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Review

Macrophage Senescence: Friend or Foe?

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ABSTRACT: Macrophages are pivotal players in innate immunity, orchestrating host defense, tissue repair, and tissue homeostasis. Accumulating studies suggest that macrophages themselves can undergo cellular senescence in response to aging, metabolic stress, and chronic inflammation, leading to a state of "immunosenescence." Senescent macrophages exhibit a distinct phenotype characterized by pro-inflammatory secretory activity (SASP), impaired phagocytosis, metabolic dysfunction, and altered polarization. These features exert context-dependent dual effects on tissue integrity: while facilitating tissue remodeling and the resolution of acute injury, they also fuel inflammaging, tissue degeneration, and the progression of age-related pathologies such as atherosclerosis, metabolic disorders, neurodegenerative diseases, and cancer. This review synthesizes current advances on the molecular mechanisms driving macrophage senescence, including persistent DNA damage, mitochondrial dysfunction, epigenetic remodeling, and cGAS–STING signaling activation. We further discuss the beneficial versus detrimental roles of senescent macrophages across organ systems and disease contexts. Finally, we explore the translational potential of macrophage-targeted interventions—including senolytics, SASP modulation, and metabolic rejuvenation—and highlight current challenges and future perspectives in harnessing macrophage senescence to combat aging and age-related diseases.

Keywords: Macrophage senescence, Cellular senescence, SASP, Inflammaging

1. Introduction

Cellular senescence represents a fundamental and conserved stress response: a state of irreversible cell cycle arrest triggered by diverse forms of damage. Initially observed in replicating fibroblasts, it is now widely recognized that senescence serves not only as an important mechanism for tumor suppression but also as a key contributor to tissue aging and functional decline [1]. A key feature of senescence is stable cell-cycle arrest mediated by conserved tumor suppressor pathways, accompanied by sustained metabolic activity and the development of a senescence-associated secretory phenotype (SASP). These secretory factors exert context-dependent effects, supporting immune surveillance in acute settings while promoting chronic inflammation and tissue dysfunction when persistent [2–5].

Macrophages are highly plastic and perform essential roles in immune surveillance, inflammation regulation, and tissue homeostasis [6–8]. While their core functions, such as phagocytosis, efferocytosis, and phenotypic adaptability, are essential for maintaining tissue integrity, they progressively decline with age [9–11].

Emerging evidence indicates that macrophages, like other somatic cells, can undergo cellular senescence. Senescent macrophages exhibit stable functional arrest and persistent phenotypic remodeling, contributing to immune imbalance and age-associated tissue dysfunction [12]. Notably, macrophage senescence can exert both beneficial and detrimental effects depending on context. Transient senescence may facilitate inflammation resolution and tissue repair, whereas persistent or dysregulated senescence promotes chronic inflammation and pathological tissue remodeling, particularly under aging or metabolic stress conditions [13–15]. Therefore,

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macrophage senescence represents a double-edged process, acting as both a foe and a friend depending on its duration, context, and microenvironmental cues. Understanding the dual roles of macrophage senescence may thus offer novel therapeutic avenues for aging and age-related diseases.

In this review, we summarize current knowledge on the molecular mechanisms underlying macrophage senescence, including DNA damage responses, mitochondrial dysfunction, epigenetic remodeling, and innate immune signaling pathways. We further discuss the functional consequences of macrophage senescence across disease contexts and examine emerging therapeutic strategies and unresolved challenges in targeting senescent macrophages in aging and age-related diseases.

2. Biomarkers of macrophage senescence

2.1 General biomarkers in senescent macrophages

2.1.1 $p16^{INK4a}$ and $p21^{CIP1}$

A cornerstone for defining the senescent state is the sustained upregulation of potent cyclin-dependent kinase inhibitors (CDKIs). Increased expression of CDKN2A ($p16^{INK4a}$) and CDKN1A ($p21^{CIP1}$) is considered a gold standard in senescence assessment. $p16^{INK4a}$ reinforces the G1 cell cycle arrest by inhibiting CDK4/6, while $p21^{CIP1}$, a key downstream effector of p53, mediates cell cycle halt in response to DNA damage [16]. In macrophage senescence research, these markers can be robustly measured at the mRNA level via quantitative PCR (qPCR), at the protein level by Western blot or intracellular flow cytometry, and their cellular localization can be visualized through immuno-fluorescence.

2.1.2 Elevated SA-β-gal activity

Senescence-associated β-galactosidase (SA-β-gal) activity reflects increased lysosomal β-galactosidase activity, and is widely used as a classical marker of cellular senescence across many cell types, including fibroblasts, endothelial cells, and epithelial cells [17, 18]. Emerging evidence has shown that 4-HNE can increase the cellular senescence in the RAW264.7 cells , and up-regulated the expression of SA-β-Gal together with the SASP proinflammatory factors [19]. However, whether SA-β-gal positivity in macrophages consistently reflects bona fide senescence remains debated. Increased SA-β-gal activity does not always correlate with irreversible cell cycle arrest or loss of proliferative and regenerative capacity. Therefore, while SA-β-gal remains a useful screening tool, its interpretation in macrophages requires careful validation with additional molecular and functional markers.

2.1.3 SASP.

Cellular senescence is not only characterized by irreversible cell-cycle arrest but also by profound alterations in the secretory profile, collectively termed the SASP. SASP comprises pro-inflammatory cytokines (e.g., IL-1β, IL-6, IL-8), chemokines, growth factors, and matrix-remodeling enzymes [20, 21]. These factors exert dual effects: on the one hand, SASP promotes immune-mediated clearance of senescent cells and contributes to tissue repair and homeostasis; on the other hand, chronic SASP activity leads to persistent sterile inflammation, extracellular matrix remodeling, and tissue dysfunction, thereby accelerating age-related pathologies across cardiovascular and metabolic systems[22–24].

Senescent macrophages not only produce SASP but also respond to it, creating a feedback loop that amplifies senescence. They secrete high levels of IL-6, TNF-α, chemokines, and MMPs, which reinforce autocrine senescence and spread paracrine signals to surrounding cells [25, 26]. On the other hand, macrophages are also key responders to SASP factors secreted by other senescent cells. For instance, SASP-derived chemokines recruit monocytes and macrophages to sites of tissue injury or aging niches, where persistent exposure to IL-6 and TNF-α can skew macrophages toward a chronic inflammatory phenotype with impaired resolution capacity [27]. Such "inflammaging-associated" macrophages exhibit reduced phagocytosis, impaired efferocytosis, and sustained NF-κB activation, further exacerbating tissue damage and fibrosis [23]. Moreover, in metabolic and cardiovascular diseases, macrophage-derived SASP acts as both a biomarker and a mediator of disease progression, reflecting the dual role of macrophage senescence in tissue remodeling and inflammaging [28, 29].

2.2 Characteristic features of senescent macrophages

Beyond canonical, general biomarkers of cellular senescence, macrophage senescence is further characterized by context-dependent molecular and functional alterations that reflect their unique immune roles and tissue environments.

2.2.1 Characteristic molecular expression

Senescent macrophages often display downregulation of co-stimulatory molecules including CD80 and CD86, and decreased MHC class II expression, which impairs antigen presentation and T cell activation [30]. These

changes are particularly useful for distinguishing senescence from classical activation states.

In addition, recent studies have proposed several potential macrophage senescence biomarkers, but their specificity and exclusivity to senescence require further confirmation. Lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) was initially identified as a marker for senescent macrophages in aged skeletal muscle [31], but subsequent studies revealed its expression in non-senescent M2-like macrophages during tissue repair [32], highlighting context-dependent heterogeneity. Grancalcin (GCA) is a calcium-binding protein released by aged macrophages. It affects the balance between bone formation and fat formation in bone marrow stromal cells [33], but its upregulation has also been observed in LPS-activated macrophages [34], limiting its senescence-specificity. Similarly, CD22 and glucose transporter 1 (GLUT1) have been linked to macrophage senescence in metabolic stress models [35, 36], yet GLUT1 is elevated in glycolytically activated macrophages [37], and CD22 is involved in B cell-macrophage crosstalk independent of aging [35]. Consequently, these molecules should be considered "candidate biomarkers" rather than definitive markers, and their use requires combination with common senescence markers to avoid misclassification.

