

Perspective

The Role of Macrophage Senescence in Coronary Artery Disease: Underlying Mechanisms and Therapeutic Targets

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ABSTRACT: Coronary artery disease (CAD) remains a leading cause of mortality worldwide, and its prevalence markedly increases with age. Atherosclerosis, the underlying pathological hallmark of CAD, is characterized by plaque deposition within the coronary artery walls, leading to vessel narrowing or occlusion, ultimately resulting in myocardial ischemia or necrosis. Macrophage senescence, a key component of inflammaging, contributes to both the initiation and progression of CAD through multiple interacting mechanisms. This review systematically outlines the molecular and functional characteristics of macrophage senescence, focuses on its pathological mechanisms in CAD, and provides an in-depth exploration of therapeutic strategies targeting macrophage senescence for CAD management. It aims to offer a comprehensive overview of the relationship between macrophage senescence and CAD and provides emerging treatment perspectives.

Keywords: macrophage senescence, coronary artery disease, atherosclerosis, myocardial infarction, inflammation

1. Introduction

Coronary artery disease (CAD) encompasses a group of disorders characterized by myocardial ischemia, hypoxia, or necrosis caused by coronary artery atherosclerosis or functional abnormalities. CAD is the most prevalent cardiovascular disease, and is identified by the World Health Organization as the leading cause of death globally [1]. While advancements in diagnostic and therapeutic techniques have significantly improved the survival rates of patients with acute coronary syndrome, the prevalence of refractory angina and advanced CAD continues to rise, particularly among aging populations [2]. The underlying pathological mechanism of CAD is the formation of atherosclerotic plaques within coronary arteries, a process conclusively linked to chronic inflammation [3]. Macrophages play a pivotal role in the pathogenesis of CAD. They engulf oxidized low-density lipoproteins to transform into foam cells and secrete pro-inflammatory

factors and matrix metalloproteinases (MMPs), which directly contribute to plaque instability. Furthermore, an imbalance in macrophage polarization states regulates inflammation and repair processes, with macrophage dysfunction directly associated with plaque rupture and the onset of acute coronary syndromes [4].

Notably, under the influence of aging or pathological factors, macrophages gradually exhibit features of senescence, which are considered closely related to the initiation and progression of CAD [5]. Macrophage senescence is characterized by multifaceted dysfunctions, including reduced proliferation capacity, diminished phagocytic ability, abnormal energy metabolism, significantly increased secretion of inflammatory factors, and impaired intercellular communication. Collectively, these alterations drive the formation of an inflammatory microenvironment. By remodeling cytokine networks and disrupting immune signaling pathways, they accelerate tissue damage and impair repair processes [6].

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Macrophage senescence, accompanied by chronic low-grade inflammation, has emerged as a significant driver of various age-related diseases, including CAD [7]. Specifically, within the atherosclerotic process, macrophage senescence correlates with the excessive secretion of pro-inflammatory factors. These factors promote vascular endothelial dysfunction by activating downstream signaling pathways, thereby accelerating plaque progression [8]. Macrophage senescence exacerbates inflammatory responses and may also expand lesion areas and increase plaque rupture risk by influencing lipid metabolism and plaque stability [9]. In myocardial infarction (MI), macrophage senescence may enlarge the infarct area and worsen cardiac function by amplifying pyroptosis and inflammatory cascades. Additionally, macrophage senescence significantly affects post-MI repair [10]. Although the importance of macrophage senescence in CAD is widely acknowledged, its precise mechanisms of action remain unclear. Therefore, in-depth investigation into the regulatory mechanisms of macrophage senescence and its role in CAD pathophysiology holds promise for providing a theoretical foundation for developing novel anti-inflammatory or anti-senescence therapies.

Although several high-quality reviews have systematically summarized the general molecular features of macrophage senescence and its broad involvement in cardiovascular diseases [11, 12], the existing literature has largely emphasized the pro-inflammatory mechanisms of senescence. As a result, the dynamic evolution of macrophage senescence and its stage-specific functions throughout the complex course of CAD remain insufficiently characterized. This review focuses on the progressive changes and stage-dependent functions of macrophage senescence across different phases of CAD, thereby providing a perspective distinct from that of previous studies. We systematically examine the roles of macrophage senescence at multiple stages of atherosclerosis, including early plaque initiation, plaque maturation, and plaque instability and rupture. Particular emphasis is placed on how macrophage senescence exhibits distinct functional characteristics and engages different molecular pathways at each stage, rather than being regarded as a single, static pro-inflammatory entity. Furthermore, the discussion is extended to MI and post-infarction tissue repair by organizing current evidence along a temporal axis. We highlight how macrophage senescence, through impaired phenotypic polarization and immune dysfunction, sustains inflammatory responses, delays inflammation resolution, and hinders effective myocardial repair. By focusing on key mechanisms of macrophage senescence, including metabolic reprogramming, autophagic dysfunction, and mitochondrial impairment, we further clarify the

contribution of macrophage senescence to maladaptive cardiac remodeling in the late post-infarction stage. This mechanistic integration provides an in-depth framework for understanding the persistent progression of ischemic heart disease. Finally, to address current translational gaps, this review not only summarizes potential therapeutic targets but also critically discusses the limitations of existing intervention strategies. Rather than relying solely on inflammation suppression, we expand therapeutic considerations towards a multidimensional regulatory approach, including restoration of macrophage autophagic capacity, modulation of phenotypic polarization, correction of metabolic dysregulation, and attenuation of oxidative stress. Accordingly, we review the potential applications of various therapeutic agents in CAD to provide a rationale for future strategies to precisely target macrophage senescence and improve clinical outcomes.

2. Role of Macrophage Senescence in CAD

2.1 Atherosclerosis

The transition of macrophages from scavengers to senescence drivers is a pivotal event in the progression of atherosclerosis. Unlike young macrophages, which maintain vascular homeostasis, macrophage senescence orchestrates a multistage pathological network ranging from early lipid dysmetabolism to terminal plaque rupture.

The earliest stage of atherosclerosis is marked by a profound decline in the lipid-handling capacity of macrophages, a defect that establishes a pathological foundation for lesion development. Senescence-induced downregulation of the membrane cholesterol transporters ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) accelerates the transition from healthy macrophages to dysfunctional foam cells, which is often triggered by initial exposure to ox-LDL [13, 14]. As a key driver of atherosclerosis initiation, ox-LDL not only serves as a lipid cargo but also actively induces senescence-associated secretory phenotype (SASP) of macrophage, subsequently inhibiting their physiological proliferation and migration while triggering the secretion of pro-inflammatory factors such as tumor necrosis factor (TNF)- α , monocyte chemoattractant protein-1 (MCP)-1, and interleukin (IL)-1 β [15]. Once senescent, these macrophages exhibit significantly reduced efficiency in the uptake and metabolism of ox-LDL, leading to abnormal lipid deposition within the vascular wall and accelerated expansion of the lipid core [16]. A critical molecular regulator of this process is microRNA-33 (miR-33), an endogenous inhibitor of ABCA1, which is frequently

upregulated during macrophage senescence. Multiple *in vivo* studies have confirmed that miR-33 deficiency or inhibition can restore ABCA1 expression, elevate plasma high-density lipoprotein levels, and significantly reduce the early plaque area [17-19]. Notably, this initiation of senescence may occur even before cells infiltrate the vessel wall. Senescent circulating monocytes already display an inflammatory phenotype characterized by decreased ABCA1 expression. Upon trans-endothelial migration, these pre-sensitized cells are predisposed to rapid foam cell transformation, thereby fueling early plaque growth [20]. By compromising cholesterol reverse transport and promoting early foam cell accumulation, macrophage senescence sets the stage for the subsequent failure of clearance mechanisms and the structural destabilization of the plaque.

