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REVIEW

Senescent macrophages in cancer: roles in tumor progression and treatment opportunities

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ABSTRACT Senescent macrophages have emerged as dynamic cells within the tumor microenvironment that significantly promote tumor progression through complex cellular and molecular functional alterations. This review explores the multifaceted roles of macrophage senescence in cancer, and establishes links between senescent macrophages and tumor progression from multiple perspectives, on the basis of the first comprehensive analysis of the molecular mechanisms and pathways involved. By systematically examining the diverse changes in senescent macrophages, this review integrates and analyzes their effects on tumors, thus offering a comprehensive and novel theoretical foundation, and practical insights for cancer treatment. Notably, by integrating current molecular research and therapeutic advancements, we summarize novel therapeutic strategies targeting senescent macrophages, including senolytics, senescence modulators, and cutting-edge immunotherapies, thereby highlighting the potential of senescent macrophages as a therapeutic target and introducing new opportunities for cancer treatment.

KEYWORDS Macrophages; senescence; cancer; immunology; senotherapeutics

Introduction

Macrophages play critical roles in the tumor microenvironment (TME), where they influence tumor progression through their remarkable plasticity and environmental adaptability[1]. Typically, pro-inflammatory M1 macrophages (classically activated macrophages) are found in healthy tissues; in contrast, the macrophages in the TME predominantly adopt a pro-tumorigenic M2 (alternatively activated macrophages) phenotype, which facilitates tumor progression *via* extracellular matrix remodeling, angiogenesis, and immune suppression[2]. Consequently, tumor-associated macrophages (TAMs) are central to promoting tumor growth, invasion, and metastasis through paracrine signaling and other mechanisms[3].

The role of cellular senescence in tumor development, particularly the effects of senescent macrophages in the TME, has garnered increasing attention. Cellular senescence was initially considered a tumor-suppressive mechanism. However, senescence paradoxically promotes tumor progression, particularly *via* senescent macrophages. Senescent macrophages, after exposure to specific intrinsic and extrinsic stimuli, undergo cellular aging. These cells are typically characterized by upregulation of p16 Inhibitor of Cyclin-Dependent Kinase 4a ($p16^{INK4a}$) and distinct features associated with the senescence-associated secretory phenotype (SASP)[4]. Through intrinsic senescence, therapeutic interventions, or external stimuli, senescent macrophages exhibit functional impairments including chronic inflammation, decreased antigen presentation, and impaired phagocytosis[5-7]. These changes foster an immunosuppressive environment conducive to tumor growth.

Key in this process is the SASP, comprising cytokines, chemokines, proteases, and growth factors that disrupt the immune environment and enhance tumorigenesis[8,9]. Notably, IL-6 is a prominent SASP factor contributing to a pro-inflammatory, tumor-promoting milieu[10]. Markers such

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as p16 Inhibitor of Cyclin-Dependent Kinase 4 ($p16^{INK4}$), p21 Cyclin-Dependent Kinase Inhibitor 1 ($p21^{cip1}$), and β-galactosidase are frequently used to identify senescent cells.

Emerging evidence highlighting that senescent macrophages exacerbate tumor progression through SASP secretion and immune dysregulation has underscored the importance of understanding their mechanisms. Therapeutic strategies targeting senescent macrophages, including senolytics, senomorphics, and senoreverters, as well as immunotherapies such as Chimeric Antigen Receptor T-cell (CAR-T) cells, offer promising avenues for halting tumor growth and reversing the harmful effects of the aging TME[11-14]. Future research is expected to focus on optimizing these treatments and elucidating the interactions between senescent macrophages and tumor cells to improve clinical outcomes.

Cellular senescence: definition and mechanisms

Cellular senescence is characterized by an irreversible proliferation arrest accompanied by a progressive functional decline, as initially identified in Hayflick's 1961 observation that cultured human fibroblasts cease to divide after ~50 passages (the "Hayflick limit")[15]. Although historically associated with aging, senescence has been revealed by contemporary research to be a dynamic biological process actively participating in tissue remodeling, embryonic development, and injury repair[16].

The multifactorial mechanisms driving cellular senescence encompass both age-dependent and developmentally programmed pathways. Telomere attrition during repeated cell divisions—culminating in replicative senescence after critical shortening is reached—is a classic age-associated mechanism[17]. Senescence can also arise independently of chronological aging. Cells experience cumulative genomic instability from intrinsic oxidative stress and extrinsic insults, including radiation and chemical exposure; consequently, irreparable DNA damage triggering cell cycle arrest is a conserved senescence response[18]. Notably, programmed senescence occurs during embryonic development through p21-mediated cell cycle inhibition, and therefore has an essential role in morphogenesis[19]. These parallel mechanisms underscore that senescence operates as a context-dependent biological process that extends beyond chronological aging and performs physiological functions across the lifespan.

Gene expression changes and the emergence of senescent macrophage biomarkers

Aging cells undergo progressive loss of adaptive capacity and homeostatic control, thereby driving transcriptional reprogramming manifesting as molecular alterations and functional decline. This senescence-associated transformation is characterized by dynamic biomarker expression across cellular compartments including the cell surface, nucleus, and cytoplasm. Senescent macrophages display unique biomarker profiles that serve dual purposes by facilitating cellular identification and also reflecting functional specialization potentially critical for tumor diagnostics and prognostic evaluations. Whereas universal markers, such as $p16^{INK4a}$ and SASP, remain diagnostic cornerstones, macrophage-specific gene signatures have emerged as distinctive indicators. Notably, these cell-type-specific patterns not only underscore functional heterogeneity among senescent populations but also highlight context-dependent biological roles, particularly in oncological contexts, although their causal relationships with aging processes require further elucidation.

Universality of gene expression changes and biomarkers in senescent cells

GLB1 gene and senescence-associated β-galactosidase (SA-β-gal)

SA-β-gal, encoded by the lysosomal *GLB1* gene, exhibits hydrolytic hyperactivity in senescent cells—a hallmark that is mechanistically associated with aging processes but does not directly drive senescence[20]. In senescent macrophages, SA-β-gal expression is markedly elevated, and this biomarker has been widely used in numerous studies on senescent macrophages. However, despite being among the most well-established markers of senescence, SA-β-gal expression is not specific to macrophages. Elevated levels are observed across diverse senescent cell types, including T cells[21], dendritic cells[22], and B cells[23], as well as stromal cells, such as fibroblasts[24] and adipocytes[25]. Crucially, the finding that *GLB1* knockdown does not rescue senescence phenotypes indicates that SA-β-gal accumulation arises secondarily to lysosomal stress responses rather than initiating senescence[20]. This epiphenomenal nature compromises the diagnostic reliability in discriminating senescence from transient stress states.

Consequently, multimodal biomarker integration—combining SA-β-gal with cell-type-specific markers—is imperative for precise senescence assessment.

CDKN1A, CDKN2A, p21, p16^{INK4a}, and ARF

The *CDKN1A*-encoded protein p21 orchestrates cell cycle arrest by inhibiting cyclin-dependent kinases, thus exhibiting context-dependent regulatory mechanisms. During replicative senescence, p53/Sp1-mediated transcriptional activation upregulates p21, whereas DNA damage-induced senescence requires sustained p21 expression to enforce irreversible proliferation arrest. Prolonged p21 activation exacerbates mitochondrial dysfunction *via* GADD45-p38-transforming TGF-β signaling, thereby establishing a self-reinforcing senescence loop[26].

