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Review Article

The Role of Macrophages in Atherosclerosis Development

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Abstract

Atherosclerosis is a chronic inflammatory vascular disease in which macrophages play central roles in lipid uptake, foam cell formation, plaque progression, plaque instability and, under certain conditions, plaque regression. This narrative review summarizes current knowledge on macrophage biology in atherosclerosis, with emphasis on macrophage phenotypic diversity, monocyte-endothelial interactions, foam cell formation, extracellular matrix remodeling, immune-cell interactions, cytokine signaling, mitochondrial dysfunction and cellular senescence. The review also discusses emerging macrophage-targeted strategies, including modulation of inflammatory activity, macrophage polarization, cholesterol efflux and lipid homeostasis. Although these approaches provide promising mechanistic and therapeutic insights, many remain at the preclinical stage. Further studies are needed to validate macrophage subtype-specific biomarkers, clarify the interaction between mitochondrial dysfunction and senescence, and evaluate safe and effective combination strategies for clinical translation.

Introduction

Atherosclerosis is a cardiovascular disease characterized by thickening of the intima of elastic-type arteries and chronic inflammatory processes. Atherosclerosis is one of the leading causes of death in developed countries and can also provoke the development of other cardiovascular diseases. Atherosclerosis involves both metabolic disorders and chronic inflammation in arterial walls. In the intima of the artery, macrophages absorb atherogenic low-density lipoprotein (LDL), inducing the formation of foam cells. In later stages, processes occur that lead to the formation of atherosclerotic plaque: synthesis of chemokines, increased inflammatory processes, synthesis of extracellular matrix (ECM) components by smooth muscle cells (SMCs), and penetration of other immune cells into the intima of the artery. Macrophages are an important link in the induction of inflammatory processes in the intima of the arteries. Therefore, studying macrophages may help identify new therapeutic approaches for atherosclerosis. In this review, much attention is paid to the pathological processes associated with macrophages: their adhesion, formation of foam cells, localization of macrophages in atherosclerotic lesions, interaction with the ECM and immune cells, as well as methods of macrophage-mediated therapy of atherosclerosis.

This narrative review aims to systematize current knowledge about the role of macrophages in the pathogenesis of atherosclerosis, with a focus on their phenotypic diversity, activation mechanisms, interactions with other cells and the ECM, and the potential for modulating their functions. In addition, it seeks to identify gaps in understanding the functional overlap of macrophage subpopulations and the synergistic effects of mitochondrial mutations and cellular aging, and to systematize potential therapeutic approaches targeting macrophages in order to provide a theoretical framework for clinical translation and future research. By integrating basic research findings with clinical implications such as biomarker development and targeted therapies, this review provides a theoretical framework that bridges cellular and molecular mechanisms with translational applications in cardiovascular medicine.

Keywords: Atherosclerosis; Macrophages; Cardiovascular disease; Monocytes; Endothelium; Foam cells; Inflammation.
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Pathology and progression of atherosclerosis

Atherosclerosis is a disease of the cardiovascular system characterized by chronic inflammation.[1] Atherosclerosis can lead to stroke, heart attack, coronary heart disease, myocardial infarction, circulatory disorders, heart failure, and other cardiovascular diseases.[2]

Atherosclerosis can be caused by various genetic and environmental factors. The risk factors promoting the development of atherosclerosis include stress, hypercholesterolemia, hypertension, diabetes, smoking, high cholesterol, aging, and hereditary predisposition.[3] Diabetes may be one of the causes of atherosclerosis. Macrophages of patients with diabetes and atherosclerosis showed elevated levels of histone deacetylase 3 (HDAC3). In ApoE$^{-/-}$ mice with HDAC3 knockout receiving a high-fat diet (HFD), a decrease in the size of atherosclerotic lesions and a decrease in the level of lipids in atherosclerotic plaques were observed.[4]

Atherosclerosis is a disease associated with both metabolic disorders and a chronic inflammatory process in the artery wall induced by subendothelial deposition of lipoproteins containing apolipoprotein B (apoB).[5] Atherosclerosis is a focal disease, the cause of which mainly lies in a violation of laminar flow, primarily manifested at sites of arterial branching and bifurcation.[6] Atherosclerosis affects large and medium-sized arteries; the progression of the disease is slow, and symptoms usually appear in the fifth decade of life.[7]