As the atherosclerotic plaque transitions from initiation to progression, the pathological burden shifts from simple lipid accumulation to the failure of cellular maintenance systems. This stage represents a critical turning point at which the plaque loses its stability. In a healthy physiological state, macrophages alleviate the plaque burden by degrading damaged organelles via autophagy and clearing apoptotic cell debris through efferocytosis [21]. However, the onset of senescence leads to dysfunction of these clearance mechanisms, driving the expansion of the necrotic core.

In the senescent state, macrophages exhibit a significant decline in autophagic activity, particularly when exposed to pro-atherogenic aggregated LDL. This defect is largely driven by the upregulation of the MST1 protein, which inhibits macrophage autophagy and promotes apoptosis, thereby compromising the ability of the cell to clear metabolic waste and damaged organelles [22]. The importance of this pathway is further underscored by studies showing that the deletion of the essential autophagy-related gene 7 (ATG7) results in a phenotype that closely resembles macrophage senescence, characterized by suppressed housekeeping functions and significantly enhanced inflammatory responses [23]. Complementary to autophagic defects is the impairment of efferocytosis, the process of clearing dead cells. Macrophage senescence impairs the effective recognition and engulfment of apoptotic foam cells within the plaque. This "efferocytosis gap" leads to secondary necrosis of apoptotic debris, which subsequently spills its pro-inflammatory contents into the extracellular space, further exacerbating the inflammatory milieu. The synergy between impaired autophagy and failed efferocytosis prevents the regression of the lesion. Research using bone marrow transplantation models has confirmed that mice with senescent bone marrows exhibit a failure to decrease plaque autophagy and insufficient clearance of apoptotic cells within the plaque [24].

Ultimately, this dual failure of clearance mechanisms leads to the formation of a massive necrotic core, a hallmark of plaque vulnerability that sets the stage for the final catastrophic phase of the disease: structural rupture.

In the advanced stages of atherosclerosis, macrophage senescence and foam cells transition from being disease markers to being active drivers of plaque instability. This terminal phase is characterized by an intensified inflammatory storm and active erosion of the structural integrity of the plaque, primarily mediated by SASP. The persistent inflammatory milieu in advanced plaques is maintained by a self-amplifying cycle of monocyte recruitment and SASP secretion. Multiple key pathways regulate this process. Mechanistic studies indicate that bromodomain-containing protein 4 (BRD4), activated by the nuclear factor- κ B (NF- κ B) pathway, serves as a master regulator of SASP-related genes, whereas ABI3 is upregulated in advanced plaques to further drive senescence via NF- κ B signaling. MiR-216a triggers a Smad3/NF- κ B signaling cascade that drives the polarization of intraplaque macrophages from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype [25-27]. These senescent cells secrete elevated levels of C-C motif chemokine ligand (CCL) 2, C-X-C motif ligand (CXCL) 2, and TNF- α , which synergistically enhance monocyte chemotaxis. This continuous recruitment of fresh inflammatory cells into both local and distal vascular beds creates a cascade that accelerates plaque maturation [8, 15]. The most critical pathological impact of macrophage senescence in advanced lesions is its direct assault on the mechanical stability of plaques. High expression of MMPs, specifically MMP-3, MMP-12, and MMP-13, allows senescent foam cells to aggressively degrade the extracellular matrix. This enzymatic erosion results in elastin fiber destruction and progressive thinning of the fibrous cap. By compromising the mechanical strength of the vascular wall, these proteases increase plaque fragility and the risk of spontaneous rupture, ultimately triggering acute cardiovascular events such as thrombosis [28, 29]. Conversely, the pathological role of senescence can be antagonized by specific regulatory axes. For instance, the overexpression of La-related protein 7 has been shown to enhance SIRT1 activity. This counter-regulatory mechanism inhibits senescence-associated signaling (such as the p53/p65 pathway) and reduces the release of SASP factors, thereby significantly decreasing the plaque burden and promoting stability [30].

In conclusion, Macrophage senescence drives the lifecycle of atherosclerotic plaques through an interconnected pathological network. This process begins with lipid-handling failure (initiation), progresses through impaired clearance and necrotic expansion (progression), and culminates in SASP-driven structural destruction

(rupture). These synergistic mechanisms highlight the therapeutic window for preventing acute ischemic events (Fig. 1).