At the 9p21.3 tumor suppressor locus[27], *CDKN2A* generates 2 transcripts: p16^{INK4a} (a direct Cdk4/6 inhibitor) and ARF (an MDM2 antagonist that stabilizes p21)[28]. Beyond cell cycle control, p16^{INK4a} modulates macrophage inflammatory responses, and its deficiency impairs cytokine production[29], whereas ARF regulates pro-inflammatory activation and may potentiate tumor-associated chronic inflammation[30]. Interspecies divergence exists in regulatory pathways: murine p19^{ARF} and p21 expression rely on STAT6/IL-4 signaling, whereas humans have p53-dependent p21 regulation. The finding that STAT6 deficiency in mice upregulates p16^{INK4a} highlights its dual role in cell cycle regulation and immune homeostasis[31].

Elevated p16^{INK4a}/p21 levels have been observed in senescent macrophages in various models, such as deoxynivalenol-exposed RAW264.7 cells[32], lipopolysaccharide (LPS)-treated periodontal macrophages[33], and alveolar macrophages in Kras-driven lung carcinogenesis[34]. These findings mirror patterns observed in fibroblasts and urothelial cells[24,35]. Despite their universality, these markers lack cellular specificity; consequently, microenvironmental contextualization is necessary to distinguish senescence from transient stress responses.

SASP-associated genes and molecular markers

The SASP, a hallmark feature of senescent cells, is observed in cells including senescent epithelial cells[36], fibroblasts[24], and bone marrow and adipose-derived mesenchymal stromal cells[37]. Consequently, it is widely used in senescence research, and provides important molecular targets for the diagnosis and treatment of age-related diseases. SASP refers to a collection of molecules secreted by senescent cells, which exert a wide range of effects on the surrounding microenvironment, including modulating immune responses and regulating tissue function. Senescent macrophages in hyperglycemic environments express SASP-associated genes, such as IL-1α, IL-6, IL-8, TGF-β, CCL18, matrix metalloproteinases (MMPs), IL-10, and vascular endothelial growth factor (VEGF)[38]. The expression and regulatory mechanisms of these genes are listed in **Table 1**.

MicroRNAs miR orchestrate SASP regulation through multi-layered control mechanisms, thereby modulating inflammatory biomarker secretion *via* transcriptional and post-transcriptional cascades. miR-146a/b attenuate SASP factors (IL-6 and IL-8) by targeting IRAK1 mRNA[84], whereas miR-34a, miR-22, and miR-217 amplify pro-inflammatory SASP components (IL-6 and TNF) through SIRT1 suppression[85,86]. Notably, miR-9 exhibits IL-6 inhibitory effects, in contrast to miR-21's cytokine-promoting activity[87]. This intricate miRNA network enables dynamic SASP fine-tuning, and balances inflammatory biomarker levels through coordinated epigenetic regulation.

Unique gene expression changes and markers in senescent macrophages

Glycoprotein non-metastatic melanoma protein B (GPNMB)

The 7p15 locus-encoded transmembrane glycoprotein GPNMB is regulated by CSF-1, LPS, and IFN-γ. Its expression is elevated in macrophages in aged mice and in reparative M2 macrophages, which suppress inflammatory responses. High expression of GPNMB, a biomarker of senescent and M2-like macrophages, reflects the unique characteristics of these cells and their critical roles in the immune microenvironment. In the tumor microenvironment, senescent and M2-like macrophages with elevated GPNMB levels activate tumor cells *via* CD44, and subsequently lead to the induction of IL-33 and IL-1R1 L expression. This interaction promotes the formation and expansion of cancer stem cells, and ultimately enhances tumor growth and survival.

Major histocompatibility complex class II (MHC class II)

In tumor immunology, macrophages present tumor antigens to CD4$^+$ T cells *via* MHC class II molecules, thereby activating Th1-type immune responses. Subsequently, the secretion of cytokines such as IFN-γ enhances the anti-tumor activity of CTLs and NK cells. This process bridges the innate and

Table 1 SASP-associated genes

Gene names	Gene locus	Change trend	Regulatory mechanism	Pathways involved
IL-6	7p21[39]	Increased mRNA expression[32,40]	Enhanced binding of NF-κB to the IL-6 gene promoter[41]; two polymorphisms in the IL-6 promoter region (−174G/C and −572G/C) affect transcription rates[42]; miR-142-3p knockdown–induced IL-6 upregulation at mRNA and protein levels[43]	gp130 homodimerization–mediated activation of JAK (JAK1, JAK2, TYK2) STAT (STAT1, STAT3) and SHP-2/ERK/MAPK pathways[44-46]
IL-8	4q12-q21[47]	Increased mRNA expression[32,48]	Derepression of the gene promoter; transcriptional activation *via* NF-κB and JNK pathways; mRNA stabilization *via* p38[49]	Activation of CXCR1 and CXCR2 receptors; downstream activation of AKT, PKC, calcium mobilization, and MAPK cascades[50]
IL-1α	2q13[51]	Increased mRNA expression[32,52]	NF-κB–mediated induction[53]; DNA damage–induced upregulation in senescent cells[54]; IL-1α cleavage into 22, 18, and 15 kDa fragments by IL-1β[55]	Regulation of NF-κB and C/EBPβ DNA binding; involvement in IL-6/IL-8 transcriptional control[56]
VEGF	6p12[57], 11q13, 4q34[58]	Increased protein expression[59]	STING signaling *via* HIF-1α and NF-κB in response to oxidative stress-induced DNA damage[59]; Alternative splicing–mediated loss of regulatory RNA elements[60]	VEGFR-2 dimerization–mediated activation of PLC-γ, PI3K, AKT, Ras, Src, and MAPK; initiation of downstream pathways[61]
MMPs	11q22-23[62], 20q12.2-13.1[63]	Increased mRNA expression[64,65]	Transcriptional regulation by AP-1, PEA3, Sp-1, β-catenin/Tcf-4, and NF-κB; Cytokine-induced transcription *via* AP-1/PEA3 (IL, IFN, HGF, VEGF, TNF-α, TGF-β)[66]	ECM degradation and cleavage of cell surface proteins; activation of latent growth factors, cytokines, and chemokines[67]
TGF-β1	19q13.1-q13.3[68]	Increased mRNA expression[69,70]	AP-1 binding site–dependent promoter transactivation by Tax[71]	Signaling through serine/threonine kinase receptors and SMAD proteins; regulation by p53 and Ras signaling pathways[72,73]
IL-10	1q32[74]	Increased mRNA expression[75]	Promoter regulation by TATA box and CCTCCT motif; positive regulation by Sp1 and Sp3[76]; Post-transcriptional regulation *via* AUUUA and A+U–rich instability sequences in 3′-UTR[77]	JAK-STAT signaling activation; enhanced pSTAT3 and ERK1/2 MAPK phosphorylation in endothelial cells[78,79]
CCL18	17q12[80]	Increased mRNA expression[81]	TNFα-induced CCL18 mRNA expression; IL-10 and vitamin D3–dependent protein synthesis[82]	Receptor interaction with PITPNM3/PYK2, Nir1, CCR8, and GPER1/GPR30; inhibition of CXCL12/SDF-1 receptor signaling[83]

MMPs, matrix metalloproteinases; SASP, senescence-associated secretory phenotype; VEGF, vascular endothelial growth factor.

adaptive immune systems, and plays a crucial role in inhibiting tumor growth and metastasis. In senescent macrophages, the transcriptional activity of MHC class II genes decreases because of decreased binding of transcription factors to W and X regulatory elements upstream of the transcription start site[88]. This decline correlates with tumor progression, because tumor-associated macrophages with low MHC II expression contribute to immune evasion and tumor advancement[89].

Lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1)

LYVE1, a membrane marker distinguishing macrophage subsets, is associated with anti-inflammatory macrophages involved in angiogenesis and tissue repair, whereas LYVE1$^-$ macrophages exhibit pro-inflammatory M1-like traits[90]. LYVE1 expression, regulated by Antisense Noncoding RNA in the INK4 Locus (ANRIL), declines with macrophage aging. In skeletal muscle, the shift from LYVE1$^+$ to LYVE1$^-$ in aging macrophages reflects a pro-inflammatory trend[90].

In the tumor microenvironment, depletion of LYVE1$^+$ macrophages, which are responsible for hyaluronic acid (HA) degradation, leads to HA accumulation, drives extracellular matrix remodeling, and enhances tumor cell motility and invasion[91]. Therefore, aging macrophages with diminished LYVE1$^+$ expression may promote tumor progression through altered HA dynamics.

Application of senescence biomarkers in tumor diagnosis and prognosis

The unique biomarkers distinguishing senescent macrophages remain incompletely characterized, and current research focuses primarily on comparative analyses with respect to their non-senescent counterparts. Although some molecules have shown significant downregulation in senescent macrophages, their diagnostic specificity for senescence identification remains controversial, and further experimental validation is required.

The development of senescence-specific macrophage biomarkers may have dual benefits in advancing fundamental research and elucidating these macrophages' distinct roles in tumor microenvironments. Notably, conserved senescence markers p16^{INK4a} and p21—which are upregulated in both macrophages and fibroblasts—exhibit tumor-promoting potential *via* microenvironmental modulation[24], thus underscoring their dual functionality as senescence indicators and mediators of oncogenic progression. The SASP further exemplifies this mechanistic link by driving tumorigenesis and malignant transformation across multiple malignancies, including breast, pancreatic, and oropharyngeal cancers, through paracrine signaling[92]. Clinically, quantitative changes in macrophage SASP components correlate with disease prognosis and therefore offer actionable insights for patient stratification. Concurrently, senescence-specific macrophage alterations—such as GPNMB upregulation and MHC class II downregulation—directly reflect aging-associated functional reprogramming; moreover, these molecular shifts strongly correlate with adverse clinical outcomes.

These findings collectively highlight the translational potential of senescent macrophage biomarkers, and offer dual utility in deciphering tumor immune evasion mechanisms and serving as novel targets for early cancer detection. Furthermore, their integration into prognostic models may enhance therapeutic response prediction by bridging fundamental senescence biology with clinical oncology.

Changes in the functions of senescent macrophages affecting tumors

Macrophages, known for their plasticity, undergo functional changes during aging that profoundly affect immune responses[93]. Aging macrophages exhibit metabolic impairments, diminished phagocytic activity, and altered abilities in tissue infiltration and inflammatory regulation. These changes weaken immune defenses and contribute to diseases including cancer. Notably, senescent macrophages accumulate in the TME and influence tumor progression through a distinct secretory phenotype. Because their functional changes affect immune evasion, angiogenesis, and cancer cell invasion, these macrophages are critical players in tumor development (**Figure 1**).

Senescent macrophages promote tumor progression through inflammation

Aged macrophages show heightened inflammation, driven by systemic increases in IL-1, IL-6, IL-8, and TNF levels[94]. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway is central to this process, by inducing the SASP. Persistent inflammation often involves non-canonical NF-κB activation *via* NF-κB Essential Modulator (NEMO)