In the context of the brain, brain border macrophages (BAMs) show unique aging characteristics [38]. Aβ40 accumulation in BAMs has been identified as a key factor driving their senescence. Moreover, the expression of tetraspanin 4 (TSPAN4), a protein crucial for migrasome formation, is significantly upregulated in senescent BAMs, and the number of migrasomes produced by BAMs increases with age [39]. Notably, TSPAN4 expression is rarely detected in non-senescent BAMs or other brain-resident immune cells [40], suggesting it may be a tissue-specific senescence marker, though validation in human samples is still needed.

In summary, identifying reliable biomarkers for macrophage senescence is a crucial research goal. Future studies should prioritize large-scale, multi-disease models to screen for molecules with high specificity and stability, which will advance the accurate identification and functional characterization of senescent macrophages.

2.2.2 Functional alterations

2.2.2.1 Decreased phagocytosis

Phagocytosis is a fundamental functions of macrophages, allowing them to engulf and digest pathogens, apoptotic cells, and cellular debris [41]. In senescent macrophages, the phagocytic ability is notably reduced. Studies have reported that macrophages exhibit impaired immune surveillance under chronic hyperglycemic conditions, resulting in reduced capacity to recognize and clear senescent cell–derived signals. This functional decline indirectly reflects alterations in macrophage phagocytic and efficiency of immune clearance, which may lead to the accumulation of senescent cells and cellular debris in tissues, thereby exacerbating inflammatory responses and tissue damage. This is more pronounced in aging-related diseases such as diabetes [42].

At the molecular level, changes in the expression and function of phagocytic receptors contribute to this phenomenon. For example, the expression of scavenger receptors, which are crucial for recognizing and binding to a wide range of ligands on target particles, may decrease with aging [43]. A study on macrophages in the context of aging - related diseases like atherosclerosis showed that the reduced expression of scavenger receptors led to a decreased capacity of macrophages to uptake oxidized low - density lipoproteins (ox - LDLs). This, in turn, results in the accumulation of lipid-laden foam cells within atherosclerotic plaques [44].

2.2.2.2 Impaired antigen presentation

Senescent macrophages also fail to present antigens effectively. As professional antigen-presenting cells (APCs), macrophages play a pivotal role in initiating adaptive immune responses by presenting antigens via MHC class I and MHC class II molecules to activate T lymphocytes [45]. However, macrophage - mediated antigen presentation is severely impaired during senescence. The expression levels of MHC class I and class II molecules, which are critical for presenting antigens to CD8+ and CD4+ T cells respectively, are reduced in senescent macrophages [46]. A recent study in the field of tumor immunology demonstrated that in tumor - associated macrophages (TAMs), the downregulation of MHC - I expression was associated with a decreased ability to present tumor antigens to CD8+ T cells, leading to tumor immune escape [47].

The antigen - processing machinery within macrophages is also affected. Proteases involved in antigen degradation and peptide generation, such as cathepsins, show altered activity in senescent macrophages. Additionally, the transport of antigenic peptides to the endoplasmic reticulum for loading onto MHC molecules may be disrupted. This overall impairment in antigen presentation not only weakens the activation of T cells but also makes the immune response more immunosuppressive, which is often observed in aging - related diseases and cancer [48].

The diminished antigen-presenting capacity of senescent macrophages may lead to reduced efficiency of the adaptive immune response, thereby compromising the body's immune surveillance against infections and cancer

[12]. Immunosenescence is an age-associated process characterized by a decline in immune system function, in which macrophage senescence represents a critical component. Functional impairments of senescent macrophages, including defective antigen presentation, are considered to contribute to diminished vaccine responsiveness and increased susceptibility to infections in the elderly [49].

2.2.2.3 Impaired migratory capacity

Beyond impaired antigen presentation, senescent macrophages display reduced migration, a defect attributed to the downregulation of chemokine receptors (e.g., CCR2). This impairs their response to cognate ligands (e.g., CCL2), ultimately diminishing their efficient recruitment to inflammatory or injured tissues [50].

Single-cell tracking of murine peritoneal macrophages revealed a 40–60 % decrease in net path length and velocity once animals exceeded 18 months of age; this kinetic deficit preceded measurable changes in phagocytic capacity, indicating that cytoskeletal dysregulation is a primary, rather than secondary, consequence of cellular aging [51].

2.2.2.4 Impaired Metabolic Capacity

Metabolic dysfunction is a central feature of macrophage senescence and underlies many of the attendant functional deficits. Senescent macrophages frequently display mitochondrial impairment, altered NAD^+ homeostasis, disrupted oxidative phosphorylation (OXPHOS), and rewired glycolytic and lipid metabolic pathways. These changes together reduce the ability to switch between different energy sources and respond to environmental signals [52].

Mitochondrial decline in aged or senescent macrophages manifests as decreased mitochondrial membrane potential, increased mitochondrial reactive oxygen species (mtROS), and impaired electron transport chain function; these defects constrain ATP production and promote pro-senescent signaling. Consequent reductions in OXPHOS force a compensatory, but often insufficient, reliance on glycolysis or aberrant substrate use, impairing processes that require sustained energy supply such as phagocytosis, efferocytosis, and tissue-repair activities [53].

Perturbations in NAD^+ metabolism and diminished activity of NAD^+-dependent enzymes have been linked to the senescent phenotype in macrophages. NAD^+ decline impairs mitochondrial biogenesis, mitophagy, and redox balance, thereby reinforcing metabolic dysfunction and SASP secretion. Hu et al demonstrated restoration of NAD^+ levels or activation of sirtuin pathways rejuvenate macrophage metabolic function and downstream immunity [54].

In addition, senescence macrophages often show defective fatty-acid oxidation (FAO) and dysregulated cholesterol handling, which not only disrupts energy production but also promotes inflammatory lipid mediator accumulation. Such lipid metabolic shifts are particularly relevant in metabolic and cardiovascular diseases, where dysfunctional macrophage lipid metabolism accelerates pathology. Comparative serum metabolomics between young (3-month-old) and aged (21-month-old) mice demonstrated that aging was associated with dysregulation of the PPAR signaling pathway, which is known to be involved in lipid metabolism, inflammation, insulin resistance, cardiac aging and renal age-associated fibrosis was significantly suppressed during aging [55].

2.2.2.5 Downregulated autophagy level

Autophagy is an essential cellular process of self-digestion that recycles components to maintain internal balance [56]. The lifespan-extending and anti-degenerative effects of autophagy are attributed to its key protective functions. These include the clearance of toxic protein aggregates, the elimination of damaged mitochondria, and the suppression of cell death [57]. Studies have revealed that autophagy levels decreased significantly in aged mice, which was ascribed to ATG5 repression during aging. Mechanistically, ATG5 deficiency disrupts autophagic flux, driving macrophages toward a proinflammatory M1 phenotype and promoting the release of inflammatory mediators such as IL-6 and TNF-α, thereby exacerbating thioacetamide (TAA)-induced acute liver injury. Restoration of ATG5 activity in senescent bone marrow–derived macrophages (BMDMs) has been shown to reverse polarization defects, with protective effects comparable to those elicited by IL-4–induced M2 macrophages [58]. Moreover, in high glucose–induced senescent BMDMs, electron microscopy revealed a marked reduction in autophagosome formation, accompanied by a decreased LC3-II/LC3-I ratio [59]. Both STING inhibition and autophagy enhancement (rapamycin following BafA1 washout) effectively reversed $p16^{INK4a}$ overexpression and SASP secretion, thereby demonstrating that the STING–autophagy axis represents a central mechanism underlying macrophage functional decline in the hyperglycemic senescent milieu.

2.2.2.6 Altered polarization state

Macrophages exhibit remarkable plasticity, switching between pro-inflammatory (M1) and anti-inflammatory/

tissue-remodeling (M2) phenotypes depending on surrounding environment [60]. With aging, this balance is disrupted, but the direction and consequences are highly context- and tissue-dependent. In aged mouse skeletal muscle, the proportion of $LYVE1^+$ M2-like macrophages is reduced, whereas $LYVE1^-$ M1-like subsets are increased, as revealed by single-cell sequencing. Moreover, the conventional CD206 marker underestimates macrophage heterogeneity, highlighting a 'complex lineage transition' rather than a simple M1/M2 dichotomy. In aged muscle, M2-associated markers such as Lyve1 and Folr2 decline, while pro-inflammatory and senescence-related genes (S100a8, S100a9, Il1β, Spp1, Gpnmb) are upregulated. Single-cell analyses have shown a decline in reparative cell clusters and an increase in pro-inflammatory subsets. Moreover, even some M2-like macrophages have developed atypical inflammatory characteristics [31].