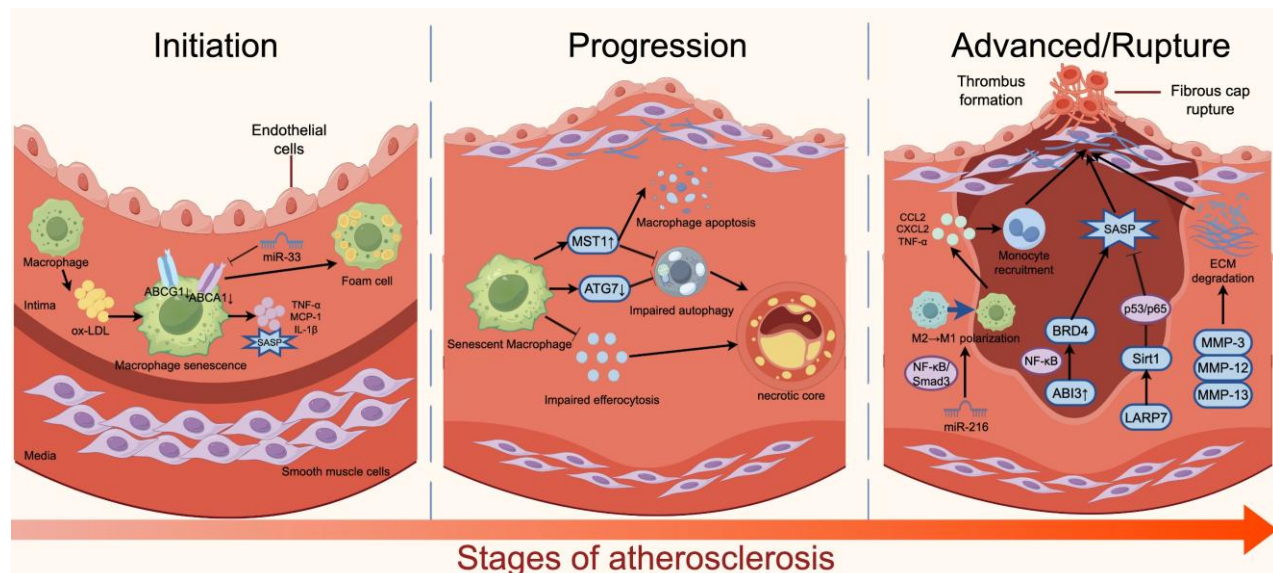


Figure 1. Senescent macrophages orchestrate the stage-specific progression of atherosclerosis from initiation to plaque rupture. This schematic illustrates the stage-specific yet mechanistically interconnected roles of senescent macrophages during plaque initiation, progression, and rupture. During the initiation stage, ox-LDL induces macrophage senescence, leading to downregulation of the cholesterol transporters ABCA1 and ABCG1, impaired cholesterol efflux, and accelerated foam cell formation. MiR-33, an endogenous inhibitor of ABCA1, contributes to this process. Concurrently, senescent macrophages secrete pro-inflammatory SASP factors, including TNF- α , MCP-1, and IL-1 β , amplifying local inflammatory responses and promoting early plaque development. As lesions enter the progression stage, senescent macrophages exhibit impaired autophagy due to MST1 upregulation and ATG7 downregulation, accompanied by increased apoptosis. Simultaneously, defective efferocytosis limits the clearance of apoptotic cells, resulting in secondary necrosis and expansion of the necrotic core. The combined failure of autophagic maintenance and efferocytic clearance progressively compromises plaque stability. In the advanced/rupture stage, NF- κ B-dependent activation of BRD4 and upregulation of ABI3 enhance SASP-related gene expression, further intensifying inflammatory signaling. MiR-216a activates the Smad3/NF- κ B pathway, promoting macrophage polarization from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype and stimulating the secretion of CCL2, CXCL2, and TNF- α , thereby sustaining monocyte recruitment in a self-amplifying inflammatory loop. Meanwhile, senescent foam cells overexpress matrix metalloproteinases (MMP-3, MMP-12, and MMP-13), accelerating ECM degradation and fibrous cap thinning, which markedly increases the risk of plaque rupture and thrombosis. In contrast, the LARP7–Sirt1 regulatory axis counteracts senescence-associated signaling (p53/p65), suppresses SASP production, reduces plaque burden, and enhances plaque stability. ox-LDL = oxidized low-density lipoprotein; ABCA1 = ATP-binding cassette transporter A1; ABCG1 = ATP-binding cassette transporter G1; miR-33 = microRNA-33; SASP = senescence-associated secretory phenotype; TNF- α = tumor necrosis factor alpha; MCP-1 = monocyte chemoattractant protein-1; CCL2 = C–C motif chemokine ligand 2; CXCL2 = C–X–C motif chemokine ligand 2; IL-1 β = interleukin-1 β ; MST1 = mammalian sterile 20-like kinase 1; ATG7 = autophagy-related gene 7; NF- κ B = nuclear factor kappa B; BRD4 = bromodomain-containing protein 4; ABI3 = Abelson interactor family member 3; Smad3 = SMAD family member 3; LARP7 = La-related protein 7; Sirt1 = sirtuin 1; MMP = matrix metalloproteinase; ECM = extracellular matrix.

2.2 MI and Post-Infarction Tissue Repair

Following MI, macrophages are the central orchestrators of the immune response. They are responsible for navigating the heart through the critical transition from acute inflammation to tissue repair. However, macrophage senescence, driven by chronological aging or the extreme stress of the ischemic microenvironment, disrupts this delicate balance.

The post-MI microenvironment is characterized by severe hypoxia and oxidative stress, which are potent triggers of stress-induced premature senescence in

macrophages. In the early stages of MI, hypoxia-driven reactive oxygen species (ROS) and mitochondrial dysfunction trigger the macrophage SASP. This is molecularly defined by the increased expression of histone H2A.X, CCL7, and IL-1 β , alongside a significant reduction in the antioxidant enzyme superoxide dismutase 2 (SOD2), which collectively aggravates myocardial ischemic injury [31]. This pro-inflammatory surge is further fueled by specific signaling hubs. For instance, neogenin (Neo1), a multifunctional receptor, is markedly downregulated during macrophage senescence post-MI. The deficiency of Neo1 activates the JAK1-STAT1

signaling pathway, which promotes excessive macrophage infiltration into the ischemic myocardium and shifts them towards a pro-inflammatory phenotype [32]. Similarly, Galectin-3 (Gal-3) is upregulated during macrophage senescence after acute MI. Gal-3 not only

promotes M1-type polarization but also correlates significantly with other SASP components, such as MCP-1 and MMP-3, driving an aggressive inflammatory cascade that correlates with adverse clinical remodeling [33, 34].