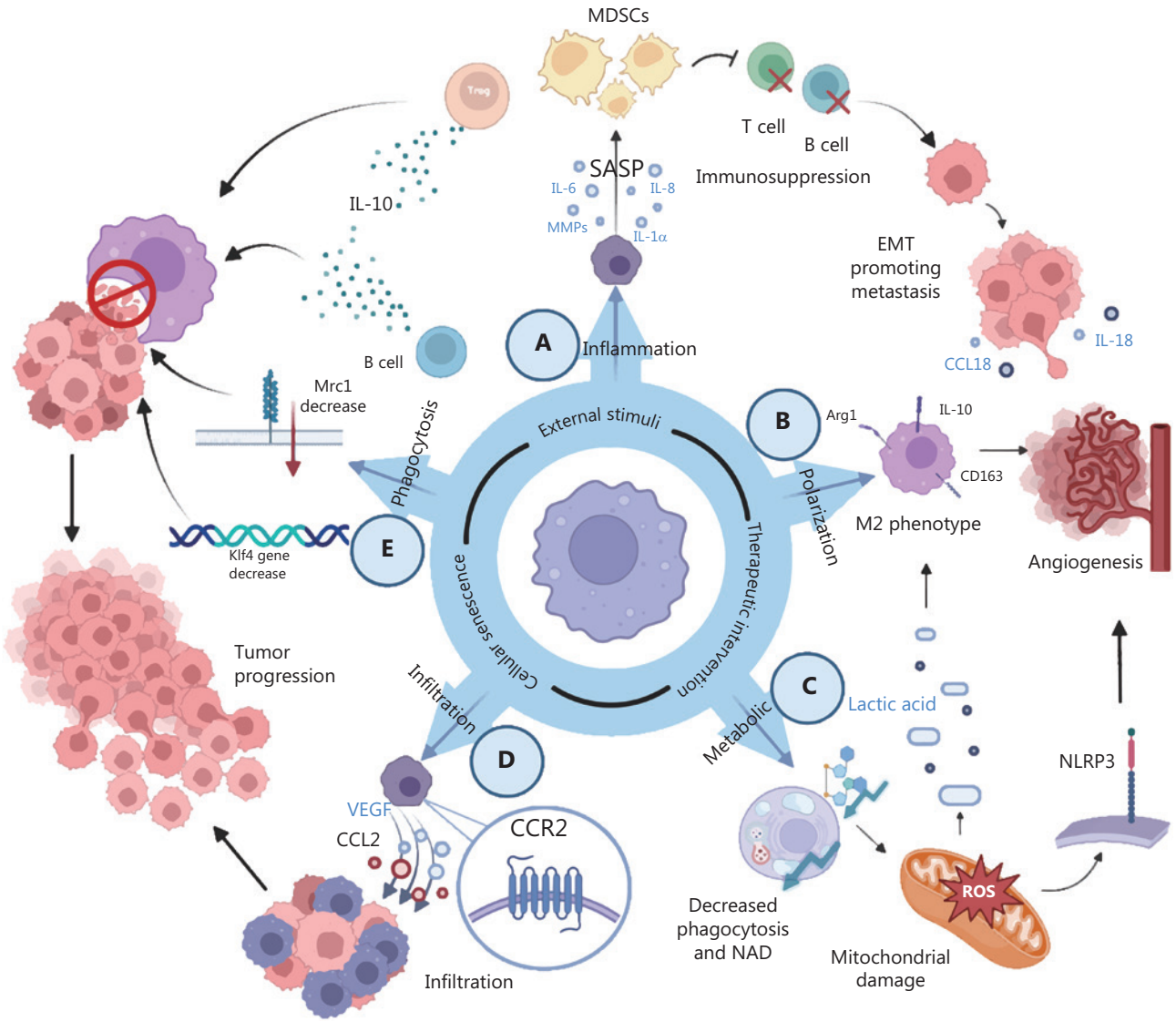


Figure 1 Effects of senescent macrophages on tumors. (A) Inflammation: senescent macrophages secrete factors, such as IL-6, IL-8, and IL-1α, that form the SASP, which establishes an immunosuppressive environment. SASP factors activate NF-κB, thus promoting MDSC and Treg infiltration, suppressing T and B cell functions, and advancing tumor progression. (B) Polarization: aging macrophages often polarize to the M2 phenotype, which promotes tumor progression through expression of IL-10, Arg1, and CD163, thereby enhancing angiogenesis and immune evasion. (C) Metabolic changes: aging macrophages show diminished NAD^+ levels, impaired phagocytosis, and mitochondrial dysfunction. Lactate accumulation maintains the M2 phenotype and promotes tumor survival, whereas mitochondrial damage and oxidative stress worsen inflammation *via* NLRP3 activation. (D) Infiltration: increased CCR2 expression in senescent macrophages enhances their response to tumor-secreted chemokines (CCL2 and VEGF) and leads to stronger infiltration and tumor progression. (E) Phagocytosis: senescent macrophages show impaired phagocytosis because of IL-10 secretion by peritoneal B cells and decreased scavenger receptor expression, such as Mrc1, thus weakening tumor-clearing ability. Additionally, dysregulation of circadian genes, such as *Klf4*, worsens functional decline, impairs tumor suppression, and promotes tumor development, thus affecting treatment outcomes. SASP, senescence-associated secretory phenotype; IL, interleukin; MMPs, matrix metalloproteinases; MDSCs, myeloid-derived suppressor cells; EMT, epithelial-mesenchymal transition; NAD, nicotinamide adenine dinucleotide; ROS, reactive oxygen species; NLRP3, NOD^-, LRR^- and pyrin domain-containing protein 3; VEGF, vascular endothelial growth factor; CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2.

protein, genotoxic stress, and IL-1/TNF signaling[95]. The signaling cascade of p38 mitogen-activated protein kinase (p38MAPK), which responds to various cellular stresses[96], is enhanced by the activation of mitogen- and stress-activated protein kinase (MSK)1 and MSK2. These kinases phosphorylate the p65 subunit of the NF-κB complex at Ser276[97], and subsequently amplify the inflammatory response by further activating the transcription factors cAMP response element-binding protein (CREB) and STAT3[98]. Beyond these signaling events, aging leads to the accumulation of ceramides. Ceramide-1-phosphate (C1P), a multifunctional signaling molecule, activates several kinases, including protein kinase C (PKC) zeta, p38MAPK, and c-Jun N-terminal kinase (JNK), which together further stimulate NF-κB signaling and promote cellular inflammation.

The inflammatory environment drives the secretion of SASP factors, such as IL-6, IL-8, and MMPs, and promotes tumor initiation by disrupting epithelial cell cohesion and enhancing mitogen availability[69,99]. Additionally, macrophage-derived osteopontin activates MAPK signaling in pre-neoplastic cells and subsequently promotes their proliferation[100].

Beyond direct tumor cell modulation, senescent macrophages indirectly drive tumor progression *via* microenvironmental crosstalk. Macrophage senescence is considered to promote the transformation of stromal cells into cancer-associated fibroblasts, which reciprocally amplify macrophage polarization toward TAMs through feedforward signaling[101].

The chronic inflammatory milieu sustained by SASP secretion critically impairs cytotoxic immunity by suppressing NK cell tumoricidal activity and $CD8^+$ T cell function. Concurrent NF-κB activation recruits immunosuppressive populations—myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)—that establish an inhibitory network *via* IL-6, IL-10, and TGF-β secretion, thereby disrupting antigen recognition and adaptive immunity[102,103].

Notably, SASP propagates senescence through paracrine factor exchange[104], and induces cell cycle arrest in neighboring cells and systemic immunosenescence marked by attenuated antigen responsiveness and chronic inflammation[105]. $CD8^+$ T cells, which are essential for tumor clearance, exhibit a profound functional decline, whereas $CD4^+$ T helpers, B cells, and dendritic cells also experience varying degrees of dysfunction[106]. This immunosuppressive cascade facilitates epithelial-mesenchymal transition (EMT) and enhances metastatic potential through heightened tumor cell motility[107].

Pro-inflammatory mediators, such as TNF-α and IL-8, further enhance EMT by upregulating transcription factors, such as Snail and activating pathways, including JAK2/STAT3/Snail[108]. TGF-β secreted by senescent macrophages increases MMP production in tumor cells, thus facilitating invasion and metastasis[109]. Pro-inflammatory proteins, such as high mobility group box 1 (HMGB1), amplify NF-κB signaling *via* Toll-like receptor (TLR) activation and consequently sustain inflammation[110]. HMGB1 is primarily localized in the nucleus and is often released following cell death, but its release from macrophages can also occur independently of cell death. Inflammatory stimuli such as IFN-γ also trigger the release of HMGB1 through secretory lysosomes in macrophages and further contribute to the inflammatory response[111]. Three redox isoforms—all-cysteine-reduced, disulfide, and all-cysteine-oxidized HMGB1—differentially regulate macrophage-mediated inflammation. Notably, the all-cysteine-oxidized form specifically drives age-related inflammatory priming, thus underscoring its roles in chronic inflammation and aging pathogenesis[112]. Aging-associated changes in TLR signaling prolong inflammatory responses, as observed in aged macrophages with delayed resolution of LPS-induced cytokine expression[113]. Furthermore, IL-1α activation *via* caspase cleavage, particularly by caspase-5, which facilitates mature IL-1α release in human macrophages, is critical for the IL-1α-dependent SASP in aging macrophages *in vitro*[114]. These findings highlight the role of non-canonical inflammasome activation in driving inflammation in senescent macrophages. IL-1β and IL-18, which share structural homology but divergent pro-inflammatory functions[115], are monocyte-derived cytokines released after exposure to senescence-associated stimuli[116]. Whereas IL-1β drives tumor progression through miR-101 suppression and subsequent Lin28B upregulation[117], thereby establishing its role in sterile inflammatory pathogenesis[118], IL-18 converges on NF-κB activation, thereby amplifying inflammation-associated malignancy[119].

Changes in the polarization of senescent macrophages affect tumor development

Macrophages polarize into 2 distinct phenotypes: M1, which is characterized by pro-inflammatory responses, and M2, which is involved in tissue repair, angiogenesis, and immunosuppression[120]. In the context of senescence, macrophages frequently adopt an M2-like phenotype. This shift is particularly pronounced in TAMs, which exhibit M2-like traits. TAMs contribute to poor prognosis in metastatic tumors by

promoting immunosuppression through the secretion of specific cytokines[121]. Markers such as $p16^{INK4a}$ and SA-β-gal indicate that senescent macrophages resemble the M2 phenotype, with high arginase 1 expression promoting tumor initiation[122]. Aging also impairs cholesterol efflux in macrophages; drives polarization changes; and increases M2 markers, such as IL-10 and CD163, while decreasing M1 markers[123].