Functionally, these polarization changes reduce macrophage plasticity and impair timely resolution of inflammation: a net result is increased inflammaging, defective pathogen/tissue clearance, and propensity for fibrosis and metabolic dysfunction. Importantly, recent work shows that restoring specific signaling (e.g., type-2 cytokine/STAT6 pathways) or correcting metabolic deficits can partially rescue youthful polarization and improve tissue outcomes, supporting the idea that macrophage polarization in aging is a modifiable contributor to age-related disease [61].

To provide an integrated overview, the molecular hallmarks, phenotypic alterations, and functional consequences of senescent macrophages are summarized in Table 1.

Table 1. Molecular and Functional Features of Senescent Macrophages.

Category	Representative markers/pathways	Characteristic changes	Functional outcomes	Reference
Cell-cycle arrest	p53, p21CIP1, p16INK4a, Rb	Irreversible growth arrest, SA-β-Gal positivity	Loss of proliferative capacity	[62]
DNA damage response	ATM, γH2AX	Persistent DDR signaling, telomere shortening	Genomic instability, nuclear enlargement	[63]
Epigenetic remodeling	H3K9me3, heterochromatin foci	Senescence-associated heterochromatin formation	Stable transcriptional repression of cell-cycle genes	[64]
Metabolic reprogramming	mTOR, AMPK, PGC-1α, mitochondrial ROS	Shift from OXPHOS to glycolysis, impaired mitophagy	Energy exhaustion, ROS accumulation	[52]
SASP secretion	NF-κB, cGAS–STING, IL-1β, IL-6, TNF-α, CCL2	Sustained pro-inflammatory cytokine release	Chronic low-grade inflammation, paracrine senescence	[65]
Phagocytosis and efferocytosis	MerTK,	Impaired engulfment of apoptotic or necrotic cells	Accumulation of debris, secondary inflammation	[66, 67]
Antigen presentation	MHC-II, CD80/86,	Downregulation of MHC-II and costimulatory molecules	Weakened adaptive immune activation	[35, 46]
Phenotypic polarization	CD206, IL-10	Loss of M1/M2 plasticity, mixed inflammatory phenotype	Reduced resolution of inflammation	[58, 68]
Functional consequence summary		Impaired tissue repair, persistent inflammation, immune dysfunction	Contribution to metabolic and cardiovascular aging	[12]

Abbreviations:ATM, ataxia-telangiectasia mutated; DDR, DNA damage response; SA-β-Gal, senescence-associated β-galactosidase; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; IL, interleukin; TNF-α, tumor necrosis factor-alpha; CCL2, C-C motif chemokine ligand 2; MerTK, Mer tyrosine kinase; MHC-II, major histocompatibility complex class II M1/M2, classically activated/alternatively activated macrophage phenotypes.

2.3 Conceptual Delineation and Research Limitations

Throughout this review, we use the term macrophage senescence to describe a state characterized by stable cell-cycle arrest accompanied by acquisition of a senescence-associated secretory phenotype (SASP). However, we acknowledge that many studies in the macrophage aging field do not formally demonstrate all canonical features of senescence. Consequently, terms such as senescence-like, aged, dysfunctional, or metabolically stressed macrophages are frequently used to describe overlapping but not identical phenotypes. In this review, we explicitly distinguish bona fide macrophage senescence, supported by evidence of stable cell-cycle arrest and SASP, from broader age-associated macrophage phenotypes that reflect functional decline or metabolic stress without definitive senescence markers.

This conceptual overlap between dysfunctional aged phenotypes and bona fide cellular senescence in macrophages can be attributed, in significant part, to

inherent methodological constraints. A primary challenge is that tissue-resident macrophages exist predominantly in a terminally differentiated, non- or low-proliferative state in vivo. This fundamental biological feature makes it challenging to apply and definitively interpret standard assays used to confirm irreversible cell-cycle arrest, such as assays showing sustained negative results for EdU/BrdU incorporation [69]. Consequently, reliance on substitute markers becomes necessary but difficult.

Moreover, the expression of widely used senescence-associated biomarkers is not exclusive to the senescent state in macrophages. For instance, SA-β-gal activity, a hallmark lysosomal response, can be elevated in activated macrophage subsets independent of senescence. Similarly, $p16^{INK4a}$ expression can be transiently induced by inflammatory stimuli (e.g., LPS) or metabolic stress, potentially reflecting a reversible stress response rather than a permanent growth-arrest program [70]. This marker plasticity, heavily influenced by the dynamic tissue microenvironment, polarization cues, and specific pathological milieus, significantly complicates the explicit identification of senescent macrophages and underscores a critical limitation in the current literature.

3. Experimental Models and Techniques for Inducing and Detecting Macrophage Senescence

Macrophage senescence has been investigated using a variety of experimental models and methodological approaches, reflecting the heterogeneous nature of senescence-inducing stimuli and tissue contexts. In vitro, senescence is commonly induced in primary bone marrow–derived macrophages (BMDMs) or macrophage cell lines (e.g., RAW264.7, THP-1–derived macrophages) through replicative exhaustion, genotoxic stress (such as doxorubicin or etoposide), oxidative stress, or metabolic challenges including high-glucose, palmitate, or advanced glycation end product exposure [71–73]. These models summarize key features of stress-induced premature senescence and are particularly relevant for studying metabolic and age-related inflammatory conditions. In vitro, prolonged culture of primary macrophages or macrophage cell lines has been shown to induce a replicative senescence–like state, characterized by sustained upregulation of $p16^{INK4a}$ and $p21^{CIP1}$, increased SA-β-gal activity, and progressive functional decline, including reduced efferocytosis and cytokine imbalance [74].

Table 2. Experimental models for inducing macrophage senescence: methods, mechanisms, markers, and advantages.

Senescence model	Experimental method	Major mechanisms	Common senescence readouts	Advantages	References
Replicative / long-term culture	Prolonged culture of primary macrophages	Replicative exhaustion; cumulative oxidative stress; metabolic imbalance	↑ $p16^{\wedge INK4a}$, ↑ $p21^{\wedge CIP1}$, SA-β-gal activity, ↑ SASP (IL-6, TNF-α), ↓ phagocytosis/efferocytosis	Physiologically relevant; mimics gradual aging	[35, 74]
Genotoxic stress–induced senescence	Doxorubicin, etoposide, ionizing radiation	Persistent DNA damage response; ATM/ATR–p53–p21 pathway	γH2AX/53BP1 foci, ↑ p21, ↑ p16, SA-β-gal, SASP	Rapid and robust induction; high reproducibility	[78, 79]
Oxidative stress–induced senescence	H_2O_2 or ROS-inducing agents	Excess mtROS; oxidative DNA and mitochondrial damage	↑ mtROS, SA-β-gal, DDR markers, mitochondrial dysfunction	Models redox-driven aging; links to mitochondrial damage	[80–82]
Metabolic stress–induced senescence	High glucose, palmitate, AGEs, lipid overload	Metabolic rewiring; mitochondrial dysfunction; NAD^+ decline; cGAS–STING activation	↑ p16/p21, SASP, altered glycolysis/OXPHOS, ↓ efferocytosis	High disease relevance (diabetes, obesity)	[83–85]
Oncogene- or inflammatory signaling–driven senescence	Chronic NF-κB activation; prolonged TLR stimulation	Sustained inflammatory signaling; senescence-associated inflammatory loops	↑ SASP, ↑ p21, inflammatory gene signatures	Models inflammation-driven immunosenescence	[86, 87]
Naturally aged animals	Macrophage isolation from aged mice	Systemic aging milieu; cumulative DNA, mitochondrial, and metabolic damage	↑ p16/p21, SA-β-gal, SASP, functional decline	Highest physiological relevance	[35, 77, 88]

Disease-associated aging models	HFD, T2DM, atherosclerosis, fibrosis models	Chronic metabolic/inflammatory stress; immune–tissue crosstalk	Senescence markers + disease-specific dysfunction	Links senescence to pathology	[19, 89–91]

Abbreviations: ROS, reactive oxygen species; mtROS, mitochondrial ROS; DDR, DNA damage response; OXPHOS, oxidative phosphorylation; AGEs, advanced glycation end products; cGAS–STING, cyclic GMP–AMP synthase–stimulator of interferon genes; TLR, Toll-like receptor; HFD, high-fat diet; T2DM, type 2 diabetes mellitus; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; SA-β-gal, senescence-associated β-galactosidase.

