotype (SASP). In the aging microenvironment, ILs and TNF-α regulate the expression of PD-L1 through multiple signaling pathways. IL-6 enhances the expression and stability of CD274 mRNA through the STAT3/c-MYC/miR-25-3p axis; TNF-α upregulates PD-L1 transcription *via* the NF-κB pathway; IFN-γ activates the JAK−STAT pathway, with STAT1 and IRF-1 promoting PD-L1 transcription, promoting immune evasion in tumor cells.

which not only significantly increases the expression of CD274 mRNA but also enhances its stability[64]. Meanwhile, TNF-α upregulates CD274 transcription *via* the NF-κB signaling pathway[71]. In certain tumor types, such as renal cell carcinoma, TNF-α and IL-4 synergistically activate NF-κB, IκB, and STAT6, further enhancing PD-L1 transcription[72]. In addition to transcriptional regulation, PD-L1 expression is also subject to post-translational modifications modulated by the aging microenvironment. After being translated in the endoplasmic reticulum, CD274 mRNA undergoes glycosylation and other modifications, stabilizing PD-L1 protein expression and facilitating its translocation to the cell membrane, where it serves as an effective immune evasion molecule[73]. Further studies suggest that senescent cancer cells induced by radiotherapy or chemotherapy exhibit high levels of PD-L1 expression to escape T-cell-mediated immune surveillance. This phenomenon is achieved not only by enhancing PD-L1 transcription[74] but also through the induction of RPN1, which promotes the glycosylation of PD-L1, stabilizing the protein and supporting its translocation to the cell membrane[75]. Although it remains unclear whether other mechanisms drive the accumulation of cytoplasmic DNA in senescent cells, the discovery of RPN1 provides new insights into this complex regulatory network and highlights the multi-layered molecular mechanisms of PD-L1 in senescence-associated tumor immune evasion.

2.2. *Heterogeneity of SASP*

To study the heterogeneity of SASP, it is essential to thoroughly examine key variables such as the tissue context in which it arises and the senescence-inducing factors. The impact of SASP on tumorigenesis cannot be simply summarized in a "one-size-fits-all" manner; rather, it is profoundly influenced by factors such as the tissue microenvironment and the mechanisms driving senescence. Notably, TIS, which is closely related to clinical treatments, holds significant research value, as different therapeutic approaches can distinctly influence the heterogeneity of SASP. For example, DNA-damaging agents typically induce a pro-inflammatory senescence state, whereas CDK4 and CDK6 inhibitors do not activate the expression of NF-κB target genes, leading to divergent regulatory effects on SASP composition[76]. Moreover, at the level of tissue context, the heterogeneity of SASP is profoundly shaped by factors such as physiological oxygen levels, metabolic rates, and nutrient availability across different tissues. For instance, during aging in mice, the expression levels of SASP-related genes vary significantly among different tissues, such as the eyes, kidneys, heart, spleen, lungs, liver, and colon[77]. Importantly, scenarios where senescence is driven by a single inducing factor are exceedingly rare in actual biological contexts. Instead, the overlapping and combined effects of multiple inducing factors contribute to the complex heterogeneity of SASP.

2.2.1. *Dependence on temporal dynamics*

Temporal dynamics represent a crucial regulatory mechanism underlying SASP's functional roles in the TME, where its immunosuppressive or pro-inflammatory effects are dynamically modulated by temporal progression and microenvironmental conditions. The induction of diverse SASP components constitutes a temporally regulated and intricately orchestrated process[78]. Currently, LINE1-driven interferon signaling is recognized as a hallmark of deep senescence[79]. Concurrently, SASP factors regulated by distinct signaling pathways exhibit stage-specific characteristics during the senescence process. For instance, Notch signaling plays a pivotal role in mediating the transition from early-phase SASP components (*e.g.*, TGFβ) to late-phase components (*e.g.*, IL-6 and IL-8). Specifically, Notch signaling modulates SASP dynamics by suppressing enhancer-binding protein β (C/EBPβ), thereby interfering with IL-1α and NF-κB activity[80,81]. Given the highly complex nature of SASP's temporal dynamics, traditional experimental approaches alone are insufficient to fully elucidate the patterns of its dynamic changes. Consequently, the integration of mathematical modeling with multi-omics technologies has emerged as a powerful tool for understanding and predicting the temporal evolution of SASP[82].

2.2.2. *Diverse composition*

The composition of SASP exhibits remarkable diversity, encompassing a wide array of factors, including IL family members such as IL-6 and IL-1β, chemokines like CCL2 and CXCL8, matrix metalloproteinases (MMPs), and growth factors such as vascular endothelial growth factor (VEGF). This article focuses on those factors that are more closely associated with immune regulation, notably the IL family and chemokines[4].

ILs are crucial central regulators in both inflammation and immunity. IL-6 and IL-8, as key members of the IL family[83,84], play distinct yet highly complementary roles in immune regulation through complex molecular signaling pathways. IL-6 regulates the expression of acute-phase proteins *via* the JAK/STAT3 pathway and further activates PI3K/Akt and MAPK signaling to promote immune cell recruitment and activation. However, under chronic inflammatory conditions, its sustained high-level secretion may lead to immune tolerance and immunosuppression in the TME[85]. In contrast, IL-8 primarily drives neutrophil chemotaxis and activation by binding to CXCR1 and CXCR2 receptors, playing a prominent role in inflammatory diseases. While IL-8 aids pathogen clearance in acute inflammation, its overexpression often supports tumor progression by enhancing angiogenesis and promoting immune escape. Moreover, the functions of IL-6 and IL-8 are not entirely independent; they interact through shared downstream pathways (*e.g.*, NF-κB), forming a complex regulatory network that determines the balance between pro-inflammatory and anti-inflammatory responses. Thus, despite their distinct roles, IL-6 and IL-8 collectively establish a multi-layered, dynamically regulated network, underscoring the central role of ILs in inflammation and immune homeostasis[86].

Chemokines are precise regulators of immune cell migration and inflammation. CCL5, CXCL1, and CXCL2, as key chemokines, precisely guide the spatial and temporal distribution of immune responses by regulating immune cell migration, exhibiting high specificity and complexity in both innate and adaptive immunity[87,88]. CCL5 primarily drives the chemotaxis of T cells, monocytes, and NK cells by binding to CCR1, CCR3, and CCR5 receptors, while promoting the directional migration of effector immune cells through enhanced intracellular Ca^{2+} signaling and activation of the PI3K/Akt pathway. However, the role of CCL5 is not always immune-promoting, as its overexpression may contribute to chronic inflammation or immunosuppression within the TME. In contrast, CXCL1 and CXCL2, by binding to the CXCR2 receptor, primarily mediate the migration and aggregation of neutrophils, playing a critical role in acute inflammatory responses[89,90]. Unlike CCL5, CXCL1 and CXCL2 also exert pro-tumorigenic effects by regulating TAMs and stimulating angiogenesis. Furthermore, these chemokines form a dynamic interactive network under the upstream regulation of NF-κB and MAPK signaling, thereby finely balancing pro-inflammatory and

immunosuppressive functions. Thus, CCL5, CXCL1, and CXCL2 not only achieve spatial precision in immune cell migration through specific receptor-ligand interactions but also regulate the immune microenvironment *via* shared or unique signaling pathways, providing critical insights into the dynamic regulation of the immune system and its role in disease mechanisms.