M2 polarization increases with age in various tissues, and is driven by IL-13 and IL-4 secreted from adipocytes and increased expression of markers such as transglutaminase-2[124,125]. IL-10, a key immunosuppressive cytokine, induces regulatory Tregs, amplifies immune senescence, and suppresses NK cell activity, thus enabling tumor escape[126,127]. IL-10 also promotes angiogenesis *via* STAT3 signaling, whereas SASP components such as IL-1β and TGF-β1 enhance VEGF-A expression and consequently fuel tumor-associated angiogenesis[128,129]. Although NF-κB primarily supports M2 polarization, it indirectly facilitates angiogenesis and metastatic tumor progression by inducing the production of cytokines such as CCL17, CCL18, and TGF-β1[130].

Nonetheless, aging shows contrasting effects in certain contexts. In aged SAMP8 mice, cardiac tissues display increased pro-inflammatory markers and diminished M2-specific markers, such as IL-10[131]. Similarly, the SASP components S100A8 and S100A9 drive M1 macrophage accumulation in inflamed kidneys[132]. Aged kidneys exhibit high frequencies of $CCR2^+$ pro-inflammatory macrophages with elevated inflammatory mediators, whereas M2 markers show minimal changes[133]. In visceral adipose tissue, aging decreases M2 macrophages and increases M1 macrophages, associated with a decrease in PPARγ expression and increase in TLR4 activation, which are commonly related to dead and dying adipocytes[134].

Metabolic alterations in senescent macrophages and their effects on tumor cells

Metabolic alterations in macrophages are shaped by intrinsic aging, impaired autophagy, decreased nicotinamide adenine dinucleotide (NAD) availability, and mitochondrial dysfunction[135]. Aging cells exhibit decreased autophagy, which in turn leads to upregulation of glycolytic enzymes and increased glycolysis, with regulatory mechanisms varying by senescence stimuli. Oncogene-induced senescence enhances glycolysis *via* retinoblastoma protein-mediated upregulation of glycolytic enzymes, whereas radiation-induced senescence activates AMPK and NF-κB signaling that drive glycolysis[136]. In pancreatic ductal adenocarcinoma cells, CCL18 from senescent macrophages interacts with phosphatidylinositol transfer protein membrane associated 3 (PITPNM3) and activates NF-κB signaling, which in turn induces VCAM-1 expression, aerobic glycolysis, and lactate secretion, thus creating a feedback loop promoting M2 macrophage polarization and tumor survival[137].

SASP-associated inflammatory cytokines in aging environments increase pro-inflammatory macrophages expressing CD38, a key NAD^+-consuming enzyme. Subsequently, decreased NAD levels impair both mitochondrial NAD^+-dependent respiration and phagocytic activity, thus hindering inflammation resolution[138,139]. Aging macrophages also show diminished autophagic flux, thus leading to mitochondrial dysfunction marked by increased ROS, decreased oxidative phosphorylation, and decreased energy utilization, and collectively impairing phagocytosis[140].

Mitochondrial dysfunction and oxidative stress amplify inflammation *via* NLRP3 activation, thereby triggering caspase-1-mediated maturation of IL-1β and IL-18. IL-1β further activates hepatocyte growth factor (HGF), which is crucial for angiogenesis and tumor initiation[141].

Enhanced infiltrative capacity of senescent macrophages influencing tumors

Macrophages, crucial infiltrative components in most malignant tumors, are typically recruited after tumor formation *via* chemokines, such as TNF, IL-1, and CCL2, which attract monocytes that subsequently differentiate into tissue macrophages[142]. Senescent macrophages exhibit elevated expression of CCR2, which enhances their responsiveness to CCL2 and promotes recruitment and infiltration. Tumor cells often overexpress CCL2, which activates NF-κB and other tumorigenic pathways, thus further driving macrophage accumulation in the tumor microenvironment[143].

Hypoxia upregulates VEGF and consequently amplifies macrophage recruitment, whereas hypoxic conditions also induce an M2 polarization *via* elevated CSF-1 levels and consequently enhance tumor-promoting functions[144]. This synergy between senescence and hypoxia facilitates tumor cell migration and proliferation, as observed in murine gliomas, in which microglia drive glioblastoma progression *via* mTOR-mediated immunosuppression[145].

Aging alters macrophage infiltration across tissues. In aged mice, lung-resident alveolar macrophages decline, whereas

brain tissues exhibit elevated expression of CCL2, which promotes macrophage infiltration and neuroinflammation[146]. Similarly, aging and obesity accelerate macrophage accumulation in adipose tissue, in a manner driven by adipose tissue aging and monocyte recruitment[147].

Diminished phagocytic and antigen presenting function of senescent macrophages decreases tumor clearance

M2 macrophages are highly phagocytic, and can clear apoptotic cells and mediate antibody-dependent phagocytosis, thereby playing dual roles in tumor progression and suppression[148]. However, aging impairs phagocytic function in peritoneal and bone marrow-derived macrophages, because of IL-10 secretion by peritoneal B cells and decreased expression of scavenger receptors, such as mannose receptor C-type 1 (Mrc1/CD206) and CD14[149]. Additionally, p53 inhibits phagocytic activity in senescent macrophages and consequently further decreases their tumor-clearing capacity[150].

Circadian rhythms also regulate macrophage phagocytosis, and peak activity in young macrophages occurs at the dark phase onset. In senescent macrophages, dysregulated circadian genes, including Krüppel-like factor 4 (KLF4), disrupt this rhythmicity and exacerbate their functional decline[151]. This shift compromises the dual roles of macrophages, thus favoring tumor promotion and impeding therapeutic efforts.

Interestingly, aged peritoneal macrophages show variable phagocytic responses depending on environmental factors, such as increased macrophage receptor with collagenous structure receptor expression and decreased TLR4 expression, thereby enhancing their ability to phagocytose specific particles, such as polymethyl methacrylate bone cement[152]. These findings highlight the influence of origin and microenvironment on macrophage function.

Macrophage senescence fosters a pro-inflammatory milieu that impairs dendritic cell maturation and compromises adaptive immunity. Pathogens' evasion of senescent macrophage clearance triggers self-sustaining inflammatory amplification through unresolved microbial persistence[153]. Moreover, aging-associated declines in macrophage antigen presentation—marked by impaired chemotaxis and MHC class II downregulation[154]—are exacerbated by decreased CD86 co-receptor expression. This co-stimulatory deficit further dysregulates TLR signaling[155], and collectively undermines both innate and adaptive immune functionality in senescence.

Common factors affecting functional changes with senescence in macrophages and tumor progression

Cancer is often considered a disease closely associated with aging, because many aging characteristics share similarities with cancer. Over time, various factors not only alter the phenotype and function of normal cells but also contribute to tumor progression.