In vivo macrophage senescence has been characterized in naturally aged mice, progeroid models, and disease-specific contexts such as obesity, diabetes, atherosclerosis, and fibrotic disorders. Lineage-tracing and reporter mouse models have facilitated the identification and functional interrogation of senescent macrophage populations within tissues, providing insights into their spatial distribution and contribution to age-associated pathology [12, 75, 76]. Consistent with findings from naturally aged mouse models, macrophages isolated from aged tissues exhibit increased expression of senescence markers such as $p16^{INK4a}$ and $p21^{CIP1}$, accompanied by impaired phagocytosis, altered metabolic profiles, and a pro-inflammatory secretory phenotype.

Detection of macrophage senescence relies on a combination of molecular, functional, and phenotypic indicators. Classical senescence markers include cell cycle inhibitors (p16^Ink4a, p21^Cip1), senescence-associated β-galactosidase (SA-β-gal) activity, and persistent DNA damage markers such as γH2AX and 53BP1 foci. Considering the immune-specific characteristics of macrophages, functional changes, which encompass compromised efferocytosis, shifted polarization capacity, and increased secretion of pro-inflammatory SASP factors, are now more and more acknowledged as fundamental criteria for identifying macrophage senescence. Table 2 summarizes the commonly used experimental models for inducing macrophage senescence, highlighting their induction methods, underlying mechanisms, representative senescence markers, and specific advantages in different research contexts [77].

Importantly, no single marker is sufficient; thus, a multiparametric approach integrating molecular signatures with functional assessment is recommended to accurately characterize macrophage senescence across experimental systems.

4. Core Mechanisms of Macrophage Senescence

Macrophage senescence arises from a confluence of cell-intrinsic damage responses and microenvironmental cues that reprogram function and promote chronic inflammation. Several interconnected mechanisms repeatedly emerge across experimental models and human studies. A schematic overview of the mechanisms and hallmarks of macrophage senescence is presented in Figure 1.

4.1 Persistent DNA damage response and cell-cycle arrest

Accumulation of DNA damage and activation of the p53/p21 and p16 pathways enforce a stable growth arrest in macrophages and upregulate senescence markers (p16, p21, SA-βGal), establishing the classic senescent state. This cell-intrinsic program also drives production of pro-inflammatory mediators [62].

DNA damage has been implicated as a potential driver of senescence-associated changes in macrophage through activation of the DNA damage response (DDR) pathway. In macrophages, unresolved DNA lesions trigger ATM–γH2AX signaling and enforce cell-cycle arrest via $p21^{\wedge CIP1}$ and $p16^{\wedge INK4a}$, thereby promoting senescence-associated functional decline. Defective DNA repair in macrophages, including impaired DDR components, results in persistent DNA damage and amplifies pro-inflammatory outputs characteristic of the senescence-associated secretory phenotype [92]. Moreover, metabolic and inflammatory stress further exacerbate DNA damage accumulation in aging macrophages, linking DDR dysfunction to immunometabolic decline [93]. Recent evidence demonstrates that IL-4/STAT6 signaling enhances DNA repair capacity in macrophages and protects against senescence, highlighting DDR regulation as a key determinant of macrophage aging [61].

4.2 Senescence-associated secretory phenotype (SASP)

Senescent macrophages and neighboring senescent stromal cells secrete a complex SASP (cytokines, chemokines, proteases, growth factors) that (a) reinforces autocrine senescence, (b) skews macrophage polarization, and (c) remodels the tissue microenvironment to sustain inflammaging. While SASP is primarily an output of senescent cells, accumulating evidence suggests that SASP-rich milieus can reinforce and stabilize senescent states in macrophages under chronic inflammatory conditions. Chronic exposure to SASP components sustains inflammatory signaling and oxidative stress in macrophages, exacerbating DNA damage, impairing autophagy, and promoting cell-cycle inhibitory pathways that are hallmarks of macrophage senescence[13, 35, 94]

In vitro and in vivo studies indicate that senescent stromal cells can attract and modulate macrophages via SASP factors, which coincides with upregulation of macrophage senescence markers such as p16^INK4a and p21^CIP1 and enhanced pro-inflammatory profiles [92]. Moreover, SASP from neighboring senescent cells has been reported to alter macrophage behavior and contribute to persistent low-grade inflammation that is characteristic of immunosenescence and aging tissues [95, 96]. Current evidence is consistent with a framework in which SASP functions as a permissive and reinforcing factor that can potentiate macrophage senescence in concert with metabolic, genotoxic, or innate immune stress, thereby contributing to chronic inflammation and age-related immune dysfunction.

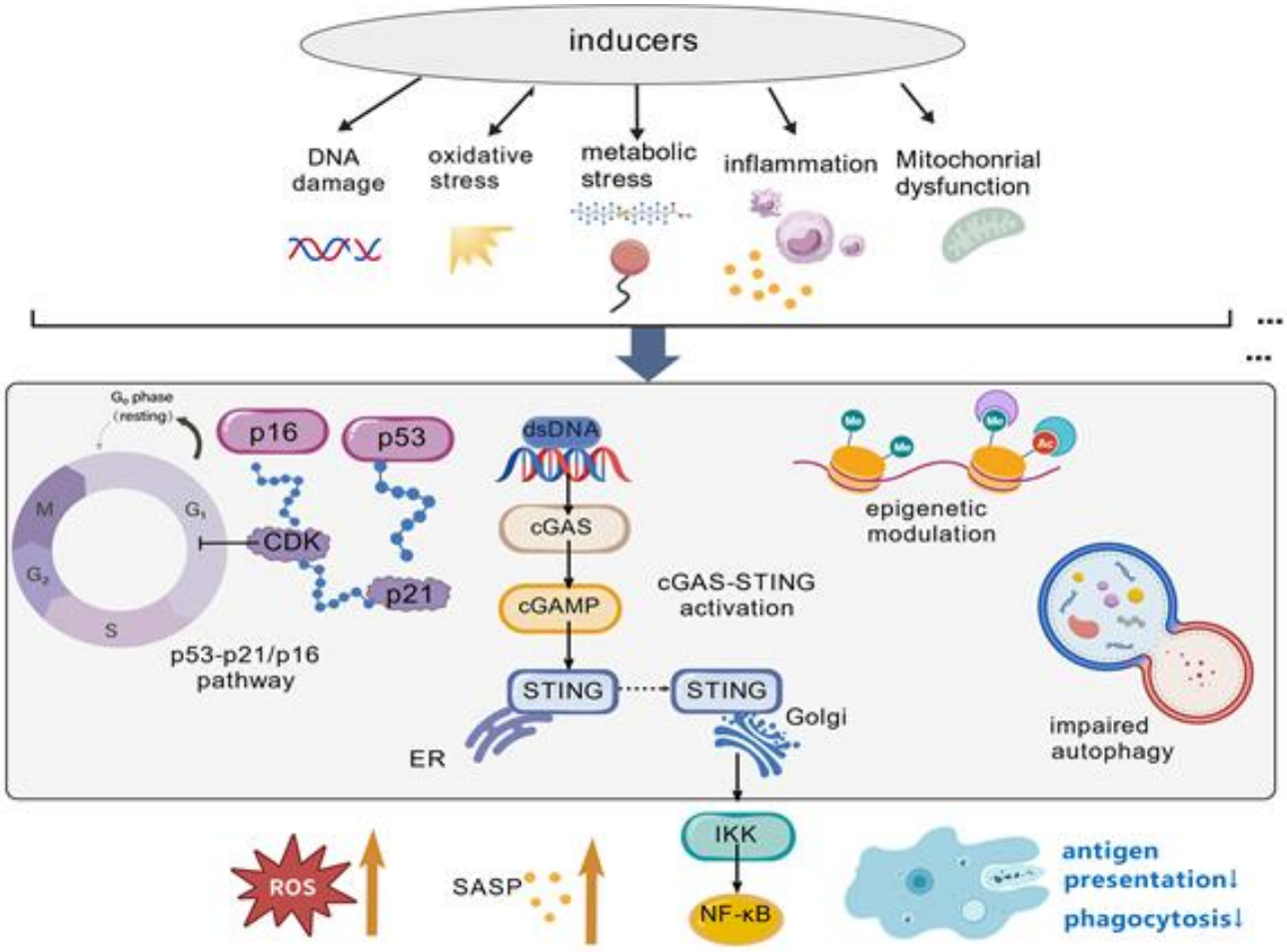

Figure 1. Overview of macrophage senescence: triggers, markers, and functional outcomes. Senescent macrophages arise in response to multiple cellular stressors, including DNA damage, oxidative stress, metabolic stress, inflammation, and mitochondrial dysfunction. These stimuli activate canonical signaling cascades such as the p53–p21/p16 cell-cycle arrest pathway, cGAS–STING–NF-κB axis leading to the senescence-associated secretory phenotype (SASP), epigenetic modulation (e.g. acetylation), and impaired autophagy/mitophagy. Together, these pathways enforce the senescent phenotype and result in functional decline, including reduced phagocytic capacity and diminished antigen presentation, accompanied by increased secretion of SASP cytokines and excessive reactive oxygen species (ROS) production. These changes collectively drive chronic inflammation and contribute to age-related tissue dysfunction.