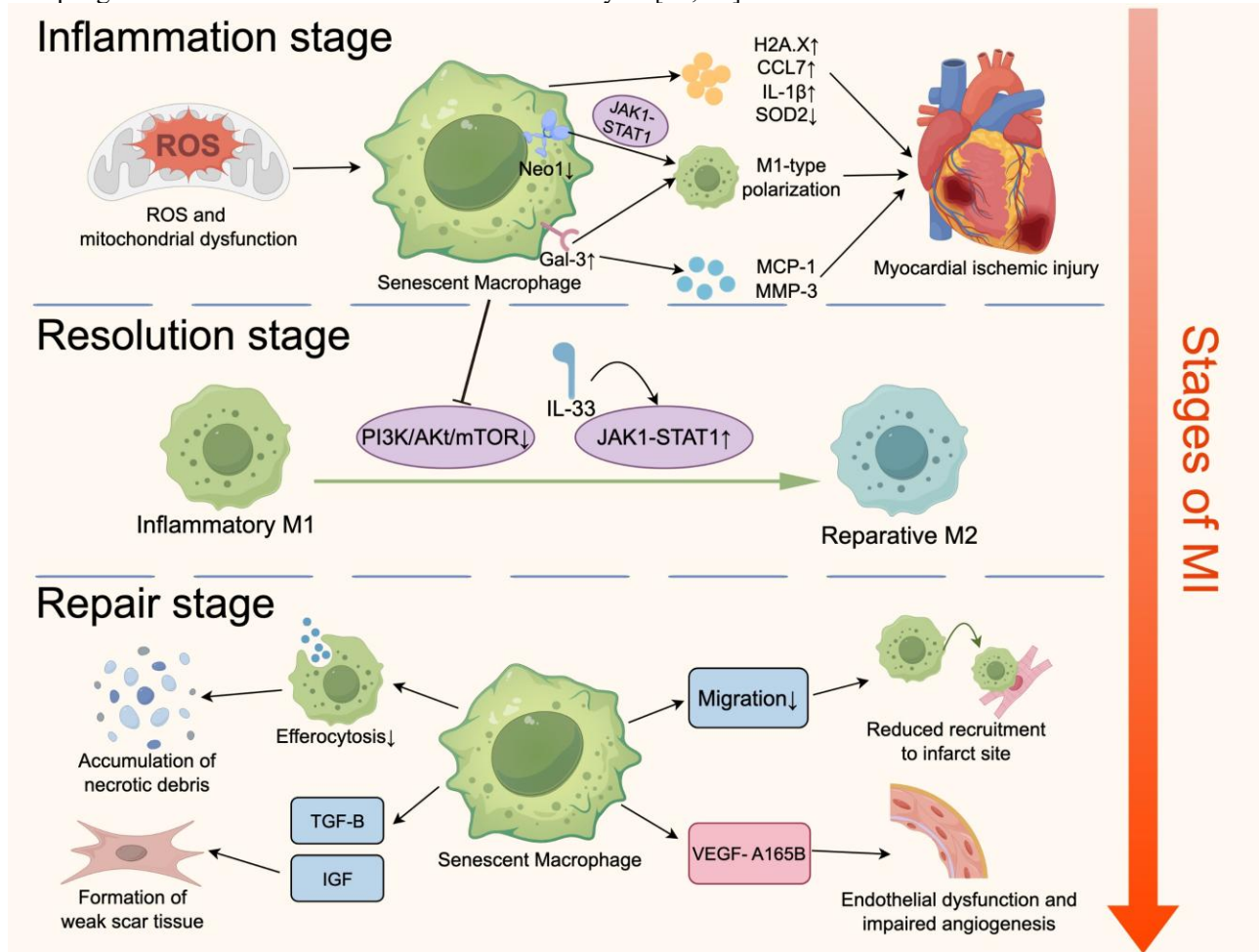


Figure 2. Senescent macrophages disrupt the inflammatory–resolution–repair program after MI. This schematic illustrates the stage-specific pathological roles of senescent macrophages during post-MI remodeling, spanning the inflammation, resolution, and repair phases. In the inflammation stage, ischemia-driven hypoxia, excessive ROS, and mitochondrial dysfunction induce stress-associated macrophage senescence. Senescent macrophages exhibit a characteristic SASP signature marked by increased H2A.X, CCL7, and IL-1β expression, alongside reduced SOD2 levels, collectively aggravating myocardial ischemic injury. Downregulation of Neo1 activates the JAK1–STAT1 signaling pathway, promoting M1-type polarization and excessive inflammatory infiltration. Concurrently, upregulated Gal-3 further enhances M1 polarization and stimulates the production of MCP-1 and MMP-3, amplifying inflammatory cell recruitment and extracellular matrix degradation, thereby exacerbating tissue injury. During the resolution stage, effective recovery requires macrophage transition from pro-inflammatory M1 to reparative M2 phenotypes. However, senescence impairs this phenotypic switch. Reduced PI3K/Akt/mTOR signaling limits M2 polarization, creating a “resolution gap” characterized by persistent low-grade inflammation. Although IL-33 can partially rescue this defect by activating JAK1–STAT1 signaling and promoting M2 polarization, senescent macrophages overall maintain an inflammatory bias that delays cardiac functional recovery. In the repair stage, senescent macrophages exhibit profound defects in regenerative functions. Their migratory capacity is diminished, reducing recruitment to the infarct zone. Impaired efferocytosis leads to the accumulation of necrotic debris, preventing timely activation of reparative pathways. Decreased secretion of growth factors such as TGF-β and IGF compromises fibroblast activation and collagen deposition, resulting in weak scar formation. Additionally, increased production of the anti-angiogenic isoform VEGF-A165B induces endothelial dysfunction and impairs angiogenesis, further limiting revascularization. MI = myocardial infarction; ROS = reactive oxygen species; H2A.X = histone H2A variant X; SOD2 = superoxide dismutase 2; CCL7 = C–C motif chemokine ligand 7; Neo1 = neogenin-1; Gal-3 = galectin-3; JAK1 = Janus kinase 1; STAT1 = signal transducer and activator of transcription 1; PI3K = phosphoinositide 3-kinase; Akt = protein kinase B; mTOR = mechanistic target of rapamycin; IL-33 = interleukin-33; TGF-β = transforming growth factor beta; IGF = insulin-like growth factor; VEGF-A165B = vascular endothelial growth factor A 165B isoform.

Successful recovery from MI requires the timely resolution of inflammation, a process that hinges on the phenotypic transition of macrophages from a pro-inflammatory M1 state to an anti-inflammatory reparative M2 state. Macrophage senescence creates a critical "resolution gap" by obstructing this switch. During macrophage senescence, the signaling pathways essential for M2 polarization, most notably the PI3K/Akt/mTOR pathway, exhibit significantly reduced activity. This molecular blockade prevents the effective transition to a reparative phenotype, leading to persistent, low-grade "inflamm-aging" which delays the healing process and sustains cardiac tissue damage [35, 36]. The importance of this transition is underscored by the role of IL-33, which has been shown to bypass this senescence-induced blockade. By activating the JAK/STAT pathway, IL-33 induces M2 polarization and inhibits cardiomyocyte apoptosis, thereby alleviating post-MI ventricular remodeling and improving both systolic and diastolic functions [37].

During the later stages of MI, the reparative capacity of the macrophage is essential for scar formation and revascularization. However, macrophage senescence is associated with profound defects in these regenerative functions. The migratory capacity of macrophages is significantly reduced during macrophage senescence, which hinders their recruitment to the infarct site [10]. Furthermore, their ability to perform efferocytosis, the phagocytic clearance of apoptotic and necrotic debris, is severely diminished. This failure leads to the accumulation of necrotic material, which prevents timely activation of myofibroblasts and stalls the initiation of the repair sequence [38]. Through aberrant paracrine signaling, macrophage senescence leads to reduced secretion of critical growth factors such as transforming growth factor (TGF)- β and insulin-like growth factor (IGF). This deficiency leads to sluggish fibroblast proliferation and insufficient collagen synthesis, resulting in the formation of fragile malformed scar tissue [10, 39]. Finally, macrophage senescence indirectly impairs tissue repair by compromising angiogenesis. It drives increased secretion of VEGF-A165B, an anti-angiogenic isoform that induces endothelial dysfunction and impairs revascularization [40]. The resulting nutrient and oxygen deprivation within the infarct zone further exacerbates repair impairment and increases the risk of progression to heart failure.

In summary, macrophage senescence acts as multistage disruptors of the MI recovery process. By forming an intricate pathological network that amplifies early inflammation, prevents its resolution, and ensures structural repair failure, macrophage senescence is a primary driver of adverse post-MI outcomes (Fig. 2).