Extracellular: aged microenvironment

The "aged microenvironment" concept, originally described in murine models, is now being translated to human pathophysiology. This phenomenon describes age-dependent tissue remodeling involving progressive alterations in extracellular matrix composition, cellular constituents, and signaling networks, which collectively establish a permissive niche for chronic low-grade inflammation (inflammaging) and functional decline. Clinical manifestations include attenuated immune surveillance, compromised tissue repair, and systemic deterioration of cellular homeostasis. The aged microenvironment is operationally defined by multidimensional biomarkers including inflammaging, SA-β-gal activity, and upregulation of $p16^{INK4a}$/p21 coupled with SASP components, encompassing not only intrinsic cellular aging but also dynamic cell-cell and cell-matrix interactions[156].

From the perspective of immune aging, aging is associated with the activation and infiltration of immunosuppressive cell populations, particularly in older people[157]. As previously described, macrophages often adopt an M2 phenotype during aging. The inability of macrophages to perform effective immune phagocytosis results in an immune-excluded TME and reflects a decline in immune function. Interestingly, some studies have highlighted the role of aging in the development of an immune-cold TME, a phenomenon associated with increased lactate secretion[158].

In aged mice, heightened intestinal permeability promotes microbial translocation and LPS accumulation, thus driving TNF-α-dependent macrophage activation that sustains inflammatory amplification and pathogen clearance deficits, and exacerbates macrophage dysfunction[159,160]. Concomitant age-related declines in macrophage responsiveness manifest as GM-CSF resistance and TLR dysregulation in alveolar subsets, thereby reflecting adaptive plasticity to oxidative and microbial stressors[161-163]. Furthermore, tumor progression

is potentiated by aging-induced extracellular matrix (ECM) degradation, particularly in lung and breast malignancies, in which diminished HA and HAPLN1 levels disrupt collagen cross-linking[164]. This structural ECM disintegration generates permissive fiber networks that promote melanoma invasion through biomechanical microenvironmental alterations[165].

Intracellular: impaired organelle function, DNA damage, and regulation of SASP secretion

Senescent macrophages orchestrate tumor progression through interconnected mitochondrial, lysosomal, and endoplasmic reticulum (ER) dysfunction. Mitochondrial impairment drives NF-κB activation *via* stress-induced NEMO accumulation and consequently perpetuates chronic inflammation[166], whereas diminished mitochondrial fission decreases cancer cell phagocytic capability[167]. LPS-induced mitochondrial ROS modulate MAPK signaling[168], and parallel ROS accumulation in cancer cells enhances ERK-dependent proliferation[169].

Lysosomal dysfunction manifests as impaired acidification and protease activity during M2 polarization, thus compromising antigen cross-presentation and antitumor immunity. Concurrently, mTORC1-mediated autophagy suppression and LPS-triggered lysosomal expansion disrupt organelle dynamics[170]. Defects in the age-related ATG5-12/LC3 system impede LC3-associated phagocytosis and exacerbate lipofuscin accumulation through lipid droplet-lysosome interactions[171].

ER stress activates NF-κB *via* the unfolded protein response, although aging decreases this response through chaperone deficiency[166]. The JNK-PPARγ pathway links ER stress to M2 polarization[172], whereas breast cancer-derived exosomal miR-27a-3p upregulates macrophage PD-L1 *via* PTEN-AKT/PI3K signaling and consequently fosters immune evasion[173].

DNA damage in senescent macrophages arises from ROS-induced strand breaks, epigenetic modifications, and dysregulated extracellular vesicles (EVs). ROS, including superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^{\cdot}OH$), induce DNA damage and activate JNK, and subsequently compromise tumor suppression mechanisms[174]. Replication fork defects and DNA synthesis errors further contribute to pre-cancerous changes[175]. Moreover, senescent macrophage-derived EVs, which carry pro-inflammatory RNA, induce telomere shortening and activate the DNA damage response in recipient cells, thereby promoting genomic instability[176]. These EVs also influence tumor-host interactions by altering miRNA profiles and enhancing immunosuppressive phenotypes in reprogrammed cells[177]. Therefore, the mechanisms of DNA damage in senescent macrophages are closely associated with tumorigenesis, thus illustrating their dual roles in aging and cancer development.

Although DNA damage initiates SASP secretion, its regulation involves multilayered molecular crosstalk. The p53-p21 and p16-pRB axes govern senescence: p53 deficiency selectively upregulates pro-inflammatory SASP components[178], whereas p16 orchestrates a distinct "p53 arm" SASP profile encompassing interferon-related factors[179]. NF-κB activation *via* IκB coactivation[180], oxidative stress-sensing PKD interactions[181], and surface receptors (CD36/CD40L)-p38 MAPK signaling[182] converge in driving IL-6/IL-8 expression[183]. C/EBPβ amplifies SASP through promoter binding and NF-κB synergy, thus accelerating tumorigenesis[175,184]. In the TME, p38 MAPK stabilizes SASP transcripts[185], whereas mTOR enhances SASP *via* IL-1α/NF-κB feedback and translational control[186], thereby concurrently activating oncogenic pathways (PI3K/AKT) and suppressing tumor suppressors (PTEN/TSC1/2)[177]. Senescence-associated loss of Lamin B1 derepresses SASP genes *via* chromatin remodeling[176], and is paralleled by cGAS-STING-mediated interferon responses to cytoplasmic DNA[187]. The Notch1 intracellular domain induces TGF-β-dependent non-inflammatory SASP[188], whereas epigenetic regulators (METTL3-METTL14, BRD4, KDM4, and EZH2) and miR-125a modulate context-specific SASP secretion[189,190]. Many lipids contribute energy or building blocks for the expression and secretion of SASP factors[191]. Critically, senescence-associated pathways—including epigenetic, inflammatory, mTOR, cGAS-STING, and AhR signaling pathways—drive PD-L1 upregulation. Senescent macrophages additionally adopt immunosuppressive phenotypes *via* SASP-mediated tumor cell PD-L1 induction[192], thus collectively explaining immune checkpoint blockade (ICB) resistance through both cellular senescence and aging-activated pathways.

Tumor treatment strategies targeting senescent macrophages

Building on the previous discussion, the comprehensive understanding of the significant influence of macrophage senescence in the tumor microenvironment on tumor

progression provides a compelling theoretical foundation for clinical treatments. On this basis, we summarize tumor treatment strategies targeting senescent macrophages. To date, substantial progress has been made in the development of drugs targeting senescent cells, which can be categorized into 3 types according to their mechanisms of action: senolytics, senomorphics, and senoreverters (**Figure 2**).

Senolytics eliminating senescent macrophages

Senolytics are drugs that induce apoptosis in senescent cells by targeting senescence-associated anti-apoptotic pathways, and effectively eliminate these cells from the tumor microenvironment. Senolytics, which are among the most thoroughly researched classes of senescence-targeting therapies, have shown promise in clearing $p16^{+}$ senescent macrophages[11,184]. Flavonoids such as quercetin and fisetin are common senolytic agents. Quercetin exhibits strong pro-oxidative activity, which is enhanced in the presence of copper or iron. Fisetin demonstrates even greater senescence-clearing activity and stronger pro-oxidative effects, probably because of its modulation of pathways such as HIF-1, BCL-2, insulin/IGF-1, and PI3K/AKT.