In addition to ILs and chemokines, MMPs are closely associated with immune regulation in the aging microenvironment[91]. Through their unique proteolytic activity, MMPs modulate multiple layers of immune responses, demonstrating a complex and dynamic mechanism of action[92-94]. MMPs not only remodel the tissue microenvironment by degrading extracellular matrix (ECM) components[95,96], such as collagen and elastin, but also release matrix-bound bioactive factors (*e.g.*, TGF-β, VEGF), thereby significantly influencing the migration, activation, and functional states of immune cells. Notably, MMP-2 and MMP-9 promote the recruitment of immune cells (*e.g.*, neutrophils and monocytes) to senescent tissues by degrading basement membrane components, triggering early immune responses. However, under prolonged inflammatory conditions, this pro-inflammatory role may sustain chronic inflammation by enhancing the release of inflammatory factors (*e.g.*, IL-6, IL-8), further disrupting immune homeostasis. Moreover, MMPs finely regulate the distribution of immune cells within the aging microenvironment by modulating the axis of chemokines (*e.g.*, CXCL12) and their receptors (*e.g.*, CXCR4). Importantly, MMPs not only play a critical role in immune activation but also contribute to the immunosuppressive mechanisms of the aging microenvironment by cleaving immune inhibitory molecules (*e.g.*, PD-L1) or remodeling immunosuppressive matrix components. Thus, the role of MMPs in the aging microenvironment extends beyond mere matrix degradation; they profoundly influence immune cell behavior and function through intricate signaling networks, providing critical insights into their mechanisms in aging-related diseases and potential intervention strategies.

3. Dual effects of SASP-mediated tumor immune regulation

3.1. *Mechanisms of immune suppression*

Under conditions of prolonged chronic inflammation, the negative effects of SASP factors may become dominant, manifesting as immune evasion and the maintenance of chronic inflammation. These detrimental effects primarily occur through two mechanisms: the chronic activation of related immune pathways and the paracrine propagation of senescence. These processes not only make it difficult to eliminate senescent cells but also contribute to the formation of a tumor-promoting microenvironment, supporting the survival and progression of cancer cells[97].

3.1.1. *Chronic activation of signaling pathways*

Exploring immune regulatory pathways within the aging microenvironment-particularly those involving NF-κB, cGAS−STING, and PPARγ (peroxisome proliferator-activated receptor γ)-represents a crucial direction for understanding the tumor immune microenvironment specific to senescence (as shown in Fig. 4). SASP, as a key mediator, plays a central role in these signaling pathways. A deeper understanding of the molecular interactions of SASP within these pathways not only

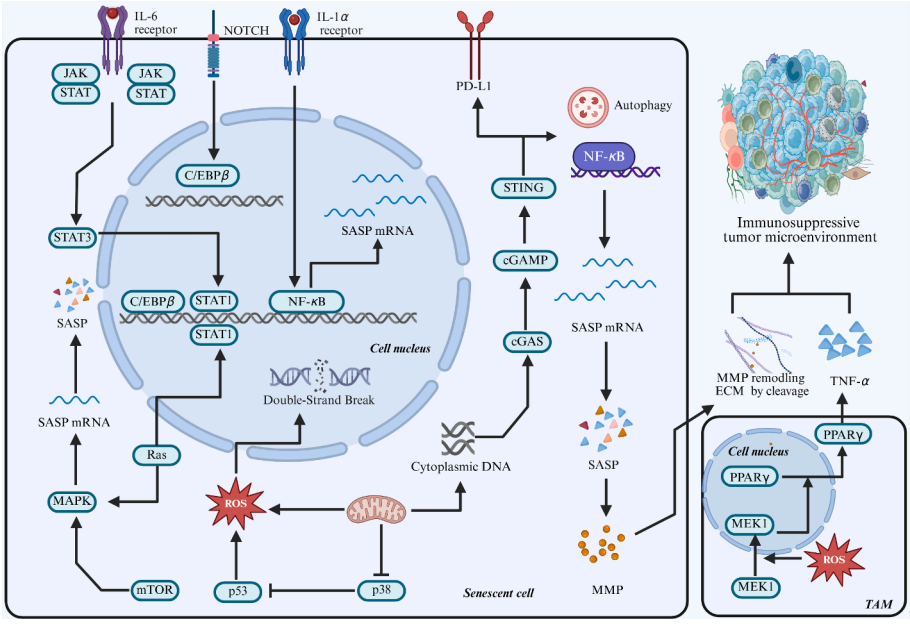

Figure 4 Chronic activation of immune-related signaling pathways in the aging microenvironment. In the aging microenvironment, dysfunctional mitochondria accumulate over time, leading to elevated levels of ROS. This oxidative stress triggers cell cycle arrest, NF-κB activation, and other changes closely associated with tumor progression. Transcription mediated by NF-κB, combined with mTOR-dependent translation, drives the robust secretion of SASP-associated inflammatory cytokines, chemokines, angiogenic growth factors, and ECM degradation signals. Oxidative stress also promotes the cytoplasmic translocation of PPARγ *via* the MEK-1 signaling pathway, resulting in increased secretion of TNF-α. TNF-α enhances the invasiveness and metastatic potential of tumor cells. Chronic activation of the STING signaling pathway creates an immunosuppressive microenvironment by upregulating the non-canonical NF-κB pathway, thereby promoting metastasis. Furthermore, STING contributes to immune evasion by regulating PD-L1 expression on tumor cells and inducing autophagy in immune cells. These interconnected signaling pathways highlight how mitochondrial dysfunction, ROS accumulation, and chronic inflammatory signaling sustain tumor progression and suppress anti-tumor immunity within the senescent tumor microenvironment.

enhances our knowledge of senescence-associated tumorigenesis and therapy resistance but also provides a solid theoretical foundation for developing precise immunotherapeutic strategies tailored to elderly patients.

Senescent cells, including senescent cancer cells, produce a variety of cytokines through the activation of the NF-κB signaling pathway[98,99]. As the master regulator of SASP, NF-κB plays a pivotal role in shaping the TME by driving the transcription of these cytokines. In this process, the loss of p53 combined with increased oncogenic RAS activity significantly upregulates MAPK protein translation *via* activation of the mTOR signaling pathway, thereby enhancing NF-κB activity[100-102]. This heightened NF-κB activity not only exacerbates the malignant paracrine effects of SASP but also amplifies its transcriptional activity by promoting the translation of membrane-bound IL-1α, resulting in the production of a complex SASP mixture. This mTOR−NF-κB axis effectively links oncogenic signaling to SASP production, creating a tumor-promoting microenvironment through chronic inflammation and dynamic remodeling of the ECM. By fostering conditions that support tumor progression and metastasis, this pathway plays a crucial role in advancing cancer development.