Summary Box

Macrophage Senescence in Atherosclerosis

- Macrophage senescence drives pathological progression in atherosclerosis ranging from early lipid dysmetabolism to terminal plaque rupture.
- In the initiation stage, macrophage senescence impairs cholesterol efflux (e.g., ABCA1/ABCG1 downregulation), promoting foam cell formation and initiating plaque development.
- During the plaque progression, macrophage senescence promotes defective autophagy and impaired efferocytosis, leading to necrotic core expansion and loss of plaque stability.
- In the advanced stage, macrophage senescence drives a self-amplifying inflammatory loop through SASP secretion and enhanced monocyte recruitment, while promoting extracellular matrix degradation and fibrous cap thinning via upregulation of MMPs, thereby increasing plaque vulnerability.

Macrophage Senescence in MI and Post-Infarction Repair

- Following myocardial infarction, macrophages orchestrate the transition from acute inflammation to tissue repair, a process that is profoundly disrupted by macrophage senescence.
- In the early inflammatory stage, macrophage senescence induced by hypoxia and reactive oxygen species triggers excessive SASP production, amplifying inflammatory responses and exacerbating myocardial injury.
- In the resolution stage, macrophage senescence impairs the critical phenotypic transition from M1 to M2, sustaining chronic inflammation and delaying cardiac healing.
- During the repair stage, macrophage senescence leads to defective migration and efferocytosis, along with reduced secretion of pro-reparative factors (e.g., TGF- β , IGF) and increased anti-angiogenic signaling, which collectively lead to impaired fibroblast activation, weak scar formation, and compromised angiogenesis, ultimately driving adverse cardiac remodeling.

3. Therapeutic Strategies Targeting Macrophage Senescence in CAD

Research on macrophage senescence in CAD involves core mechanisms, such as inflammatory regulation, metabolic imbalance, impaired autophagy, mitochondrial dysfunction, and oxidative stress. These findings not only deepen the understanding of disease pathogenesis but also provide a theoretical basis for targeted interventions. Targeting the regulation of macrophage senescence demonstrates significant therapeutic potential for

inhibiting SASP-associated inflammation, modulating polarization phenotypes, regulating metabolism, promoting autophagy, protecting mitochondrial function, and exerting antioxidant effects. Relevant

pharmacological agents can effectively alleviate the decline in macrophage function and ameliorate the pathological progression of CAD (Table 1).

Table 1. Summary of Therapeutic Strategies Targeting Macrophage Senescence in CAD.

Therapeutic Category	Drug Name	Mechanism	Ref.
Inhibiting SASP-associated inflammation	Berberine	Activates PPAR γ , promotes ubiquitination-mediated degradation of the GATA4/p62 complex, inhibits SASP factors (TNF- α , MCP-1, IL-6)	[42]
	IOX1	Inhibits the demethylase ALKBH5 and downregulates CCL5 expression, blocks the CCL5/CCR5/autophagy signaling pathway, reduces SASP secretion	[43]
	Maraviroc	Antagonizes the CCR5 receptor, blocks the CCL5/CCR5 signaling pathway and reduces SASP secretion from senescent foam macrophages	[43]
	JQ-1 / I-BET762	Inhibits BRD4, reduces autocrine and paracrine SASP expression, decreases lipid uptake	[25]
	hydrogen water	Reduces CD36 expression, inhibits infiltration of senescent macrophages and SASP expression (e.g., TNF- α)	[44]
Modulating macrophage polarization	Metformin	Activates the AMPK-dependent pathway and transcription factor ATF1, induces M2-like gene expression (IL-10, KLF4, MRC1, etc.)	[45]
	Dihydromyricetin	Modulates the miR-9-mediated SIRT1/NF- κ B pathway to inhibit M1 macrophage polarization	[47]
	Fingolimod	Promotes macrophage conversion to the alternatively activated (M2) phenotype, reduces lipid accumulation	[48]
	Yang-Xin-Shu-Mai granule	Modulates macrophage reprogramming from M1 to M2 via the TLR9/MyD88/NF- κ B pathway	[49]
	Shexiang Tongxin Dropping Pills	Promotes M2 polarization-induced angiogenesis via the PI3K/Akt/mTORC1 pathway	[50]
	Pioglitazone	Sustained release activates PPAR γ to promote polarization towards the M2 phenotype, reducing pro-inflammatory and increasing anti-inflammatory cytokines	[51]
	Fludarabine phosphate	Blocks the JAK1-STAT1 signaling pathway, eliminating the detrimental effects of Neo1 downregulation on macrophage phenotype post-MI	[32]
Modulating macrophage metabolism	Dimethyl fumarate	Enhances macrophage OXPHOS, promotes a shift towards an anti-inflammatory phenotype	[52]
	Metformin	Upregulates Akt phosphorylation, improves mitochondrial function, reduces ROS, promotes IL-10 and IGF-1	[53]
Enhancing macrophage autophagy	Rapamycin	Inhibits the mTOR signaling pathway, promotes autophagy, reduces inflammatory responses	[55]
	Quercetin	Activates the MST1-mediated autophagy pathway, inhibits senescence markers (p53/p21/p16), reduces SASP secretion	[56, 79]
Protecting mitochondrial function / Antioxidant	Alpha-lipoic acid	Inhibits SIRT1 degradation, promotes Nrf2 nuclear translocation, reduces ROS, improves mitochondrial dysfunction	[31]
	Resolvin D1	Reduces oxidative stress, improves efferocytosis, decreases plaque necrotic core	[59]
	Exenatide	GLP-1 analogue, inhibits ox-LDL-induced macrophage foam cell formation, attenuates oxidative stress and inflammation	[60]

PPAR γ = peroxisome proliferator-activated receptor; GLP-1 = glucagon-like peptide-1; other abbreviations as in Figures 1 to 2.

3.1 Targeting Senescence by Inhibiting Macrophage SASP-Associated Inflammation

Macrophage senescence significantly promotes chronic inflammation in atherosclerosis. Berberine, an antimicrobial alkaloid extracted from *Coptis chinensis*, has recently been shown to confer benefits in the prevention and treatment of atherosclerosis through anti-

inflammatory, antioxidant, antithrombotic, and lipid-modulating effects [41]. Furthermore, berberine inhibits cellular senescence. Zheng et al. found that it exerts anti-atherosclerotic effects by attenuating SASP-associated inflammation in macrophages. Mechanistically, berberine activates peroxisome proliferator-activated receptor (PPAR) γ via the RXR α -PPAR γ immunocomplex in macrophage-derived foam cells, enhancing NEDD4