The combination of dasatinib and quercetin has shown significant efficacy in senescent cell clearance, according to markers such as $p16^{INK4a}$, p53, and SA-β-gal. This combination also alleviates senescence by modulating the YTH N6-methyladenosine RNA binding protein 2 (YTHDF2)-dependent TRAF6-MAPK-NF-κB axis, whereas dasatinib alone exhibits anti-inflammatory effects that may suppress SASP through upregulation of YTHDF2[193]. However, some senolytics, such as navitoclax (ABT-263), a BCL-2 inhibitor,

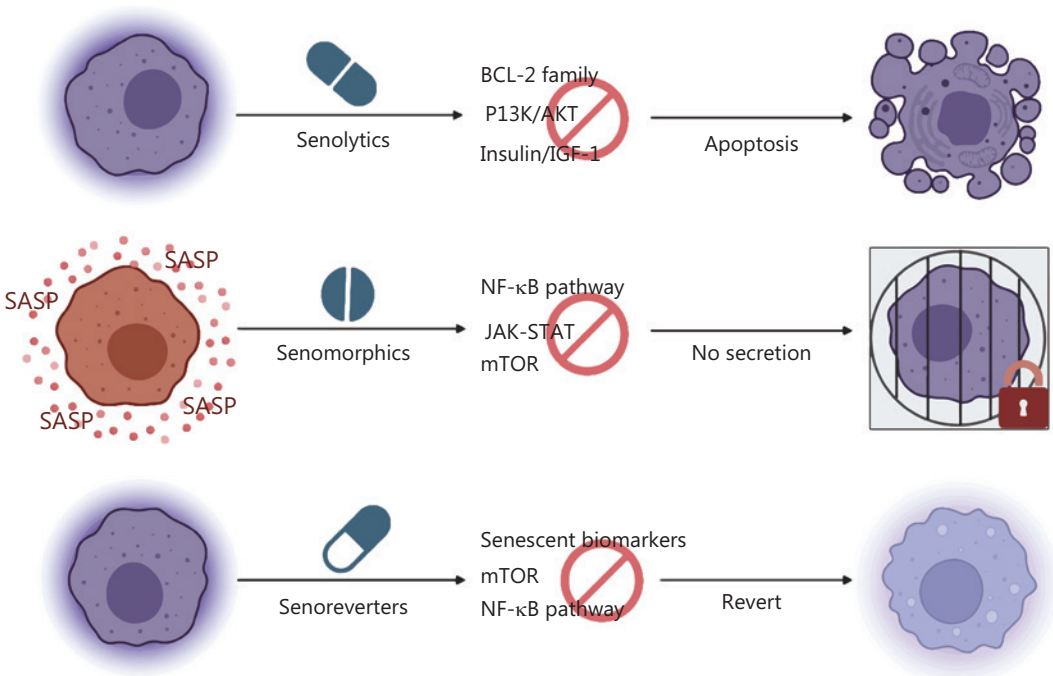


Figure 2 Three therapeutic strategies targeting senescent macrophages: senolytics, senomorphics, and senoreverters. Senolytics selectively induce apoptosis in senescent cells by inhibiting key anti-apoptotic pathways, including the BCL-2 family, PI3K/AKT, and insulin/IGF-1 signaling, thereby leading to cell death. Senomorphics, in contrast, suppress the pro-inflammatory and pro-tumorigenic effects of the SASP by inhibiting pathways such as NF-κB, JAK-STAT, and mTOR, thereby effectively blocking secretion without eliminating the cells. Finally, senoreverters reverse the senescent phenotype by targeting senescence biomarkers and key regulators, such as mTOR and NF-κB, thereby restoring cells to a pre-senescent state. BCL-2, B cell CLL/lymphoma-2; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase b; IGF-1, insulin-like growth factor 1; SASP, senescence-associated secretory phenotype; NF-κB, nuclear factor kappa-light-chain-enhancer of activated b cells; JAK-STAT, Janus kinase-signal transducer and activator of transcription; mTOR, mechanistic target of rapamycin.

induce apoptosis in non-senescent cancer cells to a lesser extent, thus resulting in potential adverse effects, including thrombocytopenia[194].

To date, first-generation senolytics have demonstrated notable effects in age-related diseases such as Alzheimer's disease, diabetes, and atherosclerosis[195]. Second-generation senolytics are being developed through high-throughput screening and other methods[196]. Although many drugs with senolytic properties were initially developed as anti-cancer agents, their limited efficiency in directly targeting cancer cells has constrained their oncology applications[197].

Nevertheless, senolytics are a promising strategy for adjunctive cancer therapy targeting senescent cells that contribute to tumor progression, and may potentially improve clinical outcomes for patients. Future advancements in senolytics, including the development of more specific and less toxic agents, may expand their therapeutic potential across a broader range of diseases.

Senomorphics suppressing SASP secretion

Senomorphics, also known as senostatics, target senescent cells by modulating their function rather than eliminating them. These drugs suppress or normalize the SASP in macrophages by inhibiting key transcription factors, such as NF-κB, the JAK-STAT pathway, mTOR, or other SASP-associated pathways, thereby mitigating the inflammatory and harmful effects of senescent cells on surrounding tissues[12,198].

Rapamycin, a well-studied senomorphic, inhibits cellular senescence across diverse cell types and suppresses SASP markers in human cell lines[199]. It decreases the expression of p16 and p21 through Nrf2-dependent mechanisms, inhibits inflammatory SASP by suppressing IL-1α translation *via* the NF-κB pathway, and blocks mTORC1 activity through FK506-binding protein 12 binding, thus decreasing the pro-tumor effects of senescent cells[200,201]. Another senomorphic, metformin, prevents NF-κB nuclear translocation and suppresses IκB and IKKα/β phosphorylation, thereby effectively decreasing LPS-induced NF-κB activation in senescent macrophages. The finding that its anti-cancer effects in patients with diabetes are associated with AMPK activation and subsequent mTOR inhibition highlights its potential for cancer therapy[198,202].

However, because senomorphics require continuous administration, concerns have been raised regarding adverse effects and off-target effects, including suppressed cytokine secretion in non-senescent immune cells[11]. For instance, high doses of rapamycin in mice have been associated with nephrotoxicity, metabolic disturbances, and elevated infection risk[203]. Therefore, improving the safety profile of senomorphics remains a critical challenge[197].

Senoreverters reversing senescent state

Senoreverters, a novel class of senotherapeutics, are pharmacological agents or interventions reversing the senescent phenotype of cells. The combination of 5-azacytidine and resveratrol treatment in senescent adipose-derived stem cells significantly enhances proliferation rates, and decreases SA-β-gal activity and ROS accumulation, thereby indicating a reversal of the senescent state[13]. Although the precise mechanisms underlying senescence reversal remain incompletely understood, the inhibition of 3-phosphoinositide-dependent protein kinase-1 has been found to suppress NF-κB and mTOR signaling pathways, and subsequently abrogate senescence markers in senescent cells[204].

Senoreverters represent a critical gap in current senotherapeutic research, yet have substantial research potential and clinical relevance. In contrast to senolytics, which selectively clear senescent cells, or senomorphics, which modulate the SASP, senoreverters have unique promise in repairing senescent cells and restoring their functionality. In the context of the tumor microenvironment, M1-polarized macrophages generally exhibit tumor-suppressive properties; however, as senescence progresses, shifts in their functional phenotype may promote tumorigenesis. Therefore, the reversal of macrophage senescence offers a compelling opportunity to reinstate their anti-tumor activities, and might potentially play a critical role in cancer therapy.