In the aging microenvironment, the cGAS−STING pathway exhibits a dual role. Short-term activation of cGAS−STING promotes anti-tumor immunity by driving the production of IFN-I, which stimulate the recruitment and activation of DCs and $CD8^+$ T cells. DCs, in turn, capture tumor antigens, forming a positive feedback loop that enhances immune responses[103]. However, chronic activation of cGAS−STING often leads to immunosenescence[104,105]. Persistent signaling induces the secretion of SASP factors, including inflammatory cytokines, chemokines, and growth factors, while also upregulating PD-L1 expression *via* IFN-I signaling[106-108]. PD-L1 suppresses local T-cell activity and recruits MDSCs and Tregs, further reinforcing the immunosuppressive microenvironment. Notably, SASP phenotypes mediated by host STING may also drive tumorigenesis in a non-cell-autonomous manner[109]. In the early stages of tumorigenesis, acute activation of STING promotes anti-tumor effects by enhancing cell cycle arrest through SASP. However, if tumor cells co-opt the STING pathway to suppress anti-tumor immune functions, excessive STING activation can paradoxically facilitate malignant progression, leading to worse clinical outcomes[110,111]. Senescent cells with nuclear envelope defects, such as the loss of Lamin B1, release cytoplasmic chromatin fragments that activate cGAS−STING. This signaling is further amplified by cDNA generated from LINE-1 retrotransposons *via* reverse transcription[79]. Additionally, genotoxic stressors, such as radiation or oncogene activation, cause nuclear envelope rupture or genomic instability, releasing cytoplasmic DNA that activates cGAS and perpetuates chronic inflammation[111,112]. Thus, the cGAS−STING pathway plays a context-dependent role in cancer progression and immune regulation. While acute activation can suppress tumors, chronic activation may exacerbate inflammation and promote immunosuppression, ultimately accelerating cancer progression and worsening outcomes. Understanding the balance between these opposing effects is critical for developing therapeutic strategies targeting cGAS−STING signaling.

PPARγ plays a central role in driving the polarization of macrophages toward the M2 phenotype, which is closely associated with tumor progression[113,114]. During aging, dysfunctional mitochondria accumulate, leading to decreased membrane potential, proton leakage, and elevated levels of ROS[115]. Persistent ROS not only enhance the survival, proliferation, and metastatic potential of tumor cells, such as melanoma, by activating signaling pathways including PPARγ, but also regulate inflammatory responses by influencing stromal cells, such as TAMs, and promoting the expression of inflammatory mediators (*e.g.*, IL-1, IL-6, TNF-α, IL-12, and inducible nitric oxide synthase)[116-118]. PPARγ activity and expression are regulated by multiple factors, including oxidative stress, ligand-induced activation, proteasomal degradation, phosphorylation by MAPKs, and subcellular localization changes triggered by MEK-1 binding[119,120]. Notably, phosphorylation of MEK-1 directly induces the translocation of PPARγ from the nucleus to the cytoplasm. This translocation downregulates its anti-inflammatory functions and enhances TNF-α secretion by TAMs[121]. Immunofluorescence studies have shown that, compared to peritoneal macrophages, TAMs exhibit significantly reduced nuclear PPARγ levels and elevated cytoplasmic PPARγ levels. This indicates that oxidative stress impairs the anti-inflammatory functions of PPARγ by altering its subcellular localization. Dysfunctional PPARγ directly enhances the ability of TAMs to secrete TNF-α, a key mediator of tumor progression. TNF-α significantly promotes tumor invasion and metastasis in various cancers, including gastric, colon, breast cancers, and melanoma[122-124]. For instance, in melanoma models, TNF-α secreted by TAMs has been identified as a critical driver of metastasis. Studies on TNF-α knockout mice further support this, showing that while some metastases persist in the lungs and lymph nodes, metastases in other sites are significantly reduced, underscoring the pivotal role of TNF-α in tumor metastasis[121]. Furthermore, research indicates that nuclear localization of PPARγ is essential for suppressing TNF-α production in TAMs. Oxidative stress exacerbates TNF-α secretion by reducing nuclear PPARγ levels, thereby weakening the immune system's ability to control tumor growth. These findings demonstrate that PPARγ and oxidative stress collaboratively regulate functional changes in TAMs, playing a key role in enhancing immune suppression and tumor invasiveness within the TME. Targeting PPARγ localization and TNF-α expression offers a promising therapeutic approach for improving cancer treatment outcomes and delaying metastasis.

Growing evidence suggests that centrosome dysfunction is closely linked to cellular senescence and immune regulation. In early-passage mouse embryonic fibroblasts, the loss of core pericentriolar material (PCM) components can lead to centrosome fragmentation, triggering premature senescence. This phenomenon indicates that CD directly accelerates the process of cellular senescence. Similarly, the inhibition of key PCM components, such as pericentrin and PCM-1, induces permanent cell cycle arrest and increased β-galactosidase activity, both hallmark features of senescence. Furthermore, the depletion of other PCM components, such as Cep192 and NEDD1, results in centrosome fragmentation, further driving cellular senescence[125]. In addition to inducing cellular senescence, centrosome dysfunction profoundly impacts the TME by remodeling immune signaling pathways. Centrosome instability causes chromosomal missegregation and replication stress, leading to the accumulation of double-stranded DNA in the cytoplasm. This abnormal cytoplasmic double-stranded DNA activates the cGAS−STING signaling pathway, a critical mechanism for sensing cytoplasmic DNA. Activation of cGAS−STING drives a robust immune response by stimulating the production of IFN-I and inflammatory signaling cascades[126,127]. Moreover, in cancer cells with centrosome dysfunction, another inflammation-related signaling pathway, the NF-κB pathway, can also be activated through a STING-dependent mechanism[128]. Persistent activation of NF-κB due to centrosome

dysfunction generates a distinct cytokine signature known as the centrosome-associated secretory phenotype. Centrosome-associated secretory phenotype includes factors such as IL-8, GDF-15, and ANGPTL4, which play critical regulatory roles in the TME. For instance, IL-8, which is also a part of the SASP, contributes to creating an immunosuppressive microenvironment by attracting Th2-type cells and M2 macrophages. Additionally, centrosome dysfunction downregulates the expression of MHC-I, reducing the presentation of tumor neoantigens. This leads to decreased $CD8^+$ T-cell infiltration and significantly enhances immune evasion[129]. Through the activation of the cGAS−STING and NF-κB pathways, centrosome dysfunction establishes an immunosuppressive microenvironment that allows tumor cells to evade immune surveillance. These changes not only enhance the invasiveness and metastatic potential of tumors but also significantly increase resistance to cancer therapies. These findings highlight that targeting centrosome dysfunction and its associated signaling pathways, such as STING and NF-κB, could provide a novel therapeutic strategy to improve outcomes in cancers associated with centrosome dysfunction.

SASP is regulated by various transcription factors, with NF-κB playing a central role in this process. Different SASP inducers, such as IL-1α, cytoplasmic DNA, or DDR, ultimately converge to activate NF-κB. However, the precise mechanisms underlying the initiation of SASP remain incompletely understood. Several studies have suggested that DDR pathways, including ATM-ATR, p38 MAPK/MAPK-activated protein kinase 2, and GATA-binding protein 4, are involved in SASP initiation. It is also known that mTOR regulates the translation of IL-1α mRNA, a critical SASP initiator that functions in an autocrine manner. Additionally, C/EBPβ is considered a major regulatory factor of SASP. Interestingly, in senescent cells induced by NOTCH signaling, C/EBPβ expression is suppressed by NOTCH, resulting in significant variation in SASP factor expression across different microenvironments. IL-1α, in particular, binds to IL-1 receptor 1 and facilitates the recruitment of IL-1 receptor-associated kinase 1, which subsequently activates downstream factors, ultimately leading to the reactivation of NF-κB. Recent studies have also revealed that cGAS plays a role in SASP by detecting cytoplasmic DNA. However, how DNA accumulates in the cytoplasm of senescent cells remains unclear. Understanding these pathways and their interactions is crucial for comprehending the regulation of SASP and its diverse roles in different cellular and microenvironmental contexts.

3.1.2. *Paracrine propagation of senescence*

The aging microenvironment effectively transmits aging signals through the paracrine mechanisms mediated by the SASP, profoundly affecting the function and activity of tumor-associated immune cells and related structures (as shown in Fig. 5)[130].