According to histological classification, there are six types of atherosclerotic lesions. Type I lesions are characterized by the presence of atherogenic LDL in the intima of the arteries, which leads to an increase in the number of macrophages and their transformation into foam cells. Type II lesions include fatty streaks consisting of layers of foam cells and lipid-saturated SMCs. Type III atherosclerotic lesions, which include scattered clusters of extracellular lipid droplets, represent an intermediate stage between types II and IV.[8] Type IV atherosclerotic lesions are characterized by a necrotic lipid core and destruction of the intima of the artery. In type V atherosclerotic lesions, a fibrous membrane forms, and calcification may also occur. In type VI lesions, thrombosis, destruction of the arterial wall, hematomas, and hemorrhages are observed.[9]

When laminar flow is disrupted, endothelial dysfunction develops, allowing LDL to enter the intima of the artery through the endothelium. LDL is oxidized in the intima of the artery, and receptors mediate the synthesis of chemokines by macrophages, which induces the penetration of monocytes into the intima.[10] Macrophages begin to absorb oxidized low-density lipoprotein (oxLDL), forming foam cells.[11] Further, processes leading to the formation of atherosclerotic plaque occur: synthesis of chemokines, increased inflammatory processes, synthesis of ECM components by SMCs, and penetration of other immune cells into the intima of the artery.[12] These processes eventually lead to blockage of the vessel. Thus, macrophages are an important link in the progression of atherosclerotic plaque. The study of pathological processes associated with macrophages is relevant to the prevention and treatment of cardiovascular diseases.

Diet and lifestyle play an important role in the development of atherosclerosis.[13] In experiments, ApoE$^{-/-}$ mice were exposed to low-, moderate-, and high-protein diets. A high-protein diet contributed to an increase in the size of atherosclerotic plaques and the necrotic core, as well as activation of mTORC1. Activation of mTORC1 in human monocyte-derived macrophages by the amino acid leucine led to suppression of autophagy and mitophagy, which was confirmed by a decrease in LC3 signaling, increased apoptosis, mitochondrial dysfunction, and reactive oxygen species (ROS) content. Exercise in ApoE$^{-/-}$ mice treated with an HFD reduced the area of atherosclerotic plaques and lipid content, increased collagen synthesis, and increased the number of M2 macrophages and expression of ARG1 and interleukin (IL)-10, while reducing the expression of pro-inflammatory genes inducible nitric oxide synthase (iNOS) and tumor necrosis factor (TNF)-α, making plaques more stable compared to those with no exercise.[14] The polarization of M2 macrophages and decreased expression of M1 markers is facilitated by inhibition of RUNX1 and demethylation of H3K36me3 and reduction of SETD2, which is mediated by lactylation of MeCP2 K271. Thus, physical exercise remodels chromatin, improving the accessibility of promoters of genes associated with M2 macrophage polarization.

It should be mentioned, of course, that the pathogenesis of atherosclerosis is far from being completely understood. Although macrophages appear to play a significant role in the development of this disease, other factors should also be taken into consideration, such as non-coding RNA,[15] autoimmune responses,[16] and infection by certain agents.[17,18]

Phenotypic diversity of macrophages

During the development of atherosclerosis, monocytes that circulate in the general bloodstream migrate to the vascular endothelium, where, depending on their origin and the local microenvironment, they differentiate into macrophages with different functions and phenotypes (Fig. 1).[19-23] The process of macrophage phenotype formation under the influence of the microenvironment is called polarization.[24] Monocytes, monocyte-derived macrophages, and tissue-resident macrophages are different groups of cells that change their functionality depending on surrounding microenvironmental stimuli.[25,26]

Macrophages can be divided into two main subpopulations by function—M1 (pro-inflammatory, classically activated) and M2 (anti-inflammatory/pro-resolving, alternatively activated)—which contribute to the regulation of immunity, inflammation, and tissue repair. M1 macrophages destroy pathogens and tumors, and M2 macrophages contribute to tissue healing and tumor progression (Fig. 1).[19-23] There are other relatively recently identified macrophage subpopulations, which will also be discussed in this section (Fig. 1).

