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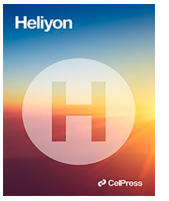

Review article

Macrophage polarisation and inflammatory mechanisms in atherosclerosis: Implications for prevention and treatment

Bo Yang [a,1], Sanhua Hang [b,1], Siting Xu [a], Yun Gao [c], Wenhua Yu [a], Guangyao Zang [a], Lili Zhang [a], Zhongqun Wang [a,*]

[a] Department of Cardiology, Affiliated Hospital of Jiangsu University, Zhenjiang, 212001, China
[b] Department of Hematology, Affiliated Danyang Hospital of Nantong University, Danyang, 212300, China
[c] Department of Pathology, Affiliated Hospital of Jiangsu University, Zhenjiang, 212001, China

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ABSTRACT

Atherosclerosis is a chronic inflammatory disease characterised by plaque accumulation in the arteries. Macrophages are immune cells that are crucial in the development of atherosclerosis. Macrophages can adopt different phenotypes, with the M1 phenotype promoting inflammation while the M2 phenotype counteracting it. This review focuses on the factors that drive the polarisation of M1 macrophages towards a pro-inflammatory phenotype during AS. Additionally, we explored metabolic reprogramming mechanisms and cytokines secretion by M1 macrophages. Hyperlipidaemia is widely recognised as a major risk factor for atherosclerosis. Modified lipoproteins released in the presence of hyperlipidaemia can trigger the release of cytokines and recruit circulating monocytes, which adhere to the damaged endothelium and differentiate into macrophages. Macrophages engulf lipids, leading to the formation of foam cells. As atherosclerosis progresses, foam cells become the necrotic core within the atherosclerotic plaques, destabilising them and triggering ischaemic disease. Furthermore, we discuss recent research focusing on targeting macrophages or inflammatory pathways for preventive or therapeutic purposes. These include statins, PCSK9 inhibitors, and promising nanotargeted drugs. These new developments hold the potential for the prevention and treatment of atherosclerosis and its related complications.

1. Introduction

Cardiovascular disease is a prevalent health issue worldwide, with atherosclerosis being its primary cause. Although atherosclerosis is more common among middle-aged and older individuals, the age of onset has gradually decreased. Annually, a staggering 20 million people worldwide die of atherosclerosis. Risk factors for atherosclerosis include obesity, diabetes, and other factors that exerts a significant burden on society and the economy [1].

* Corresponding author. Department of Cardiology, Affiliated Hospital of Jiangsu University, Jiefang Road 438, Zhenjiang, Jiangsu Province, 212000, China.
E-mail addresses: 2222213012@ujs.edu.cn (B. Yang), 1770346125@qq.com (S. Hang), 2212213030@ujs.edu.cn (S. Xu), 2222213176@ujs.edu.cn (Y. Gao), 2222213052@ujs.edu.cn (W. Yu), 2112013012@ujs.edu.cn (G. Zang), 2112113014@ujs.edu.cn (L. Zhang), wangzhongqun@ujs.edu.cn (Z. Wang).
[1] These authors contributed equally to this work.

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Patients with diabetes are more prone to developing calcified plaques and lipid-rich necrotic cores in the carotid arteries than those without diabetes. Chronic hyperglycaemia in diabetic conditions disrupts vascular homeostasis, while the involvement of miRNAs can modulate transcription and protein expression, thereby contributing to atherosclerosis. Additionally, insulin deficiency may lead to increased intestinal cholesterol absorption and hypercholesterolaemia, causing lipoprotein retention in the vascular walls, ultimately triggering an inflammatory response and promoting the development of atherosclerosis [2–4].

In obesity, adipose tissue expansion, including perivascular adipose tissue (PVAT), contributes to localised inflammation and oxidative stress. These events cause the dysfunction of vascular endothelial and smooth muscle cells, ultimately facilitating atherosclerosis progression [5].

Immune cells, such as macrophages, dendritic cells (DC), T lymphocytes, and B lymphocytes, actively regulate the inflammatory state of vessel walls. Macrophages can be categorised into two main phenotypes: M1 and M2. M1 macrophages exhibit pro-inflammatory activity, whereas M2 macrophages exhibit anti-inflammatory activity. Given that atherosclerosis is an inflammatory response, M1 macrophages play a significant role in its development.

2. Atherosclerosis and macrophages

2.1. Macrophages

Macrophages, derived from monocytes originating in the bone marrow, play crucial roles in the immune system, involved in a wide range of functions exhibiting anti-infectious, anti-tumour, and immunomodulatory properties. Macrophages are key players in both non-specific (innate immunity) and specific (cellular immunity) immunity. Their primary function is to phagocytose pathogens, senescent cells, and necrotic tissue fragments.

Upon the entry of foreign substances such as pathogens into the body, a local inflammatory response is triggered. Macrophages migrate to the site of inflammation, where they efficiently engulf and eliminate foreign invaders. Moreover, macrophages play a vital role in activating other immune cells, thereby enabling an effective response to pathogens. Ultimately, their actions assist in resolving inflammatory reactions, promote tissue repair, and facilitate healing.

Previously, classical macrophages were classified into M1 and M2 subtypes, along with additional subtypes such as Mox, Mhem, and M4 macrophages. The M2 macrophages were further divided into M2a, M2b, M2c, and M2d subtypes [6]. M1 and M4 macrophages were believed to promote the development of atherosclerosis and unstable plaques, whereas M2, MHEM, and Mox macrophages exert protective effects by promoting tissue repair and plaque stability [7]. However, recent studies using scRNA-seq to examine macrophages in mouse atherosclerotic plaques have led to the reclassification of macrophages into five categories: resident-like macrophages, inflammatory macrophages, interferon-inducible macrophages, foamy Trem2 macrophages, and newly discovered cavity macrophages [8,9]. The markers are listed in Table 1. Depuydt et al. identified three macrophage subgroups in human carotid plaques: My0 and My1 cells, which are associated with inflammation, and anti-inflammatory My2 cells [10].