transcriptional activity and promoting ubiquitination-mediated degradation of the GATA4/p62 complex. This consequently inhibits the production of SASP-associated proteins, such as TNF- α , MCP-1, and IL-6 [42]. SASP mediated by senescent foam macrophages is a key driver of atherosclerosis progression and plaque instability. Studies have revealed elevated expressions of the demethylase ALKBH5 (alkB homolog 5) in arterial plaques and infiltrating macrophages from patients and mouse models with atherosclerosis. ALKBH5 upregulates CCL5 expression, and elevated CCL5 promotes senescent foam macrophage formation via the CCL5/CCR5/autophagy signaling pathway. This increases SASP secretion and accelerates atherosclerotic plaque formation and instability. Notably, the ALKBH5 inhibitor IOX1 (a 2OG oxygenase inhibitor) and the CCR5 antagonist maraviroc represent potential therapeutic strategies for atherosclerosis [43]. Additionally, research indicates that lipopolysaccharide (LPS)-induced macrophage senescence manifests as morphological changes, increased SASP secretion, and a sustained DNA damage response. BRD4 plays a crucial role in this pathological process. Inhibiting BRD4 using inhibitors such as JQ-1 or I-BET762 prevents LPS-induced macrophage senescence by reducing autocrine and paracrine SASP expression and decreasing atherosclerosis-associated lipid uptake [25]. Molecular hydrogen water, previously reported for its antioxidant and anti-inflammatory effects in various diseases, was found to reduce macrophage senescence in atherosclerotic plaques and inhibit SASP-associated TNF- α expression in *Ldlr*^{-/-} mouse models fed a high-fat diet. Moreover, CD36, a scavenger receptor for ox-LDL, plays a significant role in establishing the senescent phenotype. Hydrogen water treatment also significantly reduces CD36 expression on macrophages [44].

3.2 Targeting Senescence by Modulating Macrophage Polarization

Macrophage polarization is a potential therapeutic target. Metformin is reported to induce macrophage expression of M2-like genes, such as *IL-10*, *KLF4*, *MRC1*, *ABCA1*, *CD163*, *IGF-1*, and *APOE*, by activating the AMPK-dependent signaling pathway and transcription factor ATF1. This promotes the formation of protective macrophages in atherosclerosis, thereby inhibiting atherogenesis in normoglycemic mouse models [45]. Furthermore, natural compounds and traditional Chinese medicines have been found to possess the potential to modulate macrophage polarization from the pro-inflammatory M1 type to the anti-inflammatory M2 type. This provides novel insights for the development of low-toxicity, high-efficiency anti-atherosclerotic drugs [46]. Dihydromyricetin (DMY), a natural flavonoid extracted

from the stems and leaves of *Ampelopsis grossedentata*, is considered a potential anti-atherosclerotic agent. Research indicates that DMY treatment significantly reduces the expression of M1 macrophage markers and the number of p65-positive macrophages in the vascular walls of ApoE^{-/-} mice. Its mechanism involves modulating the miR-9-mediated SIRT1/NF- κ B signaling pathway to inhibit M1 macrophage polarization, thereby exerting anti-atherosclerotic effects [47]. Conversely, FTY720 (Fingolimod) alleviates advanced atherosclerosis by promoting macrophage conversion to the alternatively activated (M2) phenotype and reducing lipid accumulation [48]. Multiple active ingredients from traditional Chinese medicines have also demonstrated the ability to regulate macrophage polarization. For instance, Yang-Xin-Shu-Mai granules modulate macrophage reprogramming from the M1 to the M2 phenotype via the TLR9/MyD88/NF- κ B signaling pathway, mitigating the immune-inflammatory response and significantly inhibiting atherosclerotic plaque formation [49]. Shexiang Tongxin dropping pills can promote M2 macrophage polarization-induced angiogenesis via the PI3K/Akt/mTORC1 pathway, thereby ameliorating coronary microvascular dysfunction [50].

Furthermore, in the context of MI, the modulation of macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype helps alleviate the inflammatory response and promote cardiac repair. For instance, sustained release of pioglitazone via microspheres activates PPAR γ to regulate relevant signaling pathways. This promotes macrophage polarization towards the M2 phenotype, reduces pro-inflammatory cytokine secretion, and increases anti-inflammatory cytokine production. Consequently, it alleviates myocardial inflammation, promotes tissue repair, and ameliorates adverse left ventricular remodeling and cardiac dysfunction. This suggests that regulating macrophage polarization through drug delivery systems holds promise as a novel therapeutic strategy for cardiac regeneration therapy in ischemic heart disease [51]. Additionally, specific receptors and signaling pathways on the macrophage surface can serve as potential targets. It has been demonstrated that blocking the JAK1-STAT1 pathway using fludarabine phosphate eliminates the impact of the multifunctional transmembrane receptor Neol downregulation on macrophage phenotype and function. This reduces infarct size, attenuates myocardial fibrosis and cardiomyocyte apoptosis, and alleviates left ventricular dysfunction in mice, indicating that targeting Neol may represent a novel therapeutic strategy for MI [32].

3.3 Targeting Senescence by Modulating Macrophage Metabolism

Metabolic pathways in macrophages also represent potential therapeutic targets. Following MI, macrophages undergo metabolic reprogramming, and modulation of their metabolic pathways can influence their function and phenotype. Several drugs exert their effects by regulating macrophage metabolism. Dimethyl fumarate modulates immune responses by targeting GAPDH and aerobic glycolysis, thereby influencing CAD progression. In mouse models of MI, dimethyl fumarate enhances macrophage oxidative phosphorylation, promoting their shift towards an anti-inflammatory phenotype. This consequently improves post-infarction cardiac remodeling, reducing left ventricular infarct size and dilation [52]. Beyond regulating macrophage polarization, metformin also modulates their metabolic pathways, including glucose and lipid metabolism, thereby suppressing inflammatory responses and delaying macrophage senescence. Studies have indicated that metformin improves macrophage function by upregulating Akt phosphorylation levels induced by ox-LDL and ameliorating mitochondrial function. This reduces intracellular ROS levels, decreases the secretion of pro-inflammatory cytokines, and simultaneously promotes the expression of anti-inflammatory cytokines IL-10 and IGF-1, providing a potential pharmacological target for treating coronary atherosclerosis [53]. These findings demonstrate that novel or repurposed drugs targeting macrophage metabolism hold promise for preventing and treating diabetes-accelerated atherosclerosis. Furthermore, research has revealed that aberrant regulation of metabolic pathways contributes to macrophage polarization in aged atherosclerosis. Integrated transcriptomic and metabolomic analyses can be used to identify metabolism-associated targets linked to aged plaques that regulate macrophage polarization, such as lipid metabolism pathways involving genes such as *PTGS2*, *CERK*, *CBR2*, and *LPIN2*. Inhibitors targeting these metabolic pathways, such as lipid metabolism inhibitors (e.g., C75) and glycolytic lactate dehydrogenase inhibitors (e.g., GNE-140), may ameliorate macrophage polarization and effectively reduce the risk of atherosclerosis in older people [54].