Previous studies have suggested that tissue macrophages have several different functions: (1) inhibition of the inflammatory process in tissues, (2) participation in tissue repair and remodeling, and (3) regulation of matrix metabolism through the synthesis of proteases that destroy the ECM.[27-29]

The division of macrophages into phenotypes is based on the synthesis of various surface markers and chemokine receptors in individual macrophage subtypes. Although there are markers common to several subtypes, each subtype also possesses type-specific markers.[30] Several main phenotypic subtypes of macrophages can be found in atherosclerotic plaques, which are polarized under the influence of specific microenvironmental

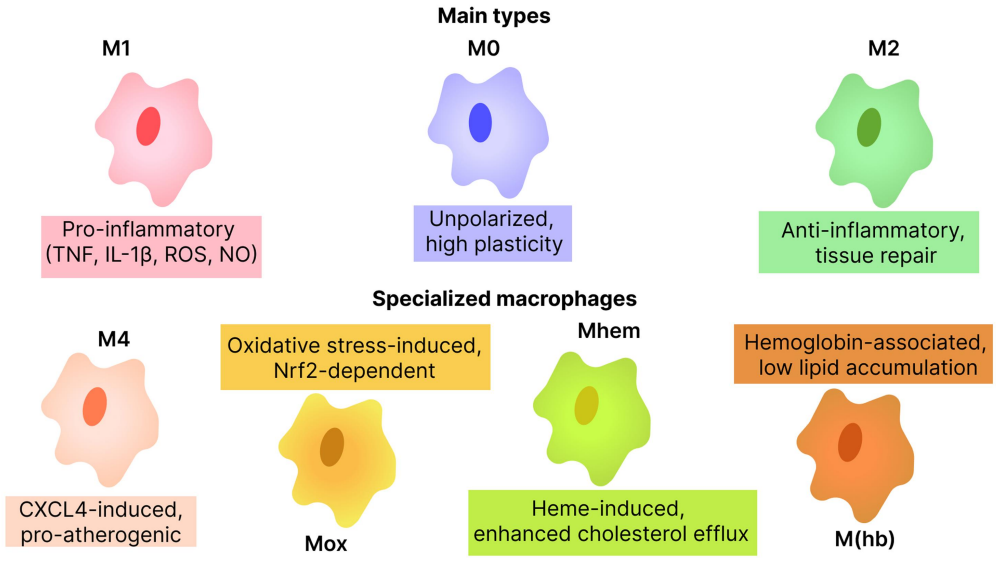

Fig. 1. Phenotypic diversity of macrophages. The main types of macrophages are M1, M2, and M0. Specialized types of macrophages include M4, Mox, Mhem, and M(Hb), among others.CXCL4, C-X-C motif chemokine ligand 4; IL-1β, interleukin-1 beta; NO, nitric oxide; NRF2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TNF, tumor necrosis factor.

factors, and their functions also vary.[29] Monocytes, macrophages, and foam cells have their own sets of markers. Monocytes express $Hp^{+}Treml4^{+}Ly6c2^{+}$. Pro-inflammatory macrophages express $Tnf^{+}Nlrp3^{+}Mgl2^{+}Il1b^{+}$, while macrophages with high levels of MHC-II express $MHC\text{-}II^{+}Cd74^{+}H2\text{-}DMa^{+}$. Foam cells are characterized by $Fabp5^{+}Mmp12^{+}Gpnmb^{+}Itgax^{+}Cd9^{+}$. Trajectory analysis showed an intermediate inflammatory population that is further divided during differentiation. Thus, monocytes entering the intermediate stage can differentiate into either foam cells or inflammatory macrophages.

Therefore, monocytes/macrophages may acquire a typical pro-inflammatory M1-like phenotype when exposed to interferon (IFN)-γ, TNF, toll-like receptor (TLR) ligands such as lipopolysaccharide (LPS),[31,32] the IFN-γ–Jagged1 axis,[33] hemolytic environments and, specifically, hemoglobin-activated platelets,[34] immune complexes from patients with systemic autoimmune diseases,[35] certain chemical compounds such as calcium oxalates,[36] less stable intravenous iron preparations,[37] and certain types of microRNAs, for example miR-148a-3p.[38] Because activated M1 macrophages secrete ROS and nitric oxide,[39,40] tissue damage occurs, while their healing properties are reduced.[41-43] It should be noted that nitric oxide and nitric oxide synthases play a significant role in signaling in different tissues in health and disease.[44]