4.3 Mitochondrial dysfunction and metabolic rewiring

Mitochondrial dysfunction and metabolic rewiring constitute another core axis driving macrophage senescence and sustaining its functional consequences. Macrophages are highly metabolically plastic cells, and their immune functions—including phagocytosis, efferocytosis, cytokine production, and polarization—are tightly coupled to mitochondrial integrity and metabolic state [97, 98]. During aging or chronic metabolic stress, senescent macrophages exhibit profound mitochondrial abnormalities, including loss of mitochondrial membrane potential, impaired electron transport chain activity, reduced oxidative phosphorylation (OXPHOS), and

excessive production of mitochondrial reactive oxygen species (mtROS) [62].

Mitochondrial damage acts as both a trigger and an amplifier of macrophage senescence. Accumulation of dysfunctional mitochondria promotes oxidative DNA damage and reinforces DDR signaling, while mtROS directly activate pro-senescent pathways such as p53–p21 and p16–Rb [81]. In parallel, impaired mitophagy leads to the cytosolic release of mitochondrial DNA, which serves as a potent activator of the cGAS–STING pathway, linking mitochondrial dysfunction to inflammatory SASP production. This mitochondria–cGAS–STING axis has emerged as a critical mechanism by which metabolic stress is translated into innate immune activation and stable senescence programs in macrophages [99].

4.4 Epigenetic remodelling and loss of plasticity

Emerging evidence indicates that epigenetic reprogramming is both a cause and a stabilizer of macrophage senescence. Age-related alterations in DNA methylation patterns, histone post-translational modifications, and chromatin accessibility bring about changes in transcriptional programs. These programs govern cell cycle progression, inflammatory responses, and phenotypic adaptability, thereby ultimately increasing the likelihood of macrophages entering a senescent state.

Both global loss and locus-specific remodeling of DNA methylation, together with reduced maintenance methyltransferase activity, are closely associated with senescence phenotypes. These epigenetic alterations can promote cell cycle arrest and SASP expression across multiple cell types, positioning DNA methylation dysregulation as an upstream driver of the senescence program [100]. Recent studies have revealed that Epigenetic mechanisms, including DNA methylation and histone modifications (such as acetylation and methylation), play a central role in regulating the activation programs of macrophages and microglia. With advancing age, these epigenetic marks undergo alterations, leading to a decline in macrophage responsiveness to tissue injury or pathogen-derived stimuli. Qi et al. demonstrated that hypomethylation of the CLEC5A gene results in its upregulated expression in macrophages. This, in turn, activates the NF-κB pathway, thereby enhancing inflammatory responses, promoting migration and lipid accumulation, while inhibiting apoptosis. Such epigenetic dysregulation accelerates macrophage dysfunction and the progression of atherosclerosis, representing a potential mechanism underlying aging-associated cardiovascular diseases [101]. Histone modifications and chromatin remodeling are likewise pivotal. Loss of repressive marks (e.g., H3K9me2/3 via reduced SUV39H1) and the accumulation of permissive acetylation modifications lead to chromatin opening at inflammatory and senescence-related gene loci. This facilitates sustained transcription of SASP genes and reduces the macrophages' ability to respond to reparative signals. These mechanisms have been observed across various aging tissues and are associated with innate immune system dysregulation [102].

Collectively, these findings support a model in which age-associated epigenetic drift, encompassing alterations in DNA methylation, histone remodeling, noncoding RNA activity, and chromatin accessibility changes. This drift operates upstream of macrophage senescence, not only promoting this process but also diminishing cellular plasticity and sustaining chronic, low-grade inflammation, known as inflammaging. Therapeutically, epigenetic modulators (DNMT or HDAC inhibitors, chromatin-targeting small molecules) and interventions that restore metabolic cofactors show promise to reset macrophage chromatin and ameliorate senescent phenotypes, although tissue specificity and off-target risk require careful evaluation [103].

These phenotypic and metabolic alterations profoundly shape the functional roles of macrophages in both tissue homeostasis and pathological aging, as discussed in the following sections.

5. Macrophage Senescence and Associated Diseases

Although macrophage senescence has been investigated across diverse disease contexts, recent findings have begun to imply that shared core mechanisms underlie its contribution to metabolic disorders, cancer, fibrosis, and cardiovascular disease. In the following sections, we highlight both common and disease-specific features of senescent macrophages, with a focus on metabolic rewiring, impaired immune surveillance, altered intercellular communication, and SASP-driven tissue dysfunction.

5.1 Atherosclerosis

In atherosclerosis, macrophage senescence develops within a lipid-rich and chronically inflamed vascular microenvironment. Rather than reflecting a distinct senescence program, senescent macrophages in atherosclerotic lesions largely exhibit conserved hallmarks of cellular senescence, which are subsequently shaped by sustained lipid accumulation and oxidative stress [85].

A defining functional consequence of macrophage senescence in atherosclerosis is the impairment of phagocytic and efferocytic capacity [104]. Senescent macrophages display reduced clearance of apoptotic cells

and lipid debris, promoting the expansion of necrotic cores within plaques. In parallel, defects in cholesterol handling and efflux further favor foam cell persistence, reinforcing lesion progression [89].

Persistent SASP signaling from senescent macrophages amplifies local vascular inflammation and matrix-degrading activity, thereby contributing to plaque instability [20]. Importantly, these effects arise from the chronic persistence of dysfunctional macrophages rather than from acute inflammatory activation, underscoring the pathological relevance of senescence in advanced lesions.

Critically, while impaired efferocytosis is a common hallmark of senescent macrophages across diseases, in atherosclerosis, this specific defect directly fuels the expansion of necrotic cores and drives plaque destabilization. This sets vascular pathology apart from metabolic or tumor-related conditions.

5.2 Malignant tumor

Within the tumor microenvironment (TME), senescent macrophages exemplify the pathological hijacking of a normally reparative cell state. Unlike in atherosclerosis or fibrosis where SASP drives destructive inflammation, in cancer, the SASP from senescent tumor-associated macrophages (TAMs) is strategically rewired to establish a dominantly immunosuppressive and tumor-supportive niche [30, 46]. This involves the coordinated secretion of factors (e.g., IL-10, TGF-β) that recruit and activate regulatory T cells and myeloid-derived suppressor cells, while directly suppressing cytotoxic $CD8^+$ T cell function. This active suppression of immune surveillance contrasts with the impaired antigen presentation seen in aged macrophages, representing a more active, micro-environment-directed form of immune dysfunction [13, 30].

At the same time, this senescent microenvironment drives tumor advancement by hijacking tissue-regenerative processes. SASP provides potent pro-angiogenic signals (e.g., VEGF) and matrix-remodeling enzymes (MMPs), mirroring the wound-healing functions of transiently senescent cells but in a persistent, dysregulated manner. Furthermore, factors like IL-6 and IL-8 directly stimulate tumor cell proliferation, stemness, and therapy resistance [95]. Thus, within the tumor microenvironment, senescent macrophages subvert their intrinsic role in wound healing. Instead, they support the “never-healing wound” that characterizes tumor growth. This function is distinct from, yet mechanistically analogous to, their role in sustaining unresolved inflammation during fibrosis [105].