3.4 Targeting Senescence by Enhancing Macrophage Autophagy

Drug development targeting macrophage senescence is currently a research focus, with several agents delaying senescence by modulating autophagy in macrophages. For instance, the autophagy activator rapamycin inhibits the mTOR signaling pathway, promotes macrophage

autophagy, improves the intracellular environment, and reduces inflammatory responses, thereby suppressing early atherosclerosis [55]. Furthermore, the bioactive phytochemical quercetin inhibits plaque macrophage senescence and attenuates atherosclerosis by activating the MST1-mediated autophagy pathway. In vitro experiments have demonstrated that ox-LDL stimulation of RAW264.7 macrophages leads to reduced cell viability, exacerbated lipid accumulation, the emergence of a senescent phenotype (upregulated P53/P21/P16 expression), and autophagy inhibition (downregulated LC3-II/I and Beclin1). Quercetin intervention significantly reverses these phenotypes, enhances macrophage autophagy, and inhibits foam cell formation [56]. However, the relationship between autophagy and macrophage senescence remains incompletely defined and lacks consistent conclusions, although, as discussed above, enhancement of autophagy has been reported to delay senescence in macrophages. In contrast to these protective effects, emerging evidence indicates that under senescence-associated stress conditions, autophagy is not merely a defensive mechanism but may also participate in and facilitate the progression of the senescence program. Narita et al. demonstrated that autophagy-related membrane structures can spatially couple with compartments involved in SASP production, forming the TOR–autophagy spatial coupling compartment (TASCC), which promotes the efficient synthesis and secretion of inflammatory mediators such as IL-6 and IL-8. These findings suggest that under specific conditions, autophagy can act as a key facilitator of SASP formation, thereby contributing to pro-senescent inflammatory amplification [57]. Thus, beyond its canonical role in maintaining intracellular homeostasis, autophagy may exert pro-senescent effects by modulating inflammatory signaling and tissue microenvironment remodeling. Subsequently, Kang et al. proposed that the impact of autophagy on senescence is not unidirectional, but instead exhibits a context-dependent dual role. By introducing the concept of selective autophagy, their study showed that the selective autophagic degradation of the transcription factor GATA4 suppresses NF- κ B signaling, thereby limiting SASP production and delaying senescence. Conversely, when selective autophagy is impaired or replaced by non-selective autophagic processes, the intracellular accumulation of GATA4 activates inflammatory signaling pathways and accelerates the development of senescence phenotypes [58]. This framework partially reconciles the discrepancy whereby autophagy has been reported to exert both anti- and pro-senescent effects, highlighting that the critical determinant is not simply whether autophagy occurs, but rather the subtype of autophagy engaged, the precision of its regulation, and its dynamic interaction with

inflammatory signaling networks. Nevertheless, this conceptual model does not fully account for the variability observed across current studies. It remains unclear under which cellular stress levels, metabolic states, or inflammatory contexts cells preferentially activate selective versus bulk autophagy, as systematic investigations addressing these determinants are still lacking. Moreover, most mechanistic insights to date are derived from fibroblast or tumor-cell models, raising uncertainty as to whether these findings can be directly extrapolated to highly plastic immune cells, such as macrophages, which exhibit pronounced metabolic reprogramming capacity. Given that macrophages display distinct metabolic and inflammatory characteristics across polarization states, the functional consequences of autophagy are likely to differ substantially among macrophage subsets. Accordingly, future studies should incorporate cell type-specific analyses, context-stratified experimental designs, and refined characterization of autophagy subtypes to develop multidimensional integrative models that more precisely delineate the bidirectional regulatory roles of autophagy in macrophage senescence and provide a stronger theoretical basis for autophagy-targeted therapeutic strategies.

3.5 Targeting Senescence by Protecting Macrophage Mitochondrial Function and Mitigating Oxidative Stress

Mitochondrial dysfunction and oxidative stress drive inflammatory responses during macrophage senescence. Interventions targeting these mechanisms are crucial for the treatment of CAD. Alpha-lipoic acid has been found to ameliorate MI injury by targeting macrophage senescence pathways. Specifically, alpha-lipoic acid inhibits SIRT1 degradation and promotes Nrf2 nuclear translocation while reducing ROS generation and improving mitochondrial dysfunction, effectively reversing macrophage senescence [31]. Research indicates that sublethal doses of radiation can induce macrophage senescence, subsequently impairing inflammation resolution programs and promoting the progression of atherosclerosis. Treatment with the pro-resolving mediator resolvin D1 reduces oxidative stress levels in macrophages within atherosclerotic plaques and improves efferocytosis. This significantly decreases radiation-induced plaque necrotic cores and increases collagen content. Therefore, resolvin D1 may represent a novel therapeutic strategy for limiting radiation-induced tissue damage [59]. Additionally, the glucagon-like peptide-1 (GLP-1) analog exenatide exerts protective effects against vascular aging and atherosclerosis in ApoE^{-/-} mice under chronic stress. Its protective mechanism likely involves the inhibition of ox-LDL-

induced macrophage foam cell formation, thereby attenuating plaque oxidative stress, inflammatory responses, and extracellular matrix proteolysis. These findings provide experimental evidence supporting the clinical application of GLP-1 receptor agonists in stress-related cardiovascular diseases [60].

3.6 Key Challenge for Clinical Translation and Prioritization of Therapeutic Strategies Targeting

A major barrier to clinical translation lies in the fact that most candidate interventions have been validated only in *in vitro* systems and small animal models. Although these studies demonstrate therapeutic potential, robust evidence from human studies and clinical trials remains lacking. Consequently, the safety, target specificity, and clinical feasibility of these interventions have not yet been fully established. Future efforts should prioritize advancement toward the clinical stage, with particular emphasis on well-designed prospective trials and rigorous translational validation. From a translational perspective, based on current evidence and feasibility, these candidate interventions can be broadly classified into three categories. First, clinically approved drugs with repurposing potential, such as metformin, represent the most immediately translatable class, given their well-established safety profiles and their ability to modulate macrophage polarization and metabolic pathways. Second, agents with promising mechanistic rationale and preclinical efficacy in animal studies, such as berberine, demonstrate considerable therapeutic potential but still require rigorous validation in clinical settings. Third, interventions characterized by complex mechanisms, novel targets, and potential off-target or context-dependent effects, such as rapamycin and quercetin, remain exploratory, as their underlying mechanisms require further clarification. Although rapamycin is already used clinically, its immunosuppressive properties and context-dependent roles in autophagy limit its applicability for targeting macrophage senescence. At the level of therapeutic strategies, targeting SASP-associated inflammation and modulating macrophage polarization emerge as the highest-priority approaches, as both play central roles in driving CAD progression and are supported by potentially clinically actionable interventions. In contrast, strategies focusing on mitochondrial protection and metabolic reprogramming, while biologically relevant, are comparatively indirect and may be constrained by systemic effects and limited specificity. Notably, autophagy modulation remains conceptually appealing but therapeutically uncertain, owing to its context-dependent and bidirectional roles in regulating senescence and inflammatory signaling.