2.2. M1 macrophages and atherosclerosis

Atherosclerosis is a chronic inflammatory disease [11] with macrophages playing a central role in its development. Macrophage retention within the arterial wall is crucial for atherosclerosis [12]. It primarily depends on the accumulation of low-density lipoproteins (LDLs) in the subendothelium following endothelial injury, and the subsequent aggregation and phagocytosis of lipids by monocyte-derived macrophages [13]. The dysregulation of the balance between lipid uptake and efflux by macrophages leads to the conversion of intracellular free cholesterol to cholesteryl esters (CEs). These accumulated CEs form foam cells [14], which are central to the pathophysiology of atherosclerosis as they participate in the formation of lipid droplets.

Macrophages play a protective role in the early stages of lesions [12]. However, as macrophage apoptosis reduces cell density and inflammation, plaque progression slows down due to effective phagocytosis by neighbouring phagocytes. In advanced lesions, increased macrophage apoptosis and impaired clearance of apoptotic macrophages by neighbouring phagocytes promote the progression of inflammation and the development of necrotic cores within the lesion [15]. Studies on endarterectomy injury in advanced human atherosclerosis demonstrated Th1-dominant as the predominant macrophage type in the diseased atherosclerotic environment [16]. Th1 cells secrete pro-inflammatory cytokines that “classically” activate M1 macrophages [17].

M1 macrophages, in the presence of bacterial, fungal, or viral infections, can produce reactive oxygen species (ROS) to clear pathogens. However, in the sterile inflammatory environment of atherosclerosis, M1 macrophages cause tissue damage and impair wound healing [18], thus contributing to the progression of atherosclerotic plaques.

Table 1
Recent classification of macrophages and their markers.

Macrophages	Makers	References
Resident-like macrophages	Lyve1, Mrc1, Pf4	Wang, Y et al., 2022 [8]
Inflammatory macrophages	Cxcl1, Cxcl2, Ccl2, Ccl3, Ccl4, IL-1β, TNF-α	Zernecke, A et al., 2020 [9]
Interferon-inducible macrophages	Ifit3, Irf7, Isg15	
Foamy Trem2 macrophages	Mmp12, Mmp14, Itgax (CD11c), Abcg1, Trem2, Fabp4, Ctsd, Ctsl、Cd9, Spp1	
Cavity macrophages	Cd226, Itgax (CD11c), Ccr2, Retnla	

3. Polarisation, metabolic reprogramming, and cytokine secretion in M1 macrophages

3.1. M1-type polarisation

Macrophages exhibit various phenotypes that are induced by different microenvironments. The concept of macrophage classification originated in the 1960s with the introduction of the term "classically activated" [19]. Macrophages derived from monocyte precursors 'can be polarised into classically activated (M1) macrophages. Pro-inflammatory monocytes, such as LY6C^{hi} monocytes, express high levels of the CC-chemokine receptor (CCR2) and are considered precursors of M1 macrophages [20].

In vitro, macrophage polarisation relies on lipopolysaccharide (LPS)-mediated activation of Toll-like receptor 4 (TLR4) [21]. TLRs are recognition receptors that detect pathogen-associated molecular patterns (PAMPs). High concentrations of saturated fatty acids and endotoxins can induce pro-inflammatory effects via TLR2 and/or TLR4, stimulating the polarisation of M1 macrophages, which mediate antimicrobial defence, tissue destruction, and other inflammatory effects [22,23]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes macrophage polarisation to the M1 phenotype [21]. Within human atherosclerotic lesions, M1 macrophages are primarily located in lipid-rich areas and in the vulnerable shoulder regions of plaques [17,24].

CD36, a transmembrane glycoprotein receptor expressed in macrophages, belongs to the scavenger receptor B family [25]. It mediates the uptake of oxidised low-density lipoprotein (ox-LDL) and the transport of free fatty acids [26]. Th1 lymphocytes recruit macrophages to obese adipose tissue in both humans and mice [22]. The lipid environment upregulates CD36 expression and promotes macrophage polarisation towards the M1 phenotype. Conversely, histone methylase G9a attenuates palmitate-induced M1 macrophage polarisation by negatively regulating CD36 expression [27]. Adipose tissue releases inflammatory mediators, including saturated fatty acids and cytokines, which stimulate macrophage differentiation into M1[28].

Furthermore, microRNAs (miRNAs), which are non-coding single-stranded RNA molecules approximately 22 nucleotides long, can bind to the 3′-untranslated region of target mRNAs in macrophages. This binding silences the associated genes, leading to translation