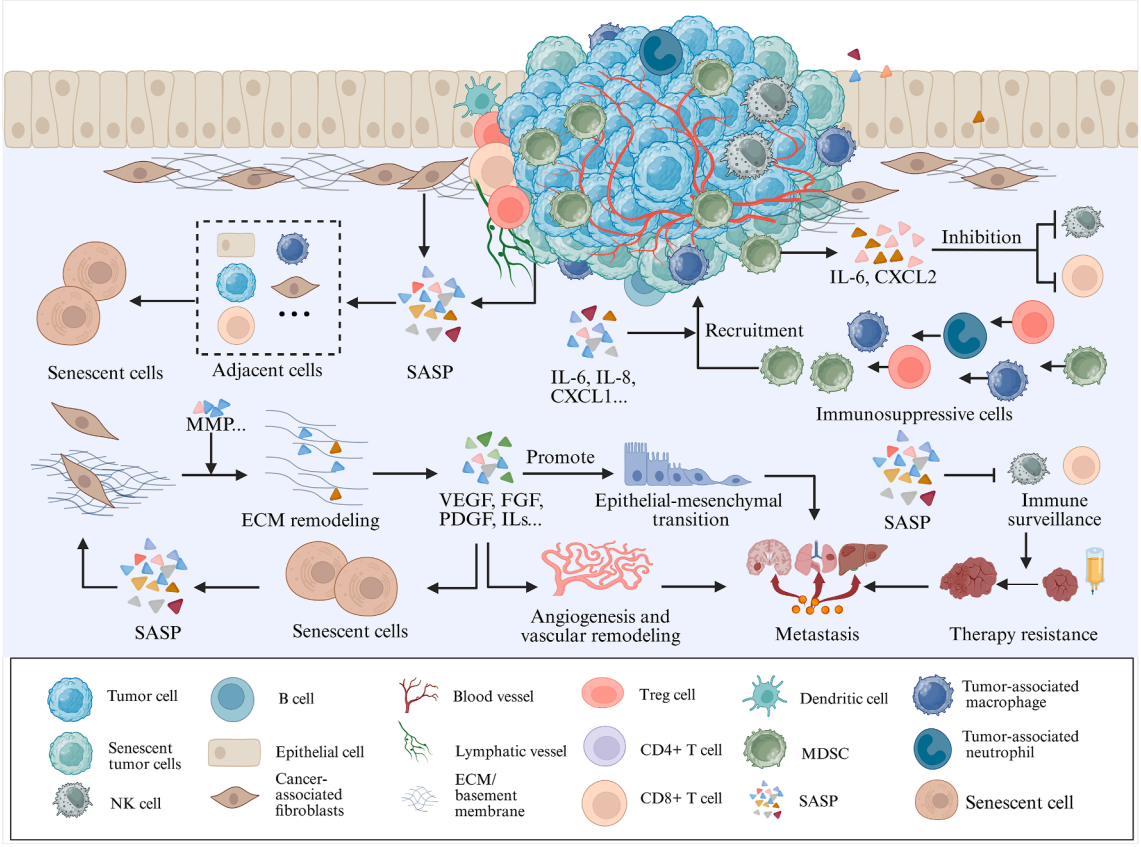

Figure 5 The aging microenvironment promotes the paracrine spread of senescence. In the aging microenvironment, the senescence-associated secretory phenotype (SASP) facilitates the senescence of neighboring cells and promotes the infiltration of immunosuppressive cells, such as Tregs and MDSCs, thereby weakening anti-tumor immune responses. Additionally, MMPs remodel the ECM and release growth factors, accelerating epithelial-mesenchymal transition. Moreover, MMPs enhance the release of other pro-tumor factors and growth factors, such as VEGF, FGF, and PDGF. These factors collectively promote angiogenesis and tumor proliferation.

Specifically, SASP factors such as IL-6, IL-8, and CCL2 play crucial roles in this process. IL-6 and IL-8 not only promote tumor angiogenesis but also enhance the survival and metastatic ability of tumor cells by activating pro-growth pathways[131-133]. Additionally, the expression of IL-6 and IL-8 upregulates the surface levels of the inhibitory receptor NKG2A ligand HLA-E, thereby impairing the anti-tumor activity of NK cells and mature $CD8^+$ T cells[134]. The secretion of CCL2 inhibits the immune response of Th1 cells and cytotoxic T cells, while recruiting MDSCs and Tregs, ultimately weakening anti-tumor immune surveillance[9,14,34,38,135]. In this context, hepatocytes with NrasG12V-induced senescence secrete CCL2 to recruit $CCR2^+$ myeloid cells, which interact with NK cells and ultimately block tumor immune surveillance[34]. More importantly, CXCL1, as a key paracrine signal, can induce neighboring cells into a senescent state, thereby exacerbating immune escape and promoting tumor progression. Moreover, IL-6 and CCL2, among other factors, suppress the effector functions of $CD8^+$ T cells and NK cells, further reducing the immune system's ability to monitor tumor cells[14,34]. Meanwhile, the polarization of macrophages leads to the secretion of inflammatory factors such as IL-6, IL-24, and GM-CSF. These factors not only maintain the homeostasis of the senescent environment but also further activate the pro-tumor phenotype of cancer-associated fibroblasts (CAFs), thereby creating a TME that continuously suppresses immune function[136]. Further research indicates that senescent fibroblasts release a large number of pro-inflammatory cytokines (such as ILs), which promote epithelial cell proliferation while weakening immune cell functions[137]. More importantly, senescent fibroblasts express atypical MHC molecules (such as HLA-E), which, by binding with the NKG2A receptor on NK cells and $CD8^+$ T cells, further suppress their immune activity[134]. This immune suppression state forms a positive feedback loop among senescent TAMs, CAFs, and other stromal cells, significantly accelerating tumor initiation and progression. Therefore, the coordinated interaction between these molecules and cells collectively creates an immune-escape and pro-tumor environment, making stromal cells a critical regulatory factor in the TME[138].

In addition, the remodeling of the ECM is closely related to the activity of SASP factors. SASP factors not only regulate ECM degradation but also play immune-modulatory roles within the TME. Specifically, SASP factors significantly accelerate ECM degradation and remodeling, thereby promoting the proliferation and invasion of tumor cells. For instance, MMPs degrade ECM components and release growth factors (such as VEGF, which promotes angiogenesis) and chemokines like CXCL1 (which enhances tumor growth). Meanwhile, the degradation of collagen is accompanied by fibrosis, elastin breakdown, changes in laminin composition, and reduced hydration of hyaluronic acid, leading to fibrosis, ECM loss, and tissue dysfunction. Clearly, ECM remodeling is closely linked to the activity of SASP factors. SASP factors not only regulate ECM degradation but also play immune-modulatory roles in the TME. Specifically, SASP factors significantly accelerate ECM degradation and remodeling, thus promoting tumor cell proliferation and invasion. For example, MMPs degrade ECM components, releasing growth factors such as VEGF (which promotes angiogenesis) and chemokines like CXCL1 (which enhances tumor growth). Meanwhile, the degradation of collagen leads to fibrosis, elastin destruction, changes in laminin composition, and reduced hydration of hyaluronic acid, resulting in fibrosis, ECM loss, and tissue dysfunction[135,139]. Additionally, collagen and fibronectin can activate the PI3K/AKT signaling pathway, significantly promoting cancer stem cell immune escape. Specifically, collagen type I monomers attract immune-suppressive cells (such as Tregs and TAMs), not only inhibiting the recruitment of effector immune cells but also supporting the survival and maintenance of cancer stem cells by enhancing immune suppression[140,141]. The excessive accumulation of senescence-associated ECM significantly promotes the release of soluble factors, which drive further ECM remodeling and result in local matrix sclerosis[142]. Physical changes in ECM structure (such as stiffness and mechanical stress) significantly affect cancer cell infiltration, migration, and angiogenesis. Cells can perceive changes in ECM composition and physical characteristics through multiple signaling pathways (such as FAK/Src, ILK-PINCH-parvin-kindlin, and α-actinin-zyxin-VASP) and respond accordingly[143,144]. This process further promotes tumor progression and metastasis by enhancing ECM crosslinking and stiffness. The high-mobility group protein HMGB1, as an important component of SASP, amplifies necrosis-related signaling in CAFs through interaction with Toll-like receptor 4, thereby further enhancing the invasiveness of tumor cells[145]. Through multi-layered signal interactions and intercellular interactions, SASP creates a complex and dynamic microenvironment, wherein senescent cells are not only affected themselves but also regulate the physiological state and function of surrounding immune cells *via* paracrine pathways, thereby promoting tumor development and progression.