In turn, M2 macrophages are responsible for tissue repair and the removal of inflammation and cellular debris.[41-43] An important role in the formation of the M2 macrophage phenotype is played by Th2-associated cytokines,[45] matrix metalloproteinase (MMP)-8,[46] monoamine oxidase A,[47] and hepatitis C virus and its core protein.[48,49] In addition, M2 macrophages can be divided into several subtypes depending on microenvironmental inducing factors.[50,51]

Macrophages M0, M1, and M2 also differ from each other morphologically: M1 cells have an elongated shape with long pseudopods, unlike rounded M0 and M2 macrophages with short pseudopods.[52] Expression of TNF-α, IL-6, IL-1β, and CD38, CD80 is characteristic of M1 macrophages, while IL-10, CCL18, CCL22, and CD163 are expressed in M2 macrophages. The non-coding RNA lnc_000048 promotes the proliferation of M1 macrophages. Knockout of lnc_000048 reduces the expression of pro-inflammatory markers TNF-α, IL-6, IL-1β, CD38, and CD80, while overexpression of lnc_000048 increases the expression of these markers, enhances the STAT1 signaling pathway, and binds to PKR, inducing its phosphorylation to enhance STAT1 activity.

The M4 phenotype of macrophages has been described, and its development is induced by the platelet chemokine CXCL4.[40] Intraplaque hemorrhage may induce erythrocyte lysis and the release of free hemoglobin, which in turn induces differentiation of macrophages into the M(Hb) subtype,[53] characterized by a low level of lipid accumulation. Moreover, under the action of heme, macrophage polarization is induced toward the Mhem phenotype.[41,54]

Currently, there are multiple ways to study the phenotypic diversity of macrophage subtypes, both *in vitro* and in dynamic atherosclerotic plaques.[55-58] In a single-cell study, 20,943 $CD45^{+}$ immune cells were profiled from carotid atherosclerotic plaques of six patients, of which mononuclear phagocytes accounted for 18% of all leukocytes.[59] Twelve mononuclear phagocyte subclusters were identified, including dendritic cell (cDC1, cDC2, mregDC, AS-DC) and eight macrophage subsets: $C1Q^{+}$ macrophages, $HMOX1^{+}$ macrophages, $TREM2^{hi}$ lipid-associated macrophages, $PLIN2^{hi}/TREM1^{hi}$ lipid-associated macrophages, IFN-responsive macrophages, $S100A8/IL1B^{-}$ macrophages, $S100A8/IL1B^{+}$ macrophages, and $IL10^{+}/TNFAIP3^{+}$ macrophages.[59] Of particular interest, the $PLIN2^{hi}/TREM1^{hi}$ subset shows increased expression of inflammatory (TREM1, IL1B, CCL2) and lipid-metabolism (PLIN2) genes, and TLR2 stimulation can drive a transition from $TREM2^{hi}$ to inflammatory $PLIN2^{hi}/TREM1^{hi}$ macrophages, which

are more frequent in human atherosclerotic plaques.[59]

In another study, single-cell RNA sequencing of 88,093 cells from atherosclerotic plaques of six patients identified 25 cell populations, including multiple immune cells, SMCs, and fibroblasts.[60] Macrophages were divided into five subtypes and seven clusters with distinct inflammatory and lipid metabolism profiles. Some clusters represented inflammatory macrophages, others foamy (lipid-rich) macrophages, as well as apoptotic, proliferating, and ACTA2$^+$ macrophages with smooth muscle–like features. The main subtypes corresponded to specific clusters, linking transcriptional profiles with functional macrophage states in plaques.

It should be noted that TREM2$^+$ macrophages expressing TREM2 can potentially protect against neurodegenerative diseases such as Alzheimer's disease and modulate immune responses.[61] In addition, it was found using a mouse model that TREM2 is potentially involved in maintaining the balance between foam cell death and their clearance from atherosclerotic plaques.[62]

There are some differences in markers between human and mouse monocytes/macrophages.[63,64] In mice, the definitive macrophage marker is F4/80, which is absent in human macrophages. On the other hand, CD14 and CD16 markers can be used to define subsets of human macrophages, whereas mouse macrophage subsets can be distinguished using the Ly6C marker.[63,64] There are human-specific, mouse-specific, and shared markers of macrophage polarization, which should be taken into account when analyzing data obtained from mouse and human macrophages.[63,64]

Proteomic and transcriptomic analyses of individual macrophage cells help improve our understanding of the phenotypic diversity of macrophages, their regulatory mechanisms and functions, and can significantly contribute to the development of potential therapies for atherosclerosis.