The net effect is the stabilization of a pathological environment that promotes tumor growth and metastasis. This highlights a darker, context-dependent facet of macrophage senescence: when occurring within a pre-malignant or malignant setting, it can be co-opted to foster disease progression. Therefore, therapeutic strategies must not only identify senescent macrophages but also disrupt this specific, tumor-supportive programming, distinguishing it from their potentially beneficial roles in other contexts.

5.3 Pulmonary Fibrosis and Fibrotic Lung Diseases

In pulmonary fibrosis, macrophage senescence arises within a milieu of chronic epithelial injury and dysregulated repair. Instead of activating a specific fibrotic program, these cells exhibit the conserved features of senescence, such as cell cycle arrest and SASP secretion. Their functional output is strongly shaped by the pro-fibrotic tissue microenvironment[106, 107].

A central pathological consequence is their failure to appropriately terminate the tissue repair program. While macrophages are indispensable for the normal resolution of injury, their senescent counterparts display severely impaired efferocytosis, often due to dysregulation of receptors like MERTK, and sustained secretion of pro-fibrotic mediators [108]. This dysfunctional state perpetuates the activation of fibroblasts and myofibroblasts, directly fueling fibrotic matrix deposition. Thus, the role of senescent macrophages in fibrosis exemplifies a critical deviation from their function in other disease contexts: whereas in metabolic diseases or cancer they primarily amplify systemic inflammation or foster immune suppression, in the lung their dysfunction is canalized toward irreversible tissue remodeling and loss of organ compliance, highlighting a context-dependent disease outcome stemming from a shared cellular phenomenon.

5.4 Metabolic diseases

In metabolic diseases such as obesity and type 2 diabetes mellitus, macrophage senescence develops in response to persistent nutrient excess and metabolic stress. Unlike atherosclerosis or fibrotic lung disease, where senescent macrophages contribute to localized structural damage, in metabolic disorders their dysfunction primarily amplifies systemic metabolic imbalance rather than tissue-restricted pathology [55].

Functionally, senescent macrophages in metabolic tissues demonstrate a decline in effective clearance of apoptotic cells and other debris, which contributes to the persistence of cellular stress and chronic inflammation. Evidence from aging and disease contexts indicates that advanced age and metabolic stress are associated with downregulation of efferocytosis-related pathways and impaired apoptotic cell removal by macrophages, thereby disrupting tissue homeostasis and promoting metabolic

dysfunction across multiple models of obesity-related disorders [109]. In addition to efferocytosis defects, metabolic disease–associated macrophages can exhibit altered intracellular signaling and nutrient handling that further constrain their functional capacity, ultimately undermining their ability to restore adipose and hepatic tissue homeostasis in the face of sustained nutrient overload [110].

At the organismal level, these functional impairments in macrophages are linked to systemic metabolic dysregulation, including insulin resistance and dyslipidemia [76]. In obese adipose tissue, macrophage dysfunction correlates with adipose remodeling and impaired metabolic flexibility, as reported in recent experimental studies demonstrating age-linked declines in key adipose tissue macrophage functions that are essential for maintaining glucose and lipid homeostasis [111].

5.5 Neurodegenerative diseases

Neurodegenerative diseases (NDDs) vividly illustrate the disastrous consequence of failed homeostasis in a post-mitotic organ. Here, macrophage senescence, primarily in microglia, transforms these crucial keeper into drivers of pathology. Their dysfunction is centrally triggered by the very entities they are supposed to clear: misfolded proteins like Aβ and tau act as persistent stressors, inducing a senescent state characterized by a detrimental shift in function [39]. Remarkably, this senescent phenotype can spread; recent work reveals that senescent-like border-associated macrophages (BAMs) propagate aging signals to microglia via migrasomes, creating a paracrine senescence cascade that amplifies dysfunction across brain immune compartments [39].

The core pathology lies in the sequential loss of homeostatic functions. First, phagocytic capacity collapses, impairing the clearance of protein aggregates and synaptic debris [67]. Second, their secretory profile becomes neurotoxic, shifting from a monitored response to a persistent senescence-associated secretory phenotype (SASP) that may include factors like CCL11, which actively inhibits remyelination [112]. This profile is distinct from the wound-healing signals co-opted in cancer or the pro-fibrotic signals driving pulmonary fibrosis, representing instead a maladaptive program directly detrimental to neural maintenance. As a result, the brain gradually loses its ability to withstand damage, resulting in permanent loss of synapses, impaired repair mechanisms, and eventual neuronal death.

Thus, in NDDs, senescent macrophages illustrate the concept of "a surveillance system gone awry." Unlike in atherosclerosis where dysfunction leads to local plaque instability, or in cancer where it remodels the microenvironment for tumor growth, here it directly enables the propagation of toxicity and the dismantling of neural networks. Therapeutic strategies aimed at removing these senescent cells or inhibiting their harmful communication (e.g., targeting migrasome formation) are therefore not merely anti-inflammatory but aim to restore the essential custodial integrity of the brain's immune system, offering a unifying approach across various proteinopathies.

Senescent macrophages exhibit distinct characteristic features and functional consequences across different organs (Table 3).

6. Fate and clearance of senescent macrophages

6.1 Physiological Clearance and Immune Surveillance

The persistence of senescent macrophages is a key driver of chronic inflammation and age-related pathologies. However, these cells are not permanent, and their ultimate fate and clearance from tissues are crucial for resolving inflammation and restoring tissue homeostasis. The removal of senescent macrophages is a dynamic process involving physiological clearance mechanisms, programmed cell death, tissue renewal, and exogenous interventions.

In healthy organisms or during the resolution phase following acute injury, senescent macrophages can be efficiently eliminated through immune surveillance mechanisms. Competent immune cells, such as natural killer (NK) cells and non-senescent macrophages, are capable of recognizing and clearing senescent cells [113]. This process relies on the upregulation of "eat-me" signals (e.g., calreticulin), and the downregulation of "don't-eat-me" signals (e.g., CD47) on the surface of senescent cells [114, 115]. Meanwhile, chemokines secreted within the SASP recruit NK cells, which mediate the killing of senescent cells through recognition of ligands for the activating receptor NKG2D [116]. Such immune clearance is particularly crucial for maintaining tissue homeostasis in highly regenerative organs such as the heart and liver, thereby preventing the excessive accumulation of senescent macrophages and preserving normal organ function.

6.2 Programmed Cell Death and Passive Clearance

When senescent macrophages accumulate beyond a certain threshold or experience extreme metabolic stress, they can activate intrinsic programmed cell death pathways [117].

Sustained activation of p53 serves as a key molecular switch that determines whether a cell undergoes senescence or apoptosis under stress conditions [23]. In particular, mitochondrial dysfunction leads to ATP

depletion and excessive production of reactive oxygen species (ROS), both of which promote apoptotic signaling cascades in senescent macrophages [82, 118]. Moreover, dysregulated autophagic flux can trigger autophagic cell death, indicating that autophagy plays a dual role in maintaining cellular homeostasis and mediating cell death when excessively activated [119]. This passive clearance mechanism acts as a background cleansing process during natural aging; although its efficiency is relatively low, it continuously contributes to the turnover and renewal of the senescent macrophage population, thereby maintaining tissue homeostasis [120, 121].

6.3 Tissue Renewal and Monocyte-Driven Replacement

In tissues with substantial regenerative capacity, such as the lungs, liver, and vascular walls, senescent macrophages can be replenished through the repopulation of the tissue macrophage niche [122, 123]. Circulating monocytes are recruited into the tissue microenvironment in response to chemokine signals, where they differentiate into new tissue-resident macrophages and progressively replace the aged or senescent macrophage pool [123]. This "replacement of the old with the new" is particularly evident following acute inflammation or tissue injury during the repair phase, as described by Sierro et al [124]. The efficiency of this replacement process serves as a critical determinant of a tissue's self-repair capacity and is markedly impaired in aged or metabolically compromised environments. The clearance of senescent macrophages is illustrated in Figure 2.