3.2. *Mechanisms of immune activation*

3.2.1. *SASP-mediated enhancement of immune surveillance*

In the early stages of the senescent TME, SASP (such as IL-1α, IL-6, and IL-8), driven by the NF-κB pathway, plays a positive role by recruiting immune cells like M1 macrophages, Th1 cells, and NK cells. These immune cells enhance immune surveillance, effectively suppressing cancer progression[83,146,147]. SASP factors release pro-inflammatory cytokines that attract and activate effector cells within the immune system, forming an anti-tumor immune microenvironment[148,149]. Specifically, M1 macrophages produce a large number of pro-inflammatory mediators, which not only directly kill tumor cells but also clear senescent cells. Th1 cells contribute to this process by secreting IFN-γ, further amplifying the immune response. NK cells, on the other hand, exert rapid cytotoxic effects, efficiently recognizing and eliminating infected or transformed cells. At this stage, the primary function of SASP is to mobilize the body's immune defense system, facilitating the clearance of senescent cells and potential tumor cells, thereby strengthening immune surveillance[135,150].

Senescent cancer cells, due to their enhanced antigenicity and adjuvanticity, can trigger effective anti-tumor immune responses[151,152]. Research has shown that senescent B16F10 melanoma cells, by secreting SASP, exhibit significant anti-tumor protective effects in immunization[151]. These cells promote the infiltration of $CD8^+$ T cells and myeloid cells, enhancing the activity of immune cells within the tumor and thereby improving the effectiveness of anti-tumor immunity. Immunization with senescent cancer cells significantly slows tumor growth and increases tumor infiltration and activation of $CD8^+$ T cells, further proving the important role of SASP in immune surveillance. It is possible that cancer vaccine strategies could be improved based on senescent cancer cells. Since senescent cells can present antigens and activate dendritic cells, senescent cancer cells could be used to generate improved dendritic cell-based vaccines. Beyond cancer,

many human diseases and age-related frailty are driven, to some extent, by the presence of senescent cells. Therefore, it can be speculated that triggering adaptive immune responses against senescent cells or using engineered T cells might bring therapeutic and health benefits.

3.2.2. *Context-dependent immune activation*

Studies have shown that the impact of senescent cells on tissue biology depends on how they receive and transmit environmental signals[153]. For example, the disruption of interferon-γ does not directly affect SASP generation but impairs subsequent tumor regression, indicating that the perception of environmental signals, in conjunction with SASP, determines the final outcome of the senescence program, such as immune surveillance. Furthermore, immune surveillance mechanisms rely on the cooperation of cells such as $CD8^+$ T cells and macrophages. However, under different conditions, the mode and extent of immune responses may vary, reflecting the context-dependent nature of immune activation driven by changes in environmental perception.

Studies have shown that the impact of senescent cells on tissue biology depends on how they receive and transmit environmental signals[153]. For example, the disruption of interferon-γ does not directly affect SASP generation but impairs subsequent tumor regression, indicating that the perception of environmental signals, in conjunction with SASP, determines the final outcome of the senescence program, such as immune surveillance. Furthermore, immune surveillance mechanisms rely on the cooperation of cells such as $CD8^+$ T cells and macrophages. However, under different conditions, the mode and extent of immune responses may vary, reflecting the context-dependent nature of immune activation driven by changes in environmental perception. As SASP factors accumulate over time, their biological functions gradually shift. Under continuous stimulation, the TME transitions into a tumor-promoting state. This transition is likely due to the excessive expression of SASP factors, which triggers chronic inflammation and suppresses the function of immune cells. For instance, factors such as IL-6 and IL-8 in later stages can recruit MDSCs and Tregs, which inhibit the activity of effector T cells and NK cells, allowing tumor cells to evade immune surveillance. At this stage, the role of SASP factors shifts from promoting immune activation to becoming key contributors to tumor progression. Thus, while SASP initially activates and enhances immune responses to suppress tumor initiation and progression, its long-term effects may create favorable conditions for tumor development. Understanding this dynamic process is critical for developing new immunotherapeutic strategies that can reverse this adverse microenvironment and achieve more effective anti-tumor outcomes.

4. Anti-tumor immunotherapy targeting SASP

In cancer immunotherapy, the selective clearance of senescent cells or the reduction of SASP accumulation may offer a novel therapeutic approach to combat tumors. This strategy not only complements traditional treatments such as immunotherapy, radiotherapy, and chemotherapy but also effectively limits cancer incidence and tumor progression. Notably, in the current research landscape, pharmacological interventions targeting SASP (as shown in Fig. 6), such as senolytics and senomorphics[97,154,155], have garnered increasing attention. These interventions aim to either promote the

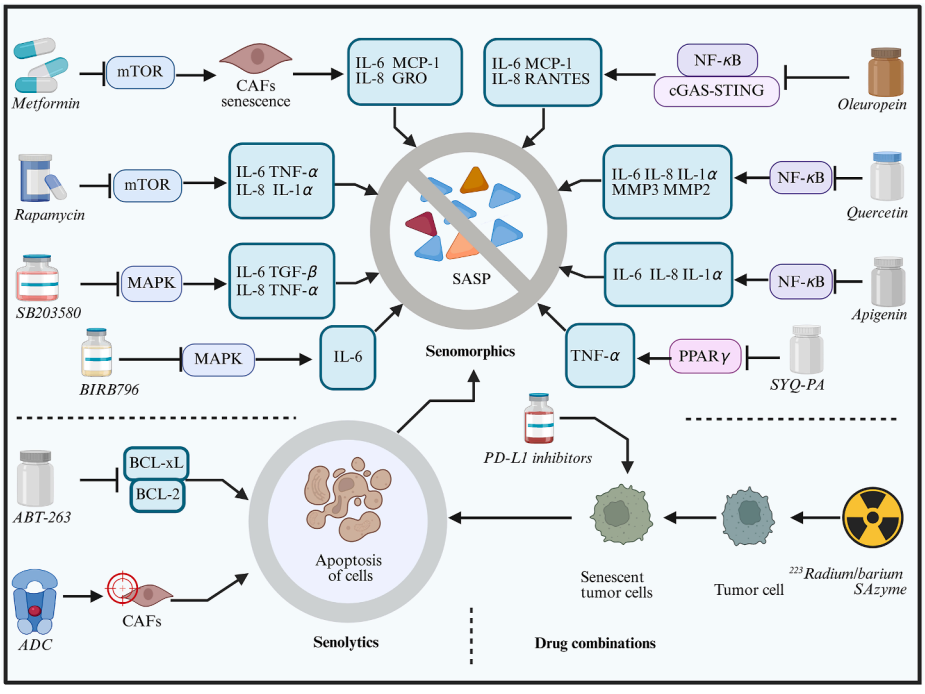

Figure 6 Antitumor immunotherapy drugs against the senescence-associated secretory phenotype (SASP). Mechanisms of action of senescence inhibitors and senescence modulators. Senomorphics prevent senescent cells from releasing SASP factors such as IL-6, IL-8, and MMP by inhibiting signaling pathways like NF-κB, MAPK, and mTOR. On the other hand, Senolytics induce apoptosis by targeting various senescence cell-associated pathways including Bcl-2 family members and ADCs. Combination immunotherapy can achieve a "one-two punch" therapeutic effect, such as the combination of Ra/Ba SAzyme with anti-PD-L1 checkpoint blockade therapy, where Ra/Ba SAzyme first induces senescence, followed by anti-PD-L1 therapy to clear senescent cells.