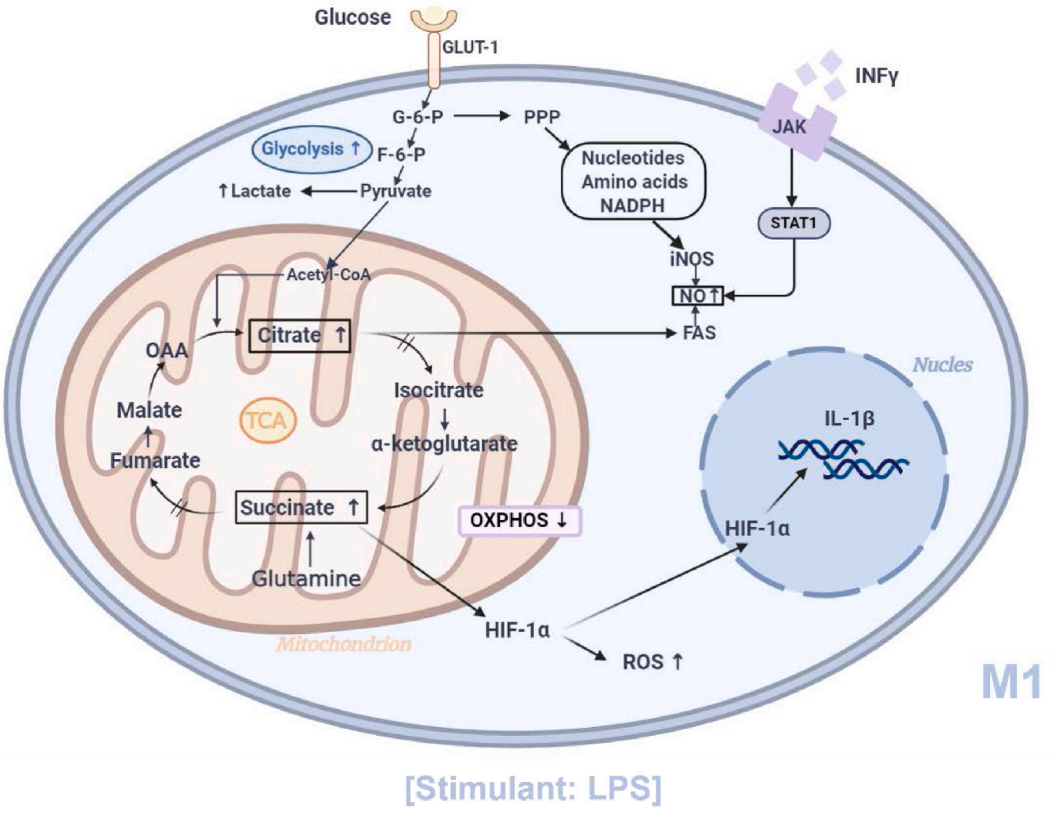

Fig. 1. Metabolism of M1 macrophages
Illustration of the metabolic changes occurring in M1 macrophages. Upon stimulation by LPS, M1 macrophages exhibit increased glycolysis. The pentose phosphate pathway generates nucleotides, amino acids, and NADPH, which in turn stimulates the expression of nitric oxide synthase (iNOS) to produce nitric oxide (NO). Meanwhile, the tricarboxylic acid (TCA) cycle is inhibited, leading to the accumulation of citrate and succinate. The accumulation of citrate can be redirected towards lipid synthesis, leading to NO production. Glutamine supplementation enhances the utilisation of TCA cycle intermediates downstream of citrate, particularly succinic acid. Additionally, glutamine stabilises HIF-1α, promotes the generation of reactive oxygen species (ROS), and triggers the production of related molecules like IL-1β in the nucleus. INF-γ generates NO through the JAK-STAT1 pathway. PPP, pentose phosphate pathway; OAA, oxaloacetic acid; FAS, fatty acid synthetase (Created with BioRender.com).

blockage, regulating macrophage function at the genetic level. Certain miRNAs, such as miRNA-125, miRNA-146, miRNA-155, miRNA-let-7a/f, and miRNA-378 drive macrophage differentiation towards the M1 phenotype [29].

3.2. Metabolic reprogramming

Cellular metabolism and its associated products play crucial roles in regulating macrophage function and phenotype. Activation of M1 macrophages can influence the expression of inflammatory genes by utilising metabolites from the tricarboxylic acid (TCA) cycle within the cellular mitochondria, which participate in both energy metabolism and inflammation. Key metabolites such as succinate, citrate, and the electron transport chain are central to the activation of pro- or anti-inflammatory responses in macrophages [30].

Stimulation of macrophage polarisation towards M1 by LPS and tumour necrosis factor-gamma (TNF-γ) is associated with increased glycolysis, reduced TCA cycle activity, and reduced mitochondrial oxidative phosphorylation (OXPHOS). Type II interferons (e.g. IFN-γ) activate classical M1 macrophages, IFN-γ increases aerobic glycolysis within a few minutes and subsequently decreases OXPHOS after a few hours. This metabolic switch enables M1 macrophages to tolerate lower mitochondrial adenosine triphosphate (ATP) production. ATP produced by glycolysis is essential for maintaining type II interferon-induced Janus tyrosine kinase-signal transducer and activator of transcription 1JAK-STAT-1) signalling. Moreover, M1-activated macrophages produce nitric oxide (NO) via the JAK-STAT1 pathway, aided by the upregulation of inducible nitric oxide synthase [31]. NO impairs mitochondrial function and promotes glycolysis mediated by nitrosative target proteins [32].

The activation of the macrophage M1 phenotype is regulated by nuclear factor-kB (NF-kB), a transcription factor that induces the expression of hypoxia-inducible transcription factor (HIF-1α). In addition, HIF-1α triggers changes in the cellular metabolic phenotype by promoting glycolysis and inhibiting OXPHOS [30,33]. This shift in metabolism is facilitated by the upregulation of lactate dehydrogenase and pyruvate dehydrogenase kinase, resulting in compromised TCA cycle activity and the accumulation of isocitrate and succinate. Excess citrate can be used for lipid synthesis via acetyl coenzyme A (CoA) [34]. Glutamine replenishes TCA intermediates downstream of citrate, whereas gamma-aminobutyric acid (GABA) shunting facilitates the conversion of glutamine to succinate, contributing to the succinate pool in M1 macrophages [35]. Succinate accumulation further stabilises HIF-1α by inhibiting proline hydroxylase activity, subsequently leading to the induction of interleukin-1 beta (IL-1β) production and ROS generation. This allows glucose metabolism to be linked to the pro-inflammatory properties of M1 macrophages [34,36–38]. Moreover, the inhibition of GABA transaminase by vigabatrin reduces glutamine-derived succinate, stabilises HIF-1α, and decreases IL-1β secretion by macrophages [35]. Disruption of the TCA cycle enhances the production of lactate, purines, and pyrimidines, providing NADPH with the ability to activate the NADPH oxidase system (Nox) in macrophages, thereby promoting inflammatory responses and tissue damage [29,39]. The interaction between NO and ROS also leads to the production of reactive nitrogen species such as peroxynitrite, which can impair NO bioavailability and damage extracellular proteins [40]. (Fig. 1).

To compensate for interruptions in the TCA cycle and prevent excessive carbon accumulation from succinate, the aspartate-arginine shunt converts aspartate to oxaloacetate via aspartate aminotransferase. Additionally, this shunt can link TCA cycle metabolites such as fumarate, malate, and oxaloacetate to NO synthesis [35]. Inhibition of the shunt using the aspartate aminotransferase inhibitor, aminooxyacetic acid, reduces NO and interleukin-6 production in M1 macrophages [36].

Gene microarray analyses revealed that M1-activated bone marrow-derived macrophages exhibited altered gene expression patterns associated with metabolic changes within cells. The upregulation of glucose transporter protein (GLUT1), hexokinase 3 (HK3), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), phosphor glucose translocase 2 (PGM2), and enolase 2 (ENO2) confirmed the increased glycolysis observed in M1 macrophages [34].