Adhesion of monocytes to the endothelium

Atherosclerosis is a disease of the cardiovascular system characterized by chronic inflammation. Endotheliosis is characterized by damage to endothelial cells and can also lead to the development of atherosclerosis and other cardiovascular diseases.[65] The early development of atherosclerosis is closely related to the pro-inflammatory activation of endothelial cells, which leads to inflammatory processes, decreased vascular tone, and structural remodeling.[66] Under the influence of a local microenvironment enriched with growth factors and pro-inflammatory cytokines, endothelial cells adhere to monocytes circulating in the blood, which then differentiate into macrophages.[22] Endothelial cells adhere to monocytes through a cascade of reactions involving the interaction of P-selectin, formed on the surface of damaged endothelial cells and expressed by monocytes, with the glycosylated glycoprotein ligand P-selectin glycoprotein ligand-1.[67] To form tight adhesion between monocytes and endothelial cells, the interaction of monocytic integrins (very late antigen-4) with vascular cell adhesion molecule 1 (VCAM-1) or intercellular adhesion molecule-1 (ICAM-1), expressed on the surface of activated endothelial cells, is necessary.[68] The endothelium continues to bind monocytes and becomes activated, secreting chemokines and adhesion molecules, for example monocyte chemotactic protein 1 (MCP-1), ICAM-1, and VCAM-1, further enhancing monocyte binding.[11]

Pro-inflammatory cytokines can promote monocyte recruitment, endothelial adhesion, and transmigration from the bloodstream into affected arterial regions.[69] Recent studies have shown increased expression of pro-inflammatory cytokines and infiltration of pro-inflammatory polarized macrophages in visceral adipose tissue compared to subcutaneous adipose tissue.[70] It was also shown that adipose tissue-conditioned media, expressing cytokines IL-1β, TNF-α, MCP-1, IL-10, and RANTES, increased the adhesion ability of monocytes to endothelial cells and also increased the expression of adhesion molecule genes (ICAM-1, VCAM-1).[71] Thus, visceral fat can induce inflammation in the intima of the aorta and have a pro-atherosclerotic effect.

Tissue-resident macrophages activate pro-inflammatory cytokines such as TNF-α and IL-1β, leading to the expression of endothelial cell adhesion molecules such as E- and P-selectin, ICAM-1, and VCAM-1. The expression of adhesion molecules and the binding of chemokines to monocytes (CCL2, CCL5) allow them to move along the endothelial monolayer of the vessel against blood flow to the site of inflammation.[72]

During the chemotactic stage, monocytes migrate to sites appropriate for transmigration. Intraluminal "crawling" depends on monocyte factors: lymphocyte function-associated antigen 1 and macrophage antigen-1, which interact with endothelial ICAM-1 and ICAM-2. The final stage of monocyte transmigration can occur at both transcellular and paracellular endothelial junctions. Endothelial cells contain endothelial cadherin (VE-cadherin), which is responsible for permeability.[73] Cellular signals originating from monocytes attached to the endothelium at the site of inflammation localize adhesion complexes by phosphorylating VE-cadherin, allowing macrophages to penetrate into the subendothelial space, also known as the intima.[74]

Accumulation of lipids by macrophages and the formation of foam cells

After monocytes have adhered to endothelial cells, they differentiate into macrophages and enter the intima of the arteries, where they absorb apoB-containing lipoproteins and become foam cells (Fig. 2).[41] To attract even more macrophages into the intima of the arteries, foam cells begin to produce ROS and induce inflammatory activity, which leads to the formation of fatty streaks on the walls of blood vessels.[30] Foam cells in the intima of the arteries have subtle mechanisms for maintaining cholesterol homeostasis and express numerous lipid-processing genes, while inflammatory genes have a reduced level of expression compared to non-foamy macrophages.[75] Cholesteryl esters inside atherosclerotic plaques are hydrolyzed by lysosomal acid lipase, while the resulting cholesterol can be re-esterified by acyl-CoA:cholesterol acyltransferase-1 in the endoplasmic reticulum (ER) and stored as lipid droplets.[76] With excessive accumulation of cholesterol in the lysosomes of foam cells, cholesterol efflux may worsen, and cholesterol crystals can form in atherosclerotic plaques.[76]