clearance of senescent cells or mitigate the harmful effects of their secreted factors through different mechanisms.

4.1. Inhibiting SASP secretion

Since the SASP is considered a major mediator of the non-cell-autonomous deleterious effects of senescence, the pharmacological suppression of SASP represents an innovative therapeutic strategy known as senomorphism[156]. This approach may have profound implications for various pathological conditions, particularly in alleviating inflammation and inhibiting tumor progression. Notably, blocking pro-inflammatory and pro-tumorigenic SASP factors downstream of pathways such as NF-κB, MAPK, and mTOR has become a key focus of research[157-159]. For instance, NF-κB inhibitors like apigenin and kaempferol, as well as mTOR inhibitors such as rapamycin, have shown promising potential (as shown in Table 1[160-169]).

In the field of aging research, mTORC1 has been identified as a highly promising anti-aging target. As a central regulator of multiple metabolic pathways, mTORC1 is closely linked to both aging and the modulation of immune function. Rapamycin, a specific mTORC1 inhibitor with caloric restriction mimetic properties, has been proven to effectively extend lifespan in various model organisms[170-172]. Its mechanisms include restoring the regenerative capacity of hematopoietic stem cells in aged mice, enhancing the effectiveness of influenza vaccines, and reversing immune system decline associated with aging. Beyond these benefits, rapamycin regulates a multifunctional protein complex that integrates nutrient, energy, and stress signals, thereby influencing critical processes such as autophagy, gene expression, mRNA translation, and mitochondrial function, all of which are strongly associated with lifespan extension. In terms of tumor immunity, research has shown that rapamycin reduces the expression of exhaustion-associated genes in PD-1$^+$ T cells, improving T cell function and enhancing the anti-tumor immune response in aging tissues[173]. Even more importantly, rapamycin suppresses mTOR signaling to reduce the secretion of SASP factors, offering dual benefits of lifespan extension and tumor suppression[174]. Therefore, mTORC1 not only represents a critical target for delaying aging but also holds tremendous potential for enhancing immune function, particularly in the TME. This dual functionality makes it an attractive therapeutic option in the fight against aging and age-related diseases. However, the inhibition of mTORC1 may affect cell growth and metabolism, especially in more sensitive organ systems, potentially triggering adverse reactions in the liver and kidneys, which requires further clinical data for verification.

The NF-κB pathway represents another critical target for addressing chronic inflammation and SASP secretion in the aging microenvironment. As the master regulator of inflammation and SASP secretion in the senescent TME, the NF-κB pathway plays a pivotal role in these processes. Specifically, aspirin and other non-steroidal anti-inflammatory drugs reduce SASP secretion by inhibiting IKKβ, thereby blocking NF-κB-dependent transcriptional activity. These drugs have demonstrated significant anti-tumor potential, such as inducing apoptosis in colorectal cancer cells and reducing the migration and metastasis of osteosarcoma cells[175-177]. In addition, the anti-diabetic drug metformin has been reported to suppress NF-κB activation in senescent fibroblasts, thereby reducing SASP factor secretion and improving immune system function. The availability of IKKβ inhibitors, such as BAY 11−7821, further underscores the therapeutic potential of targeting NF-κB in cancer treatment[178]. However, excessive inhibition of NF-κB may lead to suppression of immune system function, increasing the risk of infections and immune evasion by tumor cells. Notably, the combined use of mTOR inhibitors (*e.g.*, rapamycin) and NF-κB inhibitors holds promise for effectively blocking chronic inflammation and SASP factor release. This dual-targeting strategy may attenuate the pro-tumorigenic characteristics of the TME, offering a novel and effective therapeutic approach. Conversely, how to balance the efficacy and side effects of this therapeutic strategy remains an important direction for future research.

A study[169] found that SYQ-PA (a polysaccharide derived from a genus of the Araliaceae family) can inhibit breast cancer by reprogramming M2 macrophages into the M1 phenotype. Mechanistically, SYQ-PA regulates the NF-κB signaling pathway downstream of macrophages by inhibiting the expression of PPARγ, which induces the release of pro-inflammatory factors and ultimately inhibits the proliferation of breast cancer cells. However, despite this finding demonstrating the potential anti-cancer effects of SYQ-PA, several issues remain to be addressed. While some studies have revealed a link between the MEK/ERK signaling pathway and PPARγ (*e.g.*, through oxidative stress regulation of PPARγ function)[121,179], research in this area is still insufficient, and the relevant mechanisms have not been fully explored. Additionally, although SYQ-PA has shown strong anti-

Table 1 Drugs targeting SASP inhibition.

Type of pathway	Name of drug	An inducer of aging	Type of tumor	Species of repressed SASP	Ref.
mTOR	Metformin	Therapy-induced senescence (TIS), CDK4/6 inhibitors	Head and neck squamous cell carcinoma	IL-6, IL-8, MCP-1, GRO	160
	Rapamycin	Replicative senescence (RS)	Nephroblastoma	IL-6, IL-8, TNF-α, IL-1α	161
	Artesunate	TIS, irinotecan	Breast cancer	IL-1, IL-6, TNF-α	162
NF-κB, cGAS−STING	Oleuropein	TIS, radiation	Breast cancer	IL-6, IL-8, MCP-1, RANTES	163
NF-κB	Quercetin	TIS, Adriamycin	Osteosarcoma	IL-6, IL-8, MMP3, MMP2, IL-1α, CXCL12, VEGF	164
	Silybum marianum flower extract	RS	Breast cancer	IL-6, MMP-1	165
	Apigenin	TIS, bleomycin	NSCLC	IL-6, IL-8, IL-1α	166
	Resveratrol	RS; TIS, Adriamycin	Colorectal lung cancer	IL-6, IL-1β, TNF-α	167
MAPK	SB203580	RS	NSCLC	IL-6, IL-8, IL-10, TGF-β, TNF-α	168
	BIRB796	RS	Glioblastoma	IL-6	168
PPARγ	SYQ-PA	Induction of IL4/13	Breast cancer	TNF-α	169

tumor activity in specific experimental settings, its efficacy in clinical applications remains unclear, with potential differences in response between individuals, suggesting that its universality and therapeutic effectiveness need further validation.