3.3. Secreted cytokines

M1 macrophage activation can upregulate several genes, including interferon-induced genes and interferon modulators, which positively regulate macrophage activation and polarisation, which in turn leads to the expression of M1-philic genes such as IL-12 [41,42]. In recent years, largely based on mouse studies, IL-4 and IL-10 have been suggested to be hallmarks of M2-type macrophage polarisation. However, Gharib et al. based on the high complexity of macrophage transcriptional profiles, observed that IL-10 in response to LPS, exerts the opposite effect on IL-4, thereby promoting the activation and polarisation of human monocyte-derived macrophages to produce pro-inflammatory factors. This suggests interspecies variability in cytokine production by M1/M2 macrophages, which may be attributed to the interferon signalling pathway [23].

In diet-induced atherosclerotic mice, cholesterol crystals were observed early in the lesion area. These cholesterol crystals induce the activation of macrophage caspase-1, hexokinase 1, and pyruvate kinase M2, leading to the activation of the NLRP3 inflammasome. This activation facilitates the release of pro-inflammatory cytokines from the IL-1 family (such as IL-1β and IL-18) [33,43]. Adipose tissue macrophages (ATM) further amplify the inflammatory response by increasing the production of tumour necrosis factor-α (TNF-α), IL-6, and IL-1β, as well as actively secreting chemokines like monocyte chemotactic protein 1 (MCP-1) and LTB4, which facilitates the recruitment of additional monocytes [44]. Moreover, once circulating monocytes are recruited, pro-inflammatory macrophages secrete additional chemokines, further enhancing the inflammatory response, accelerating the development of atherosclerotic lesions, and creating a positive feedback mechanism [22,28].

Finally, macrophages that transform into foam cells produce matrix metalloproteinases (MMPs), followed by macrophage death, resulting in the transformation of lipid pools into necrotic cores. MMPs break down the extracellular matrix in plaques, resulting in the thinning of fibrous cap tissue [45] (Fig. 2). In particular, MMP9 has been demonstrated, via Mendelian randomisation studies, to be causally associated with atherosclerosis risk when present at high levels in the circulation [46].

4. Mechanisms of AS promotion by M1 macrophages

4.1. Recruitment of inflammatory cells

Hyperlipidaemia is recognised as a significant risk factor for the development of atherosclerosis. An elevation in plasma LDL leads to atherosclerosis in all mammals. Under otherwise equal conditions, the higher the LDL level, the faster the progression of plaque formation [47]. LDL concentrations exceeding physiological levels can cause the lipoproteins present in the arterial wall to undergo various modifications (such as oxidation and enzymatic degradation), rendering them pro-inflammatory. These modified lipoproteins subsequently activate the overlying vascular endothelial cells, leading to increased recruitment of monocytes into the plaques [20].

When cholesterol efflux in macrophages is hindered, the expression of the common β-subunit of interleukin-3 (IL-3) and the GM-CSF receptor on haematopoietic stem and progenitor cells (HSPCs) is heightened. This increase in HSPCs results in the amplification of monocyte precursor cells, thereby augmenting the likelihood of monocyte recruitment [48]. Monocyte recruitment is influenced by various factors, including CCR2, CCR5, and CX3CR1. Monocyte chemotactic protein-1, is an essential chemokine involved in the initiation of inflammatory responses and crucial for the early stages of monocyte recruitment. MCP-1, in conjunction with IL-8 or CXC ligand-8, triggers the adhesion of monocytes to vascular endothelial cells within the vasculature. Additionally, various adhesion molecules expressed on monocytes, such as LFA1, PSGL1, CD31, VLA-4, and CD62L, facilitate adhesion by interacting with endothelial cells. The early stages of monocyte recruitment play a dominant role in lesion progression and are necessary for the development of atherosclerotic plaques [29,49].

4.2. Foam cell formation

Excessive uptake of modified LDL by macrophages and subsequent cholesterol accumulation within these cells are the primary causes of foam cell formation and play crucial roles in all stages of atherosclerosis development [50]. Single-cell RNA sequencing of