Other approaches targeting senescent macrophages

In the field of immunotherapy, CAR-T cells targeting the surface urokinase-type plasminogen activator receptor of senescent cells have been shown to effectively ablate senescent cells both *in vitro* and *in vivo*, thereby presenting a promising strategy for senescent cell clearance[14]. Another strategy involves targeting the highly expressed GPNMB in senescent macrophages. Administration of a GPNMB vaccine significantly decreases the numbers of GPNMB-positive cells and improves senescence-related phenotypes; therefore,

vaccination against senescent antigens might be a potential new senotherapeutic approach[205]. Additionally, antibody-drug conjugates have emerged as powerful tools in the selective elimination of senescent cells. An ADC targeting β2-microglobulin has been shown to eliminate senescent cells by delivering duocarmycin into them; this effect is dependent on the expression of p53, and no toxicity has been observed in non-senescent cells treated with an isotype control ADC[206]. The proteolysis-targeting chimera (PROTAC) PZ 15227, comprising the senolytic agent ABT-263 linked to the cereblon E3 ligase ligand, has demonstrated greater efficacy in clearing senescent cells and lower cytotoxicity to platelets than navitoclax[207]. Additional senescence-associated anti-apoptotic pathway-targeting drugs are also being explored for the development of more PROTACs. Another promising strategy is the design of galactose-based prodrugs, wherein cytotoxic molecules are covalently attached to galactose or acetylgalactose moieties. Selective processing of these prodrugs within senescent cells after uptake leads to the release of active cytotoxic agents and selective elimination of senescent cells, such as SSK1, Prodrug A (JHB 75B), and Nav-Gal[208-210]. Unlike traditional senolytics, these novel senotherapeutics exhibit enhanced precision in targeting senescent cells. Future efforts may focus on further optimizing the design of these new therapeutics, developing more biomarkers for senescent cells, and improving therapeutic efficacy through combination therapies.

Studies targeting senescent macrophage functionality have demonstrated that autophagy induction *via* pharmacological strategies—such as ABT-263-mediated Trem-2 upregulation activating Beclin-1-dependent pathways—partially restores immune competence in aged murine models, thereby potentiating anti-tumor responses[211]. Notably, myostatin has emerged as a dual regulator of aging and oncogenesis, which, *via* protein glycosylation suppression, mitigates macrophage senescence and tumor-promoting microenvironmental reprogramming[212]. Mechanistically, the cGAS-STING-driven activation of Leukocyte Immunoglobulin-Like Receptor B2 (LILRB2) orchestrates p16-dependent senescence and SASP-mediated radioresistance; consequently, LILRB2 inhibition might provide a synergistic strategy to overcome therapeutic limitations in cancer radiotherapy[213].

The above therapies highlight the growing recognition of the importance of targeting senescent cells, particularly macrophages, in cancer treatment. Senolytics have shown promise in eliminating senescent cells, whereas senomorphics and senoreverters offer alternative strategies by modulating SASP or reversing senescence. However, current approaches face challenges, such as potential toxicity and limited efficacy in the tumor context. To date, research directly targeting senescent macrophages has largely been confined to the preclinical stage. Despite preclinical advances in targeting senescent macrophages for cancer therapy, clinical translation faces multifaceted barriers. Although, as described earlier, senescent macrophages express certain markers that distinguish young from aged cells, current detection methods relying on IL-10, $p16^{INK4a}$, SA-β-gal, and SASP markers[214] have insufficient specificity, because these biomarkers overlap with other senescent or macrophage subpopulations[215]. This challenge is compounded by the absence of surface markers uniquely identifying senescent macrophages, coupled with their inherent tissue-specific heterogeneity, which impedes precise targeting within the TME. This complex ecosystem—comprising dynamically interacting cellular networks—further obscures therapeutic development. Senescent macrophages engage in multifaceted crosstalk with neighboring components, thus amplifying the risks of off-target effects and safety concerns. Consequently, advancing multi-omics-driven biomarker discovery or refined identification systems is imperative to overcoming these translational roadblocks.

Although standalone therapies targeting senescent macrophages are unlikely to advance to clinical trials in the near future, owing to current gaps in research, their potential in combination therapies is highly promising. As noted earlier, the presence of senescent macrophages has been shown to impair the efficacy of ICB therapy. Therefore, integrating senescent macrophage-targeted therapies as an adjunct to ICB might substantially improve therapeutic outcomes. Moreover, given that senescent macrophages may confer resistance to chemotherapy and radiotherapy[122], combining senescent macrophage-targeted therapies with these conventional treatments also has considerable potential.

Conclusions

This review systematically elucidated the dual roles of senescent macrophages in tumor progression, highlighting the molecular mechanisms underlying their functional alterations and the therapeutic potential of targeting these processes. By integrating universal senescence markers with macrophage-specific signatures, we established a framework for identifying senescence-associated phenotypes within the

TME. Although these biomarkers currently exhibit inadequate specificity, they provide valuable diagnostic utility and mechanistic insights into pro-tumorigenic functions, thus underscoring the critical need for intensified research to identify more robust and precise markers of senescent macrophages.

Central to our discussion were the functional shifts in senescent macrophages, including chronic inflammation, metabolic reprogramming, enhanced tissue infiltration, and impaired phagocytosis. These alterations are driven by extracellular factors, such as the aged microenvironment and intracellular mechanisms involving organelle dysfunction, DNA damage, and dysregulated SASP secretion. Crucially, the interplay between metabolic rewiring and immune dysfunction highlights the metabolism-immune axis as a critical regulator of macrophage senescence. Targeting this axis through NAD^+ precursor supplementation or glycolytic pathway modulation has therapeutic potential in reversing pro-tumor polarization, thereby underscoring how mechanistic studies can directly inform intervention strategies.

Therapeutic innovations must prioritize next-generation strategies that balance efficacy with specificity. Although senolytics and senomorphics remain cornerstone approaches, emerging senoreversion techniques that restore macrophage functionality represent a paradigm shift. Combining these modalities with immunotherapies has potential to synergistically enhance tumor clearance while mitigating therapy resistance. Notably, the functional restoration of macrophages—by reversing senescence-imposed metabolic constraints or epigenetic locks—has emerged as a key strategy to transform these cells from tumor accomplices into anti-cancer effectors.

A critical priority is identifying highly specific biomarkers of senescent macrophages, because current markers often lack the precision required for targeted therapeutic strategies. Future research should prioritize elucidating tissue-specific heterogeneity through integrated multi-omics platforms—methods that may simultaneously accelerate biomarker discovery—while resolving the spatiotemporal dynamics of senescence mechanisms *via* advanced imaging techniques and organoid models. Building on these insights, efforts must also focus on refining therapeutic windows for senescence-targeting agents to preserve essential immune functions. Through synergy between mechanistic exploration and translational innovation, this rapidly evolving discipline is poised to uncover novel vulnerabilities within the tumor microenvironment and to pave the way to advanced cancer therapies that strategically leverage the biology of senescent macrophages.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Tianzi Wang, Chen Qiu, Ning Yang.
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Contributed data or analysis tools: Chang Liu, Xuefeng Hu, Ning Yang.
Performed the analysis: Tianzi Wang, Chang Liu, Xuefeng Hu.
Wrote the paper: Tianzi Wang.

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