In addition to inflammation regulation, structural abnormalities in the TME, such as centrosome dysfunction, have emerged as novel targets for immune modulation and cancer therapy. Centrosome dysfunction, a hallmark of cellular senescence, disrupts chromosomal stability and significantly impacts immune regulation and tumor progression. For instance, PARP inhibitors selectively target cancer cells with centrosome abnormalities, inducing multipolar division and further destabilizing chromosomes. This mechanism highlights centrosomal abnormalities as effective indicators for drug targeting. Moreover, PARP inhibitors can enhance antitumor immune responses by modulating the cGAS−STING pathway and activating downstream immune signaling, opening new prospects for their application in cancer immunotherapy[180,181]. In parallel, other centrosome-targeting compounds, such as GF-15 and PLK1/PLK4 inhibitors, have demonstrated tumor growth suppression by disrupting centrosome clustering. Several of these compounds are currently in clinical development, underscoring their potential as promising therapeutic strategies.

In addition, another viable strategy is to use specific antibodies to target key molecular components of SASP, such as antibodies that block IL-6 and IL-8, to enhance immune surveillance and anti-tumor responses following treatment-induced senescence. Although targeting IL-6/IL-6R alone or in combination with chemotherapy has not significantly improved the treatment outcomes of solid tumors in clinical trials[182-184], the combination of tocilizumab (an IL-6R monoclonal antibody) with chemotherapy drugs like carboplatin and doxorubicin has been shown to promote M1 macrophage polarization and activation of T cell effector functions in the treatment of recurrent epithelial ovarian cancer[185]. Therefore, this direction may become a key focus of cancer immunotherapy research in the future.

Compared to senolytics, senomorphics exert their effects by regulating the characteristics of senescent cells, rather than simply eliminating them, which may result in fewer side effects. Thus, senomorphics do not directly kill senescent cells, but instead, they achieve therapeutic effects by inhibiting the progression of the senescence process. Although senomorphics show certain therapeutic potential, they mainly target the inhibition of individual molecules such as IL-6 and IL-8, without fully considering the complex changes within the SASP profile. Therefore, while these strategies can regulate senescent cells, they may not completely eliminate the suppressive effects of senescent cells on the immune system. In other words, even though senescent cells are regulated, they may still persist in the immune microenvironment, leading to tumor immune evasion. Importantly, SASP inhibition's impact on immune responses, tumor promotion, and anti-tumor outcomes is highly context-dependent and significantly influenced by specific circumstances. For example, studies have shown that JAK2/STAT3 inhibition effectively blocks immune-suppressive SASP programs, thereby enhancing anti-tumor immune responses in Pten-deficient prostate cancer[186]. However, on the other hand, inhibition of pathways like cGAS−STING has been shown to suppress anti-tumor immune surveillance and could even promote tumor immune evasion[110,187]. Therefore, how to precisely regulate SASP inhibition strategies becomes crucial. Furthermore, long-term use of senomorphics or improper dosing could lead to unforeseen side effects, due to the significant dose-dependence of these treatments. For example, while SASP inhibitors effectively suppress SASP at low doses, high doses could lead to the dissolution of senescent cells, resulting in negative consequences[188,189]. Although senomorphics hold great potential as a cancer treatment, they may not be a one-size-fits-all solution but offer valuable insights for understanding the complex dual nature of SASP. Therefore, future research should focus on optimizing the application of senomorphics through precise molecular marker identification, which will not only help reduce side effects but also provide new perspectives and strategies for personalized immunotherapy.

4.2. *Eliminating senescent cells*

Eliminating senescent cells has been shown to fundamentally eliminate the production of SASP and can transform the immunosuppressive TME into an immune-stimulatory TME, characterized by reduced expression of regulatory T cells and increased expression of $CD4^+$ and $CD8^+$ T cells[190]. The removal of senescent cells has been shown to fundamentally eliminate SASP production, thereby slowing the progression of age-related diseases[77,191]. For example, treating senescent lung and breast cancer cells with ABT-263, which inhibits anti-apoptotic proteins Bcl-2, Bcl-xL, and Bcl-w, not only effectively clears these senescent cells but also suppresses tumor progression[192]. In addition, Takaya et al.[193] developed an antibody−drug conjugate that uses apolipoprotein D as a carrier to specifically target senescent fibroblasts in aged skin. When combined with pyrrolobenzodiazepine, this drug selectively kills senescent human dermal fibroblasts without causing significant side effects. This approach not only demonstrates the potential of targeting senescent cells but also underscores the importance of clearing these cells for therapeutic purposes[192]. Furthermore, researchers have explored the use of galacto-oligosaccharide nanoparticle delivery systems to target senescent cells[194]. This method represents a significant advancement in precisely identifying and capturing senescent cells. However, the application of senolytic therapies in elderly individuals requires careful consideration. Given the higher proportion of senescent cells in aged tissues, their removal may disrupt tissue structural integrity, impair vascular endothelial function, and lead to blood-tissue barrier dysfunction, potentially resulting in pathological changes such as fibrosis in the liver and perivascular tissues. It is worth noting that the state of different tissues and the types of cellular senescence vary significantly, and no single marker has been identified as absolutely specific for senescent cells. The current best approach to identifying senescent cells involves a comprehensive assessment of SASP, cytoplasmic, nuclear, and other specific markers to evaluate the occurrence of cellular senescence holistically[195]. More importantly, senescent cells possess unique defense mechanisms to resist apoptotic stimuli, collectively referred to as the senescence-associated cell anti-apoptotic pathways. These pathways involve multiple signaling mechanisms, such as BCL-2/BCL-xL, PI3K/AKT, p53/p21, PAI-1/2, HIF-1α, and tyrosine kinase pathways[196]. Although developing drugs targeting senescence-associated cell anti-apoptotic pathways can effectively and selectively eliminate senescent cells, ensuring the safety of these drugs for normal cells remains a significant challenge.

4.3. *Combination therapy with immune checkpoint inhibitors*

Immune drug combination therapy, such as PD-L1/PD-1 inhibitors, is of significant importance in the treatment of senescent cells and immune evasion (as shown in Table 2[197-202]). PD-L1/PD-

Table 2 Combination therapy with immune checkpoint inhibitors.

Immune checkpoint inhibitor class	Combined therapeutic measure	Type of tumor	Mechanism	Ref.
CTLA-4 inhibitors	Berberine derivative B68	Colorectal cancer	Promote PD-L1 degradation, enhance T cell infiltration, and inhibit MC38 tumor growth; when combined with anti-CTLA-4 treatment, it can further enhance anti-tumor immunity	198
PD-1 inhibitors	TM4SF1 inhibitor	Liver cancer	Enhance the efficacy of anti-PD-1 immunotherapy by increasing the total infiltration of $CD8^+$ T cells and maintaining their cytotoxic function	199
PD-1 inhibitors	Lipoic acid	–	Inhibit tumorigenesis and enhance anti-tumor immunity by inducing PD-L1 nuclear translocation	200
PD-1 inhibitors	OSU13	Colon cancer	Significantly inhibit STING and $CD8^+$ T cell-dependent tumors	201
PD-L1 inhibitors	TH1902	Melanoma	Increased CD45 leukocyte infiltration in tumors, especially lymphocytes and macrophages. Increased staining of perforin, granzyme B, and caspase-3, suggesting enhanced activity of cytotoxic T cells and natural killer cells	202
PD-L1 inhibitors	^{223}Ra/Ba SAzyme	Lung cancer	^{223}Ra/Ba SAzyme first induces senescence, followed by the clearance of senescent cells through anti-PD-L1 therapy	197