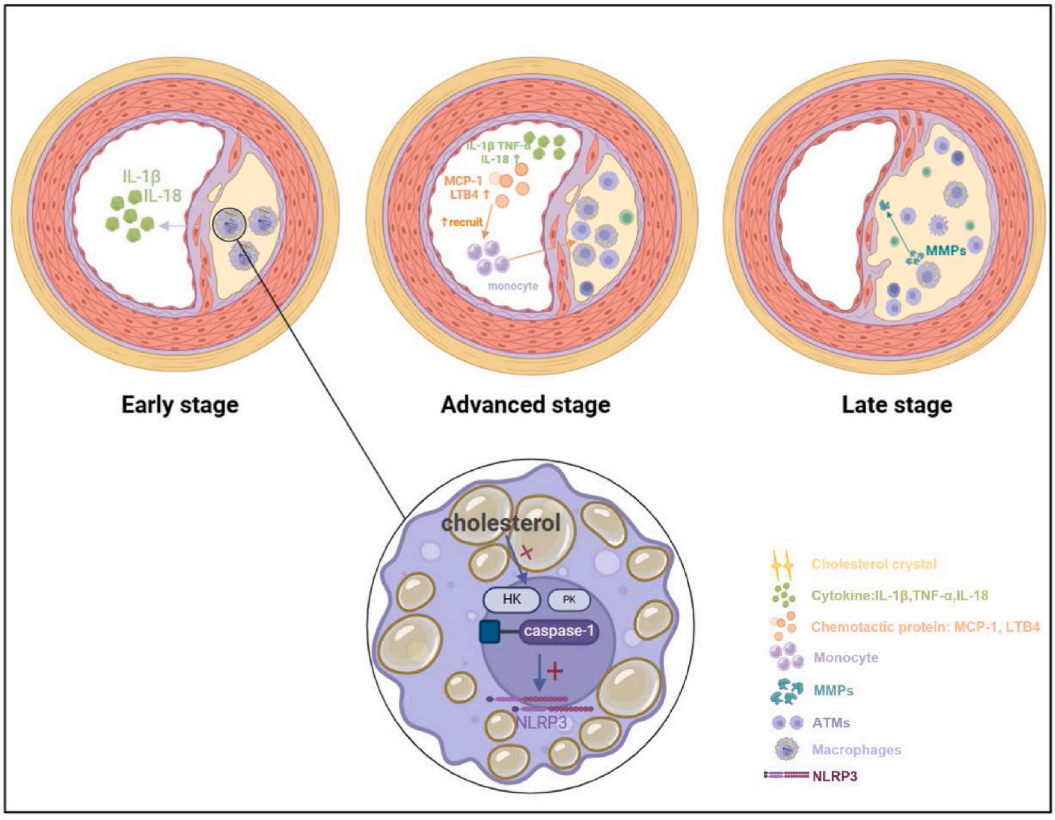

Fig. 2. Cytokines secreted by M1 macrophages
Early formation of cholesterol crystals in plaques activates the NLRP3 inflammasome in macrophages, leading to the release of pro-inflammatory cytokines IL-1β and IL-18. As the plaque progresses, adipose tissue macrophages (ATMs) continue to release pro-inflammatory factors, such as TNF-α, IL-6, and IL-1β, to sustain the inflammatory response. In addition, chemokines, such as MCP-1 and LTB4, are released paracrine or endocrine by ATMs around blood vessels to facilitate the recruitment of additional monocytes to the lesion site. As the disease progresses, macrophages, particularly MMP9, contribute to extracellular matrix degradation by secreting matrix metalloproteinases (MMPs). HK: hexokinase 1; PK: pyruvate kinase; CC: cholesterol crystal (Created with BioRender.com).

neonatal aortic leukocytes revealed a unique genetic signature of macrophages, termed as the aortic intimal macrophage (Mac^{AIR}) population, representing the cells that first differentiate into foam macrophages [51]. Mononuclear macrophages secrete protein-modifying enzymes that further modify lipids and promote the secretion of these enzymes, creating a positive feedback loop during the initiation of atherosclerosis [52].

During atherosclerosis, vascular permeability to LDL increases, and lectin-like oxidised lipoprotein-1 (LOX-1) expression is upregulated. The expression of dynein core glycoprotein 1 (DSG1) and dynein core glycoprotein 2 (DSC2), components of intercellular junctions, is reduced by LOX-1, which weakens the junctions and increases the transfer of ox-LDL between cells. Protein kinase C regulates the blockade of a key component of intercellular tight junctions and protein phosphatase 1 regulatory subunit 14A (PPP1R14A), leading to increased vascular endothelial permeability [53–55].

Macrophages express scavenger receptors on their surfaces, including SR-A1, CD36, and LOX-1, which interact with lipoproteins to uptake circulating lipids. Additionally, they express reverse transporters, such as ABCA1, ABCG1, and SR-B1, to efflux intracellular lipids [53]. The expression of SR-A1 can stimulate the upregulation of the voltage-dependent K^+ channel Kv1.3, leading to increased uptake of ox-LDL [56]. Inhibition of ubiquitin-specific peptide 9x-linked (USP9X) attenuates SR-A1 deubiquitination and promotes its internalisation, facilitating foam cell formation and inflammatory responses [57]. Additionally, nuclear factor-κB (NF-κB) mediates the upregulation of CD146 by ox-LDL in macrophages; CD146 activates pro-inflammatory activity and promotes foam cell formation by interacting with CD36. This effect is further enhanced over time by oxLDL. The presence of CD146 on macrophages not only contributes to the development of atherosclerotic plaques, but also hinders macrophage migration, leading to their retention and ultimately enhancing atherosclerotic plaque complexity [58]. The trigger receptor expressed on myeloid cell 2 (TREM2) promotes lipid influx and foam cell formation by upregulating CD36 in macrophages [59]. Deficiency of nuclear factor of activated T-cell (NFAT) family protein c3 (NFATc3) leads to an increase in SR-A and CD36 expression, resulting in increased lipid uptake and foam cell formation in macrophages [60].

Pro-inflammatory activation of macrophages upregulates hypoxia-inducible lipid droplet-associated protein (HILPDA), promoting the degradation of triglyceride lipase (ATGL), a key enzyme in triglyceride hydrolysis, leading to increased accumulation of triglycerides in macrophages. HILPDA has a similar effect on ATGL as ATGL inhibitors, increasing endogenous HILPDA levels, decreasing ATGL expression, and increasing intracellular fat [61].

Collectively, during atherosclerosis, increased vascular endothelial permeability, upregulated expression or function of scavenger receptors on macrophages (particularly SR-A and CD36), and the degradation of intracellular lipases collectively contribute to intracellular lipid accumulation, transforming macrophages into foam cells, which are key features of the early stages of atherosclerosis formation.

4.3. Plaque progress

Foam cells play an important role in atherosclerosis. These cells secrete the extracellular matrix, leading to the retention of lipoproteins and the secretion of pro-inflammatory cytokines, consequently enhancing the recruitment of more inflammatory cells. During the early stages of atherosclerosis, lipid-filled foam cells undergo apoptosis and are cleared by anti-inflammatory M2 macrophages via efferocytosis [62]. However, excessive phagocytosis of apoptotic cells by macrophages can induce endoplasmic reticulum stress, leading to macrophage death, and the release of lipids and metalloproteinases [63]. The formation of a thick fibrous cap rich in extracellular matrix contributes to the stability of atherosclerotic plaques. M2 macrophages are part of the fibrous cap, especially when vascular smooth muscle cells (SMCs), the main source of the fibrous cap, are reduced. Macrophage-to-mesenchymal-transformed macrophages play a larger role but cannot fully compensate for the loss of SMCs [64].