4. Perspectives

4.1 Gaps in Clinical Translation

Despite the five anti-macrophage senescence strategies discussed above, current therapeutic approaches largely focus on either upstream drivers of senescence (e.g., elimination of senescence-inducing stressors) or downstream consequences (e.g., suppression of SASP), whereas direct interventions targeting the core molecular pathways governing the senescence process itself remain limited. At present, the molecular mechanisms underlying the transition of macrophages from a functional state to a senescent phenotype are not completely understood, and translational studies aimed at this intermediate stage are particularly scarce. Therefore, future research should prioritize the delineation of stage-specific molecular events during macrophage senescence and identify actionable nodal points within these pathways, which may enable more direct and efficient therapeutic interventions. Specifically, single-cell multi-omics approaches, such as scRNA-seq combined with epigenomic profiling, can be employed to resolve cellular heterogeneity and identify transitional states between functional and senescent macrophages. Meanwhile, lineage tracing strategies are needed to determine the cellular origins and trajectories of these states, while *in vivo* perturbation models can uncover the causal regulators underlying this process. Moreover, elucidating the mechanistic basis of macrophage senescence is likely to facilitate the development of multi-target combinatorial strategies, allowing synergistic anti-senescent effects through the coordinated modulation of multiple regulatory axes.

From a translational perspective, macrophage-specific anti-senescence therapeutics are largely unavailable. To date, no standardized clinical treatments that selectively target macrophage senescence have been approved. Most existing senescence-targeting agents are non-specific senotherapeutics [61, 62]. Although senolytics, such as quercetin and dasatinib, can reduce the senescent cell burden and dampen inflammation, their indiscriminate clearance of senescent cells raises concerns regarding off-target effects. Indeed, depletion of senescent β -cells has been shown to exacerbate type 2 diabetes in murine models, suggesting that non-selective senescent cell elimination may accelerate disease progression in certain contexts [63]. These observations highlight the urgent need to develop therapeutic agents capable of precisely identifying and modulating macrophage senescence, thereby eliminating detrimental senescent populations while preserving essential physiological functions and homeostasis of other cell types. Currently, siRNA-based nanoparticles with selective affinity for monocytes have been developed and

shown to effectively suppress CCR2 mRNA expression in inflammatory monocytes, thereby reducing the extent of inflammation-driven atherosclerosis and myocardial infarction in mice [64]. Building on this approach, future strategies could leverage the identification of specific markers of senescent macrophages to achieve precise intervention in macrophage senescence. Furthermore, early-phase clinical trials should incorporate comprehensive safety assessments to evaluate potential off-target effects associated with senescence modulation.

Beyond these limitations, the pronounced heterogeneity of macrophages presents both challenges and opportunities for precision anti-senescence therapy. Macrophages exhibit diverse functional phenotypes (e.g., pro-inflammatory M1 and reparative M2 states) and include distinct tissue-resident populations, such as CCR2⁺ and CCR2⁻ macrophages in the heart [12]. However, the senescence-associated features and functional roles of different macrophage subsets in coronary artery-related diseases remain poorly defined, and specific markers to distinguish senescent states across these subsets are lacking. For example, the predominant cardiac tissue-resident macrophages (CCR2⁻LYVE1⁺TIMD4⁺) originate from embryonic yolk sac-derived hematopoietic progenitors and are maintained through local self-renewal, suggesting potentially unique roles in cardiac aging and repair [65-69]. Therefore, future studies should focus on elucidating the senescence mechanisms of distinct macrophage subsets, particularly tissue-resident populations, and defining their contributions to CAD progression. Specifically, future studies could combine spatial transcriptomics with fate-mapping approaches to systematically characterize the spatial and temporal dynamics of macrophage subset-specific senescence. Spatial transcriptomics enables high-resolution mapping of senescence-associated transcriptional programs within their native tissue microenvironment, thereby capturing spatial heterogeneity and niche-specific regulatory cues. However, it is inherently limited in resolving temporal dynamics and tracking state transitions of individual cells. In contrast, fate-mapping approaches provide critical insights into the temporal evolution and state transitions of macrophage populations, but lack spatial context within complex tissue architecture. Therefore, the integration of these complementary approaches is essential to achieve a comprehensive spatiotemporal understanding of macrophage senescence, particularly within atherosclerotic plaques and post-infarction myocardium. Such insights will provide a critical conceptual foundation and translational potential for the development of subset-specific targeted anti-senescence therapies.

4.2 Limitations of Animal and In Vitro Models

Animal models have inherent limitations in fully recapitulating the complexity of human diseases. Although they can reproduce selected pathological features, fundamental differences in aging trajectories, immune system organization, and tissue microenvironments exist between animals and humans. Many current studies rely on highly specific genetically engineered mouse models, such as ALKBH5 f/f, Lyz2 (lysozyme 2) Cre, and ApoE^{-/-} mice, to delineate the role of m⁶A RNA modification in the formation of senescent foam macrophages during atherosclerosis [70]. Although these models allow the precise interrogation of individual gene functions, disease development in humans typically results from the interplay of multiple genes, signaling pathways, and microenvironmental factors. Consequently, single-gene perturbation models may overlook critical components of the pathological network.

In vitro models have similar limitations. Most mechanistic studies rely on the murine RAW264.7 macrophage cell line; however, as an immortalized cell line, its genetic background, metabolic profile, and functional state may differ substantially from those of primary macrophages *in vivo*, including tissue-resident and infiltrating macrophage populations [71]. Moreover, the temporal scale of experimental modeling often poorly matches the progressive nature of cellular senescence. Senescence is a dynamic and gradual process, yet most *in vitro* studies employ short-term, high-intensity acute stimuli, such as hydrogen peroxide, bleomycin [72], *Porphyromonas gingivalis* LPS [73], or ox-LDL [74], to rapidly induce senescence-like phenotypes. Such approaches may fail to accurately reflect the gradual senescence of macrophages that occurs over months or years during chronic disease progression *in vivo*. Thus, even when primary cells such as bone marrow-derived macrophages are used [75], it is still unclear whether acutely stress-induced states are molecularly and functionally equivalent to naturally occurring or age-associated senescence. Attempts have been made to establish more physiologically relevant *in vitro* models through long-term culture of human peripheral blood monocyte-derived macrophages, extending up to 21 days. These models show a gradual accumulation of senescence markers, including senescence-associated β -galactosidase (SA- β -gal) activity and p16^{INK4a} expression, as well as altered cytokine secretion profiles [76]. Nevertheless, long-term cultured cells still lack the complex intercellular communication and systemic regulation present within tissue microenvironments, and their experimental time window remains short compared to the decades-long aging process in humans.

In addition, the criteria used to define macrophage senescence may be too narrow or incomplete. Most studies rely on classical markers, such as SA- β -gal activity [75], p16^{INK4a} expression [76], and SASP [77]. However, macrophage senescence may involve more cell type-specific features, and senescence induced by distinct stimuli may be accompanied by divergent functional alterations that are not fully captured by these canonical markers. Supporting this view, recent evidence indicates that long-term cultured senescent macrophages undergo profound structural and functional remodeling of the immunoproteasome complex, indicating deeper senescence-associated alterations beyond traditional markers [78].

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Data and materials availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

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