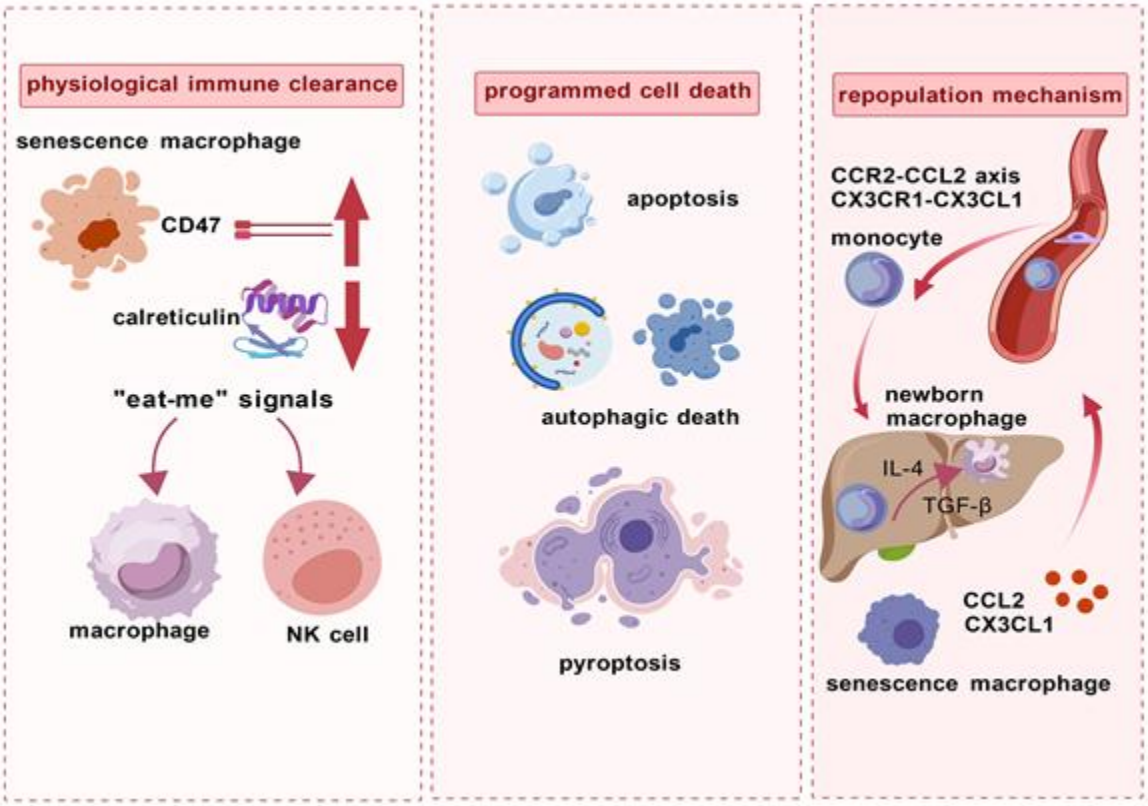

Figure 2. Clearance and repopulation of senescent macrophages. Senescent macrophages are cleared through three mechanisms. (Left) Physiological immune clearance: NK cells and macrophages recognize "eat-me" signals (calreticulin ↑, CD47 ↓) to remove senescent cells. (Middle) Programmed cell death: apoptosis, autophagic death, and pyroptosis contribute to passive elimination under stress. (Right) Repopulation mechanism: circulating monocytes are recruited via the CCR2–CCL2 and CX3CR1–CX3CL1 axes and differentiate into new macrophages under IL-4 and TGF-β signaling to restore tissue macrophage homeostasis.

7. Protective roles of macrophage senescence

Although senescent cells are often regarded as pathogenic drivers, emerging evidence indicates that macrophage senescence can exert protective and reparative functions in specific contexts. By halting the sustained secretion of pro-inflammatory cytokines such as TNF-α and IL-6 after pathogen clearance, cellular senescence acts as a braking mechanism to prevent excessive inflammation and collateral tissue damage, thereby contributing to the resolution of immune responses and tissue homeostasis [125].

Senescent macrophages also contribute to tissue repair through their SASP. In several wound-healing models, transiently senescent cells secrete specific growth factors, such as PDGF-AA, which recruit and induce the orderly differentiation of fibroblasts and myofibroblasts, thereby promoting wound contraction and extracellular matrix remodeling to accelerate healing. Notably, the early removal of senescent cells delays wound closure, whereas exogenous supplementation with PDGF-AA can rescue this defect, underscoring the essential role of SASP in orchestrating tissue repair [78].

In addition, senescent macrophages can suppress excessive fibrogenesis in certain contexts. The underlying mechanism may involve the spatiotemporally controlled release of pro-resolving factors (such as specific ratios of IL-10 and TGF-β) and matrix-degrading enzymes during the repair phase. This helps restrain persistent fibroblast activation and aberrant collagen deposition, thereby preventing pathological scarring—illustrating how transient and controlled senescence can support constructive tissue remodeling. Several reviews and modeling studies emphasize that the composition and duration of the SASP determine its dual role in promoting either repair or fibrosis [126].

Finally, from an anticancer perspective, cellular senescence serves as a crucial tumor-suppressive mechanism. By inducing permanent cell-cycle arrest in cells subjected to oncogenic stress, senescence prevents the proliferation of potentially malignant cells. Similarly, when macrophages themselves face proliferative abnormalities or genomic insults, entry into senescence can block pathological expansion, providing an additional barrier against tumorigenesis. The role of senescence as an intrinsic anticancer defense has been extensively documented in both seminal studies and comprehensive reviews. For example, a suppressive axis (CD73) in senescent TME, also shows that blocking CD73 relieves immunosuppression and enhances $CD8^+$T cell-mediated anti-tumor efficacy. This indicates that components of SASP-induced macrophage reprogramming are "druggable" and can shift the balance toward anti-tumor immunity [127].

Thus, macrophage senescence is not unidimensionally harmful: when the senescent state is induced in tumor cells (or via therapy), macrophages can partake in a cascade that leads to immune surveillance, enhanced antigen presentation, and tumor rejection. However, these beneficial effects are context-dependent. They require proper antigenicity, an immune competent environment, timely clearance of senescent cells, or modulation of their SASP. Conversely, these positive outcomes may be counteracted if macrophage senescence becomes chronic, uncontrolled, or heavily immunosuppressive.

8. Pathogenic consequences of macrophage senescence

Cellular senescence is widely regarded as a protective barrier against malignant transformation. However, when senescence persists, particularly in macrophages, it can disrupt tissue homeostasis and promote disease progression. Senescent macrophages acquire the SASP, characterized by the sustained release of pro-inflammatory cytokines, chemokines, growth factors, and proteases. This chronic pro-inflammatory milieu promotes "inflammaging" and contributes to the pathogenesis of multiple age-related diseases. For example, studies have shown that senescent macrophages in aged tissues secrete high levels of IL-1β, IL-6, and TNF-α, which amplify sterile inflammation and exacerbate tissue injury [128, 29].

One major detrimental outcome of macrophage senescence is the promotion of tissue fibrosis. Senescent macrophages release TGF-β, CCL2, and matrix metalloproteinases (MMPs), which activate fibroblasts and enhance extracellular matrix (ECM) deposition. In lung fibrosis and radiation injury models, clearance of senescent cells attenuated fibrotic remodeling, directly linking macrophage senescence to pathological ECM accumulation[129, 130]. Similarly, in metabolic disease, obesity-induced senescent macrophages in adipose tissue promote chronic inflammation, fibroblast activation, and insulin resistance, thereby aggravating type 2 diabetes progression [131]. In obese human subjects, visceral white adipose tissue (vWAT) harbors a substantial population of senescent cells, as indicated by SA-β-Gal positivity, many of which are $CD68^+$ macrophages. The abundance of these senescent macrophages correlates positively with body mass index (BMI) and insulin resistance, as measured by the HOMA-IR index. In vitro, co-culture experiments with high-glucose–treated macrophages and adipocytes demonstrate that senescent macrophages exacerbate adipocyte inflammation and impair insulin signaling, highlighting their pathogenic role in metabolic dysregulation [132]

Furthermore, senescent macrophages may contribute to tumor progression. Although senescence in epithelial or stromal cells can serve as a tumor-suppressive barrier, macrophage-derived SASP may paradoxically create a tumor-supportive microenvironment. Persistent secretion of IL-6, IL-8, and VEGF enhances angiogenesis, recruits immunosuppressive cells, and supports cancer stemness, thus favoring tumor growth and metastasis [25, 133–135]. Indeed, the accumulation of senescent immune cells in the tumor microenvironment has been associated with impaired antitumor immunity and worse clinical outcomes [136].