With the progression of the lesion, the ability of anti-inflammatory macrophages to phagocytose apoptotic cells is impaired, resulting in the accumulation of apoptotic macrophages and the formation of highly inflammatory necrotic cores [62]. The well-known macrophage phagocytic receptor c-Mer tyrosine kinase (MerTK) mediates phagocytosis by anti-inflammatory macrophages in atherosclerotic lesions. Cleavage of MerTK increases plaque necrosis, whereas resolvin D1 (RvD1) inhibits MerTK cleavage, reduces plaque necrosis, and improves phagocytosis [65]. The reduced expression of MerTK and impaired phagocytosis in macrophages in advanced atherosclerotic lesions have been associated with increased levels of Ca^{2+}/calmodulin-dependent protein kinase γ (CaMKIIγ) [66]. Another mechanism hindering phagocytosis is the decreased expression of the “Eat me” signalling molecule calreticulins on the surface of diseased cells. In addition, decreased binding of “Eat me” ligands on the surface of cells by ox-LDL or oxidised phospholipid autoantibodies, further impairs phagocytosis [62,67]. CD47, significantly upregulated in atherosclerotic plaques, and its ligand, macrophage signal-regulating protein-alpha (SIRP-α), inhibit macrophage phagocytosis, contributing to decreased phagocytic activity [68], thereby promoting the formation of necrotic cores in atherosclerotic plaques, ultimately increasing the risk of plaque rupture.

Monocyte recruitment occurs during all stages of atherosclerosis. However, monocytes are unable to penetrate deep into the plaque, and advanced lesions are primarily composed of proliferating macrophages derived from monocytes [49,69,70]. The activation of the serine/threonine protein kinase mammalian target of rapamycin (mTOR) during cell proliferation is one mechanism by which pro-inflammatory macrophages activate HIF-1α. This promotes atherosclerosis progression by increasing the expression of glycolytic and inflammatory genes [71].

As M1 macrophages play a crucial role in the progression of atherosclerosis, targeting their function may present new opportunities for the diagnosis and treatment of this condition.

5. M2 macrophages and atherosclerosis

Activated M1 macrophages are crucial for the progression of atherosclerosis, whereas alternatively activated M2 macrophages influence the regression of atherosclerosis. M2 macrophages are primarily activated by IL-4 and IL-13 through JAK-STAT, PPAR, AMPK, and/or transforming growth factor-β (TGF-β) pathways to produce anti-inflammatory cytokines such as IL-10 and pro-fibrotic factors like fibronectin, insulin-like growth factor, and TGF-β to promote inflammation resolution and tissue repair in opposition to the pro-inflammatory effects of M1 macrophages. Surface markers of M2 macrophages include mannose receptor (CD206) and arginase-1 (Arg-1) positivity within the CD68 cell subset [12,72]. Studies on atherosclerosis regression in mice have demonstrated that a characteristic of plaque regression is the decrease in lesion macrophage content, upregulation of markers of M2 macrophages such as Arg-1 and CD163, and a reduction in CCL2 and TNF-α mRNA levels, indicating the predominant role of M2 macrophages during lesion regression [12,14]. Recent research suggests that the continual recruitment of Ly6chi inflammatory monocytes and their polarisation to the M2 state, dependent on STAT6, are essential for resolving atherosclerotic inflammation and promoting plaque regression [73]. These findings highlight the crucial role of M2 macrophages in atherosclerosis regression.

M1 and M2 macrophages exhibit distinct metabolic differences. While M1 macrophages rely on increased glycolysis, M2 macrophages predominantly rely on fatty acid oxidation. Notably, although one of the characteristic features of M2 macrophages is increased fatty acid oxidation, this process depends on glucose to drive the TCA cycle and on OXPHOS for energy production (fatty acid oxidation can supplement acetyl-CoA). This metabolic pathway enables efficient and sustainable energy production, which is essential for the anti-inflammatory and tissue repair functions of M2 macrophages (Fig. 3) [33,36]. Another metabolic feature of M2 macrophages is the upregulation of arginase-1, which metabolises L-arginine into L-ornithine and urea, subsequently resulting in the generation of polyamines and L-proline, both crucial for the promotion of wound healing and tissue repair by M2 macrophages [33,74].

6. Novel atherosclerosis treatment strategies

Lipid-lowering therapy is the fundamental approach to treating atherosclerotic diseases, and its effectiveness in reducing cardiovascular events is directly related to an absolute decrease in LDL cholesterol levels. According to European guidelines, statins are recommended as the primary drugs for lipid lowering, and their efficacy in reducing LDL levels can range from 30 to 50 %, depending on the type, dosage, and effectiveness of the statin used. In patients with diabetes, statins can be combined with fibrates to provide additional benefits [75]. Notably, in patients with high cholesterol levels, PCSK9 inhibitors are also necessary because PCSK9 plays a significant role in the regulation of lipid metabolism. PCSK9 inhibitors not only reduce circulating LDL levels but also inhibit the uptake of LDL cholesterol by arterial macrophages. Moreover, PCSK9 affects atherosclerosis independent of cholesterol levels. PCSK9 also stimulates monocyte migration to the atherosclerotic areas. Recombinant PCSK9 promotes the transcription of pro-inflammatory cytokines TNF-α and IL-1β and inhibits the mRNA levels of anti-inflammatory cytokines in macrophages. Inhibition of PCSK9 can suppress the inflammatory response of M1 macrophages, thereby attenuating atherosclerosis [76,77]. Monoclonal antibodies, peptide