1 inhibitors promote immune system recognition and clearance of tumor cells by releasing immune suppression, while also indirectly clearing senescent cells, as these cells often evade immune attack through PD-L1. However, clearing senescent cells to eliminate SASP production is a more direct and effective approach targeting SASP. Combination therapy not only further reduces the pro-inflammatory factors secreted by senescent cells, alleviating immune suppression in the TME, but also significantly enhances immune responses, thereby improving the efficacy of PD-L1/PD-1 inhibitors and overcoming treatment resistance. Research demonstrates[197] that a dual approach treatment strategy, in which LLC cells are implanted in the left inguinal region of mice as primary tumors and secondary tumors are established in the right inguinal region, showed significant results. By treating the primary tumor with ^{223}Ra/Ba SAE, followed by anti-PD-L1 injection, the combination therapy significantly extended mouse survival and effectively suppressed the development of distant tumors. This combination therapy showed the powerful effects of integrated immunotherapy. Immunohistochemical analysis revealed that after anti-PD-L1 treatment, senescence markers (such as p53, p21, and IL-6) were significantly reduced in the primary tumor, confirming that anti-PD-L1 effectively cleared senescent cells. ^{223}Ra/Ba SAzyme induces senescence and enhances anti-tumor immune function by generating ROS. After combining with anti-PD-L1 therapy, this strategy effectively eliminates senescent cells and reduces the risk of tumor recurrence. This study pioneered the concept of "combination therapy" using single-atom nanomaterials and provides new insights for future cancer treatments.

4.4. Emerging strategies: targeting SASP with next-gen therapies

Gene editing and nanotechnology are widely regarded as frontier approaches for the synergistic intervention of SASP. Gene editing technologies, such as CRISPR/Cas9, demonstrate immense potential in the precise regulation of SASP core factors[203], but their application is often limited by issues related to delivery efficiency and targeting accuracy. Therefore, relying solely on gene editing to effectively mitigate the pro-inflammatory effects of senescent cells still faces significant challenges. Meanwhile, the introduction of nanotechnology offers new possibilities for gene editing[204,205]. By designing multifunctional nanocarriers, drugs or gene editing tools can be precisely delivered to senescent cells in the TME, significantly improving delivery selectivity and efficacy. Compared to traditional systemic administration methods, this nanocarrier approach minimizes damage to normal tissues and reduces side effects. More importantly, recent research has developed a novel nano-anti-aging drug system with a mesoporous framework featuring adjustable channels. This system employs a "dual-lock" mechanism, combining a galactose layer with TMPDA, to achieve smart surface modifications. It not only efficiently delivers anti-aging drugs but also specifically promotes the clearance of senescent cells, thereby improving age-related pathological conditions without causing significant adverse reactions[206,207]. This discovery opens a new platform for developing therapeutic drugs targeting senescence-associated cells, which can both delay aging and alleviate age-related diseases. The combined application of gene editing and nanotechnology not only compensates for the limitations of each but also provides a practical solution for precisely targeting SASP in the senescent microenvironment. This "gene editing + nanodelivery" strategy represents an important step toward precision and personalized treatment in the regulation of the senescent microenvironment for anti-tumor therapies.

5. Challenges and prospects

Currently, there is a lack of in-depth research and sufficient knowledge regarding how the aging cancer microenvironment affects the interaction between senescent cancer cells and immune system cells: (1) SASP components (including proteins commonly found in various cell types) are considered valuable phenotypic biomarkers. However, relying solely on SASP is not sufficient to definitively identify senescent cells. The immune

microenvironment varies across different tissues, which can significantly influence the interaction between SASP and immune surveillance. For example, the lungs are rich in NK cells, whereas the pancreas has fewer NK cells. Additionally, the SASP factors secreted by different tumor types also differ, which may further lead to tissue-specific differences in immune surveillance, reflecting the uniqueness of each tissue in immune response and TME[97]. If a specific biomarker could be identified, it would greatly enhance our understanding of the potential mechanisms of cell senescence and their unique pathology. (2) Studying how SASP influences the interaction between senescent tumor cells and the immune system is a critical direction. It is particularly important to clarify under what conditions SASP can trigger an immune response, whether this immune response can be further enhanced through immune checkpoint therapy, and under what circumstances SASP fails to effectively induce an immune response. Unfortunately, current research in this area is still insufficient, which has led to our understanding of tumor immune evasion mechanisms remaining at a preliminary stage. The lack of knowledge in this field severely limits our comprehensive understanding of tumor immune evasion mechanisms. (3) Although "dual-pronged" treatment strategies have shown potential in enhancing cancer treatment, there are still some key issues that need to be addressed. For example, determining the optimal timing for applying senescence inhibitors in anti-cancer regimens, optimizing their sequence of use, and assessing whether sequential treatments (inducing senescence followed by the use of senescence inhibitors) can achieve maximum efficacy are core issues that require further study. Moreover, clinical trials combining SASP inhibitors with anti-tumor immunity therapies have not been adequately conducted. (4) Clinically, the relationship between SASP factor expression and progression-free survival, overall survival, and peripheral blood immune responses has not been sufficiently studied[208-210]. Therefore, it is essential to intensify research in this area to fully realize the potential of SASP-related therapeutic strategies in clinical applications.

Future research should focus on how the aging microenvironment, based on the SASP, influences the interaction between tumor cells and the immune system. First, although single-cell RNA sequencing and immunological techniques have made significant progress, identifying tissue-specific SASP biomarkers using these technologies could more precisely identify senescent cells, thus advancing targeted therapies. However, exploring the potential of combining senomorphics with immune checkpoint inhibitors is equally crucial. To this end, precise selection of tumor types and patient populations suitable for senomorphics treatment is necessary to reduce adverse reactions and maximize therapeutic efficacy. Therefore, innovative genetic and pharmacological screening platforms should identify targets and drugs that can induce various senescence and SASP biomarkers, thereby enhancing treatment targeting and effectiveness. Although studies have explored the relationship between SASP factor expression and progression-free survival, overall survival, and immune responses, further research in this area is needed. Strengthening this research will contribute to a more comprehensive understanding of the potential of SASP in therapy. Additionally, the synergistic effect of immune checkpoint therapy and SASP inhibitors may offer new breakthroughs in cancer immunotherapy, but the optimal timing and treatment sequence for senescence inhibitors still require further optimization. Therefore, integrating precision medicine with clinical trial design is crucial for optimizing treatment strategies in different TMEs. Equally important is systematically identifying the SASP factors and regulatory molecules necessary for immune-mediated tumor control. Preliminary studies have been conducted in this area, such as the analysis of SASP output and immune response after TIS, but further regulation of specific SASP components remains to be explored. The optimal timing, sequence, and potential benefits of continuous treatment with senescence inhibitors are still key issues that need to be addressed. While current exploration of the dual effects of SASP has provided some clues for new anti-tumor therapies, more specific drugs targeting SASP are required to ensure clinical efficacy. It is worth noting that future research should not only focus on technological advancements but also promote deep interdisciplinary collaboration among fields such as senescence biology, immunology, and oncology. Such collaboration can facilitate the integration of diverse disciplines, especially in clinical research and technology development, thereby accelerating the translation of SASP-related therapeutic strategies. By combining cutting-edge approaches such as multi-omics technologies, gene editing, and nanotechnology, researchers can further elucidate the molecular mechanisms of SASP in tumor immune evasion, providing a theoretical foundation for the design and optimization of novel immunotherapeutic strategies. These interdisciplinary efforts are not only expected to open new avenues in cancer treatment but also to drive the development and clinical application of precise, personalized, and efficient immunotherapy regimens.

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Conflicts of interest

The authors declare no conflict of interest.

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