Finally, the detrimental impacts of macrophage senescence extend to impaired regenerative capacity. In

aged tissues, senescent macrophages display reduced phagocytosis of apoptotic cells and defective antigen presentation, leading to inefficient resolution of inflammation and impaired tissue repair [137]. This persistent dysfunction not only accelerates age-related tissue degeneration but also perpetuates a cycle of chronic inflammation and impaired healing.

Taken together, these observations highlight the "dark side" of macrophage senescence, where the prolonged presence of senescent macrophages and their SASP can shift from a protective, transient state to a chronic, harmful driver of age-related pathologies.

The functional consequences of macrophage senescence are highly context-dependent. Under physiological or transient stress conditions, senescent macrophages may exert protective roles by limiting excessive inflammation, promoting resolution, and facilitating tissue repair. However, under chronic metabolic or aging-related stress, they often shift toward detrimental functions, driving persistent inflammation, fibrosis, and impaired regeneration. To summarize these dual effects across different organs and disease contexts, Table 4 outlines the contrasting "friend" and "foe" roles of macrophage senescence in tissue homeostasis and pathology.

9. Future therapeutic strategies and challenges

Macrophage senescence represents a critical pathophysiological process in organismal aging and age-related diseases. Its effects are not inherently beneficial or detrimental but instead exemplify a classic "double-edged sword," with outcomes that are highly dependent on the cellular context, magnitude, and duration of senescence. Given this duality, future therapeutic strategies should aim for precise modulation, selectively eliminating or neutralizing deleterious senescent macrophages while preserving or enhancing their beneficial functions. The principal approaches can be categorized into the following strategies.

9.1 macrophage-targeted senolysis

A promising alternative to systemic senolysis is the precise identification and elimination of macrophages bearing the senescent phenotype, thereby eliminating the source of detrimental SASP at its origin and promoting the restoration of tissue homeostasis. In pioneering work, the team led by Amor developed a chimeric antigen receptor (CAR) T-cell therapy that targets the senescence-associated protein uPAR. This uPAR-CAR-T approach has demonstrated efficacy in animal models by clearing senescent cells and ameliorating metabolic and tissue dysfunction. Building on this foundation, future efforts could focus on engineering CAR-equipped immune cells to recognize surface antigens unique to senescent macrophages, enabling the targeted removal of these cells within pathological niches [138].

This approach requires the identification and validation of surface targets specific to senescent macrophages to avoid the inadvertent elimination of transiently senescent cells that may be beneficial during tissue repair. In addition, local delivery and careful consideration of the therapeutic window are essential to minimize systemic toxicity [139].

9.2 SASP modulation

This strategy centers on reprogramming the harmful SASP of senescent macrophages to alleviate its pathological effects without cell killing. Evidence demonstrates that JAK pathway activation in aged tissues drives age-related dysfunction, and that JAK inhibition suppresses SASP and ameliorates frailty in mouse models, providing a mechanistic basis for this therapeutic approach [65]. Additionally, both Metformin and Rapamycin have been identified as potent suppressors of the SASP, with efficacy confirmed in diverse model systems [24]. SASP-targeted interventions can be applied systemically and over prolonged periods with manageable side effects; however, given the complexity of SASP and its dynamic modulation by the microenvironment, multi-target or combination strategies are more likely to achieve therapeutic success [140].

9.3 checkpoint & macrophage reprogramming

This strategy enhances the phagocytic clearance of senescent or tumor cells by macrophages and restores anti-tumor immunity through the blockade of immunosuppressive pathways, such as those mediated by CD47, CD73/adenosine, or PD-L1. Alternatively, it directly reprograms macrophages toward a pro-clearance, low-SASP resolving phenotype. Current research is particularly focused on employing CSF1R inhibitors, TLR agonists, or STING agonists to reprogram tumor-associated macrophages (TAMs) and augment their phagocytic and anti-tumor functions. The combination of these approaches with senolytic agents or SASP inhibitors may yield interactive therapeutic effects [141].

While immune checkpoint blockade, a strategy with substantial clinical validation in oncology, can directly facilitate the clearance of senescent cells or remodel the tumor microenvironment (TME) by restoring macrophage function, careful consideration must be given to potential immune-related adverse events and the inherent heterogeneity of the TME [24].

Despite encouraging preclinical progress, several challenges hinder the translation of macrophage

senescence-targeted therapies into clinical practice. First, heterogeneity remains a major obstacle, as senescent macrophages display distinct phenotypes depending on the tissue microenvironment and disease context, complicating precise therapeutic targeting [1]. Second, there is an on-target/off-target dilemma: while clearance of senescent macrophages may alleviate chronic inflammation, senescence also exerts beneficial effects such as limiting tissue damage and promoting repair. Thus, random elimination could impair homeostatic functions [142]. Third, the lack of reliable biomarkers hampers accurate identification and selective targeting of senescent macrophages. Moreover, a significant translational gap exists, as most evidence is derived from animal studies, whereas clinical data in humans remain scarce and the safety of senolytic agents is not yet fully established [143]. Finally, the temporal dynamics of senescence pose another layer of complexity, since its functional impact may differ across disease stages, with early versus late interventions potentially yielding divergent outcomes [125]. Collectively, these limitations highlight the need for refined therapeutic approaches and robust clinical validation before macrophage senescence-targeted interventions can be safely applied in patients.

In conclusion, the future therapeutic paradigm is expected to integrate senolytic strategies, immune reprogramming, and metabolic modulation (Table 5). Utilizing targeted delivery systems and patient stratification via biomarkers, this integrated approach will enable the selective intervention of macrophage senescence, thereby offering novel therapeutic avenues for a range of conditions, including metabolic diseases, cancer, and cardiovascular aging disorders.

10. Conclusion

The senescence of macrophages is now recognized as a pivotal link between the biology of aging, immune dysregulation, and numerous age-related diseases. Distinct from uniform functional decline, senescent macrophages exhibit pronounced context dependency, contributing either to transient inflammation resolution and tissue remodeling or, when persistent, to chronic inflammation and tissue dysfunction across organs. This dual nature emphasizes both the physiological relevance and pathological potential of macrophage senescence.

Despite rapid progress, several fundamental challenges remain unresolved. A major limitation lies in the identification of bona fide senescent macrophages. Widely used fundamental markers, such as p16$^{\wedge INK4a}$ and SA-β-gal, lack specificity in macrophages, where overlapping expression can occur in activated or metabolically stressed states. Moreover, many studies infer senescence based on partial molecular or functional changes without demonstrating stable cell-cycle arrest accompanied by a defined SASP, increasing the risk of confusing true senescence with senescence-like or age-associated dysfunction [1, 144].

Compared with senescent fibroblasts or epithelial cells, the study of macrophage senescence presents additional conceptual and technical challenges. Macrophages are terminally differentiated, highly plastic, and profoundly shaped by tissue microenvironments, complicating the application of classical senescence criteria and limiting the generalizability of existing models. These features underscore macrophage-specific frameworks that integrate functional, transcriptional, and contextual evidence rather than reliance on single markers or pathways.

Importantly, translating macrophage-targeted senescence interventions into clinical applications remains particularly challenging. While senolytic and senomorphic strategies have shown promise in preclinical models of aging and fibrosis, their application to macrophages raises unique safety concerns. Non-selective elimination of senescent macrophages may disrupt host defense, impair tissue homeostasis, or exacerbate susceptibility to infection. In addition, current senescence-modulating agents generally lack cell-type specificity, and their tissue distribution, delivery efficiency, and long-term effects on immune function remain insufficiently characterized [129, 145]. Furthermore, the functional impact of senescent macrophages is highly disease- and stage-dependent, highlighting the need to carefully define therapeutic windows and patient stratification strategies.

Overall, progress in this field will depend on moving beyond descriptive associations toward rigorously defined, macrophage-centered concepts of senescence. Improved biomarkers with functional validation and context-aware therapeutic strategies will be essential for harnessing macrophage senescence as a viable target in aging and age-related diseases.

AI-Assisted Technology Statement

AI-based tools were used solely for language editing to improve grammar and readability. Literature selection, critical evaluation, synthesis of evidence, and all scientific interpretations were performed by the authors.

Consent for publication

All authors approved the manuscript for publication.

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

Yongjun Wang and Liyao Fu: Conceptualization and methodology. Xunxi Deng, Zhiyi Yin: Data curation. Xunxi Deng wrote the original draft. Shi Tai, and Liyao Fu: Writing, reviewing, and editing. Shi Tai and Liyao Fu acquired funding.

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