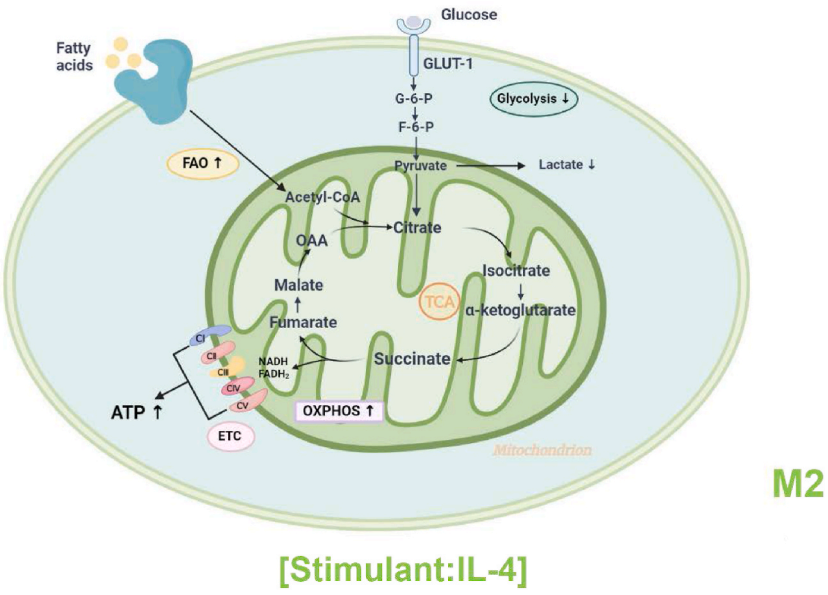

Fig. 3. Metabolism of M2 macrophages
Illustration of the metabolism of M2 macrophages. IL-4 stimulates macrophage polarisation towards the M2 phenotype. Glucose drives the upregulation of the TCA cycle, while glycolysis down-regulates it. Fatty acids enter the cell and enhance fatty acid oxidation, providing the acetyl coenzyme A required for the TCA cycle, thereby increasing oxidative phosphorylation and resulting in the production of a large amount of ATP required for tissue repair. ETC: electron transport chain (Created with BioRender.com).

inhibitors, and PCSK9 silencing are some methods used to inhibit PCSK9. Two complete human *anti*-PCSK9 monoclonal antibodies, alirocumab and evocumab, have been approved by the U.S. Food and Drug Administration for the treatment of familial hypercholesterolaemia, or ASCVD, in patients requiring further LDL-C reduction. These drugs can significantly reduce LDL-C levels (50 % reduction in monotherapy and 70 % reduction when combined with statins) and exhibit good safety profiles [77]. Recently, a new dual-stranded siRNA, called inclisiran, was developed to block PCSK9 via the degradation of PCSK9 mRNA, leading to the lowering of LDL-C concentrations in the plasma [78]. Other novel developments include three main types of PCSK9 vaccines: Peptide Vaccine AT04A (which not only reduces LDL-C but also decreases pro-inflammatory factors), Nanoliposome *Anti*-PCSK9 Vaccine L-IFPTA+ (which induces higher and more persistent *anti*-PCSK9 antibody titres compared to peptide vaccines), and Virus-Like Particle (VLP) Peptide Vaccines *Anti*-PCSK9 Qβ-003 (which reduces lipid levels and also exhibits anti-fibrotic effects related to regulating fatty acid β-oxidation) [78,79].

Although lowering cholesterol levels alone has demonstrated potential benefits, some studies suggest that it may not be sufficient to completely prevent adverse cardiovascular events [80]. A notable characteristic of atherosclerotic regression is the extensive changes observed in the transcriptomes of plaque macrophages [7]. Macrophages are not strictly categorised as M1 or M2; rather, they exhibit plasticity and can be reprogrammed and transitioned between the two phenotypes [6,81]. Understanding the mechanisms that regulate macrophage phenotypes can significantly contribute to the development of novel therapeutic approaches. For instance, ATF3, a transcription factor induced by HDL, inhibits pro-inflammatory cytokines [82]. TFKLF4 can convert pro-inflammatory macrophages into anti-inflammatory activated macrophages [83]. In vivo knockouts of HDAC3 [84] and HDAC9 [85] in mice promoted plaque stability and attenuated atherosclerosis. In $Ldlr^{-/-}$ deficient murine peritoneal macrophages, the expression of KDM6B [86] improves plaque stability. Additionally, modified LDL induces expression of microRNA hsa-let-7d-5p in macrophages, which inhibits its target gene high mobility group AT hook 2 (HMGA2), ultimately reducing foam cell production and conferring anti-resistance to atherosclerosis [87,88].

In addition to lipid-lowering therapy, maintaining the balance between macrophage pro-inflammatory and anti-inflammatory activities is crucial in determining the final outcome of atherosclerosis [89]. Targeting inflammatory pathways is a promising and novel therapeutic approach. While inflammation resolution was previously considered a passive process, recent studies have demonstrated its highly coordinated and proactive nature [90]. Specific pro-catabolic mediators (SPM), which are synthesised by various cells, including macrophages, have been shown to inhibit initiation of atherosclerosis, inactivate NLRP3 inflammatory vesicles, inhibit inflammation progression, contribute to inflammation resolution, enhance macrophage phagocytosis, and promote atherosclerotic plaque stability [89,91,92]. SPMs are metabolites of polyunsaturated fatty acids, including fatty acid enzymes, such as lipoxygenase (LOX), cyclooxygenase-2 (COX-2), and cytochrome P450. They mainly belong to four families: lipoxins (LX), resolvins (Rv), protectins (PD), and maresins (MaR) [93]. SPMs and membrane-associated protein A1 can promote macrophage polarisation towards the M2 phenotype via the ALX/FPR2 signalling pathway. MaR1 may serve as an endogenous ligand for the nuclear receptor ROR, regulating macrophage M2 polarisation and promoting inflammation resolution [89,94]. The interaction between RvD1 and GPR32/DRV1 stimulates the synthesis of mi-R-208a in macrophages, resulting in elevated IL-10 levels. Additionally, it can increase the synthesis of miR-146b, which inhibits NF-κB transcription, thereby suppressing inflammation [93]. MerTK, a tyrosine kinase, acts as a receptor for macrophage efferocytosis. It increases the levels of non-phosphorylated cytosolic 5-LOX, inhibits the activity of calcium/calmodulin-dependent protein kinase I (CaMKII), and promotes the production of SPMs by macrophages. ADAM17, which is involved in atherosclerosis, cleaves MerTK. Administration of RvE1 in atherosclerosis-prone mice reduces ADAM17 expression, TNF-α, and IFN-γ levels, and promotes macrophage polarisation towards the M2 phenotype [92,93]. In addition, SPMs recruit macrophages and enhance their efferocytic capacity. Efferocytosis, in turn, promotes the production of SPMs in macrophages, forming a positive feedback process for inflammation resolution [92]. In advanced cases of AS with deficient SPM levels, exogenous administration of SPM could be considered [95]. In addition to SPMs, canakinumab (a monoclonal antibody targeting the pro-inflammatory cytokine IL-1β) has demonstrated anti-inflammatory effects independent of lipid action [96]. Therefore, anti-inflammatory therapies hold promise as a new treatment option for atherosclerosis.

However, several inflammatory pathways are systemic, and inhibiting inflammatory factors while reducing cardiovascular events can increase the risk of infection owing to immunosuppression. Recently, nanoparticle-assisted treatment of atherosclerosis significantly improved its therapeutic efficacy and reduced systemic side effects [97]. For example, lipid nanoparticles encapsulating CCR2 siRNA target $LY6C^{hi}$ monocytes, reducing the recruitment of M1 precursor macrophages, and alleviating inflammation in lesion [98,99]. Recombinant HDL nanoparticles carrying an inhibitor of the $CD40^{-}CD40L$ cascade between monocytes and macrophages have

Table 2
The latest nanomedicine for the treatment of atherosclerosis.

Ingredients	Package	Target	Consequence	Experiment Subject
CCR2 siRNA [98,99]	Lipid	$LY6C^{hi}$ Monocyte	Release recruitment	Apoe $^{-/-}$ mice
CD40-TRAF6 Inhibitor [100,101]	rHDL-MHPC-DMPC	Macrophage $CD40^{-}CD40L$	Release recruitment	Apoe $^{-/-}$ mice
RAP Inhibitor [102]	PLGA- RV	mTOR Pathway	Inhibit macrophage proliferation	Apoe $^{-/-}$ mice
$Ac2\text{-}26^{95,104}$	NPs-Col IV	ALX/FPR2 Pathway	Stabilize plaque	$Ldlr^{-/-}$ mice
CD47-SIRP-α Inhibitor [68]	PEG-SWNTs	LY6Chi Monocyte	Recover efferocytosis	Apoe −/− mice
MCC950 [103]	PEV	Foam cell	Inhibit macrophage proliferation	ApoE-KO mice

*MHPC: phospholipids 1myristoyl-2-hydroxy-sn-glycero-phosphocholine, DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine, PLGA: Poly (lactic-*co*-glycolic) acid, RV: RBC vesicles, NPs: Nanoparticles, Col IV: Collagen IV, PEG: Polyethylene glycol, SWNTs: Single-walled carbon nanotubes, PEV: Platelet-derived extracellular vesicles.

been found to reduce inflammation by decreasing circulating monocyte recruitment without affecting other immune functions of macrophages [100,101]. Wang et al. discovered that rapamycin, an inhibitor of the mammalian target of the rapamycin pathway, when loaded in poly (lactic-*co*-glycolic acid) (PLGA) nanoparticles coated with red blood cell membranes, exhibits improved accumulation within the atherosclerotic plaques, thereby inhibiting macrophage proliferation and enhancing plaque stability [102]. Engineered platelet-derived extracellular vesicles loaded with the NLRP3 inflammatory vesicle inhibitor MCC950 can target macrophage-derived foam cells to inhibit macrophage proliferation and reduce local inflammation [103]. Controlled-release polymer nanoparticles encapsulating Ac2-26, a peptide targeting the ALX/FPR2 pathway at atherosclerotic sites by adding collagen IV (Col IV)-binding peptides, have been shown to alleviate inflammation, suppress collagenase activity, and stabilize plaques at atherosclerotic sites [95,104]. Moreover, polyethylene glycol-functionalized single-walled carbon nanotubes with CD47-SIRP-α inhibitors reactivate phagocytosis by M1 macrophages and slow plaque progression when targeted to atherosclerotic plaques [68] (Table 2).

Although lipid-lowering therapy remains the cornerstone of atherosclerosis treatment, exhibiting a good curative effect, cardiovascular disease still accounts for the majority of global deaths [105]. Therefore, there is a need to explore new therapeutic approaches that target the pathophysiological mechanisms underlying atherogenesis. Targeted nanomedicines offer the advantages of efficacy and safety, and significant progress has been made in macrophage-targeted nanomedicine research in recent decades. Most of these drugs are currently in animal or preclinical stages. Despite these challenges, nanomedical therapeutics represent a major breakthrough in the treatment of atherosclerosis.

7. Summary

Atherosclerosis is a cardiovascular disease that threatens human health. Mechanistically, apart from the dysfunction of vascular endothelial and smooth muscle cells that contribute to atherosclerosis, macrophages, especially M1 macrophages, also play a significant role in its progression. M1 macrophages primarily promote the development of atherosclerosis through inflammatory pathways, including inflammatory responses and positive feedback mechanisms. In contrast, anti-inflammatory M2 macrophages play a crucial role in atherosclerosis regression.

Currently recognised methods for treating atherosclerosis typically involve reducing low-density lipoprotein levels in the bloodstream using common approaches, including statins, PCSK9 inhibitors, and ezetimibe. In addition to lipid-lowering therapies, targeting the pro-inflammatory activity of M1 macrophages could offer a new perspective for atherosclerosis treatment. While inhibition of inflammation can alleviate atherosclerotic lesions, it may also lead to systemic immunosuppression. The emergence of nanomedicine has addressed this challenge by enabling precise targeting of lesions using specific nanomaterials and bioenvelopes, thereby slowing disease progression.

Although a substantial amount of research has explored the relationship between macrophages and atherosclerosis, several aspects of the disease remain unexplored. Advancements in technology have improved the classification of macrophages; however, the lack of standardised classification criteria may pose challenges for future studies. Furthermore, owing to the complexity of alternatively activated macrophages, the mechanism by which they promote lesion regression is unclear, despite their crucial role in its progression. Finally, the predominance of atherosclerosis studies using mouse models may not fully reflect disease progression in humans.

Despite these limitations, I believe that with technological advancements, studies on the role of macrophages in the progression or regression of atherosclerosis will continue to improve, providing new insights into its diagnosis and treatment.

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Data availability statement

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this is a review.
Informed consent was not required for this study because this is a review.

CRediT authorship contribution statement

Bo Yang: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Sanhua Hang:** Writing – review & editing, Writing – original draft. **Siting Xu:** Writing – review & editing. **Yun Gao:** Writing – review & editing. **Wenhua Yu:** Writing –

review & editing. **Guangyao Zang:** Writing – review & editing, Funding acquisition. **Lili Zhang:** Writing – review & editing, Funding acquisition. **Zhongqun Wang:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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