Atherogenic LDL plays a key role in the initiation and progression of atherosclerosis, since modified forms of LDL are the main source of cholesterol for foam cells and trigger chronic inflammation in the intima of blood vessels. oxLDL has pronounced pro-atherogenic properties: it is easily trapped in the

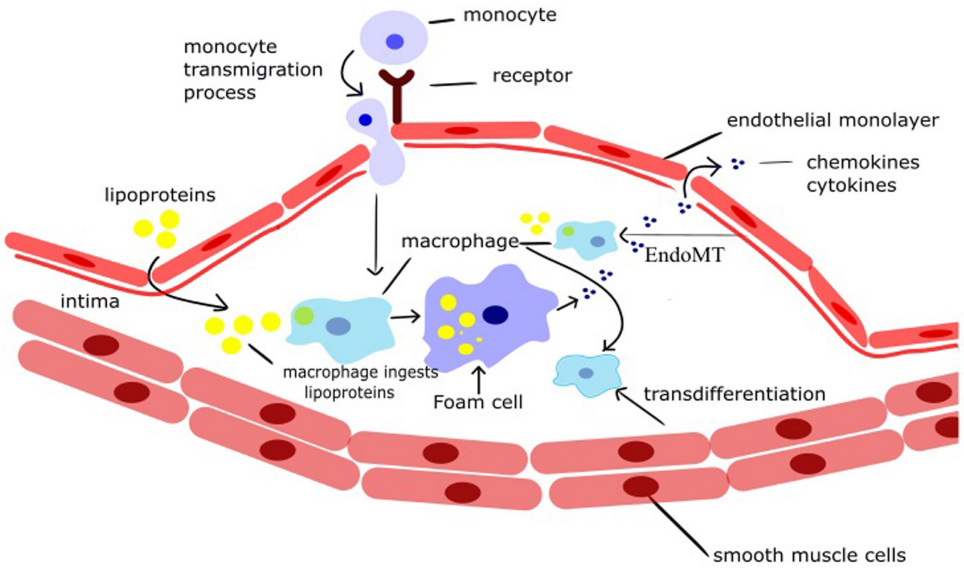

Fig. 2. Accumulation of lipids by macrophages and the formation of foam cells. Monocytes in the blood, by interacting with endothelial receptors, adhere to and penetrate into the intima of the artery. These monocytes turn into macrophages and start absorbing low-density lipoprotein (LDL), consequently becoming foam cells. To attract more blood monocytes into the intima of arteries, foam cells, tissue-resident macrophages (TRMs), and endothelial-to-mesenchymal transition (EndoMT) lead to the secretion of pro-inflammatory chemokines and cytokines. These processes lead to the progression of atherosclerotic plaque.

vascular wall, induces endothelial dysfunction, promotes the expression of adhesion molecules, attracts monocytes and their differentiation into macrophages, and is then actively taken up through scavenger receptors, leading to the formation of foam cells.[77] In addition to oxidation, LDL can undergo desialylation, glycation, and other biochemical modifications, which enhance its ability to aggregate, bind to ECM proteoglycans, form immune complexes, and stimulate the production of pro-inflammatory cytokines, macrophage apoptosis, and plaque necrotic core growth.[78] Such modified LDL is considered a central mediator of lipid-induced inflammation and vascular wall remodeling in atherosclerosis. Interestingly, there is a phenomenon of so-called atherogenic LDL, meaning that these modified LDL (as opposed to native LDL) can induce foam cell formation in certain cell lines, including macrophages.[77]

There is also evidence that deubiquitinating enzymes may take part in the development of atherosclerosis. In a recent study, it was found that with the development of atherosclerosis in mouse and human cells, the expression of ubiquitin-specific peptidase 9 X-linked (USP9X) decreased.[79] In macrophages with USP9X deficiency, lipid uptake and deposition, foam cell formation, inflammatory reactions, and the content of the necrotic core increased compared to control apolipoprotein E knockout ($ApoE^{-/-}$) mice. USP9X, when interacting with the class A1 scavenger receptor (SR-A1), was shown to remove the polyubiquitin chain K63 in the K27 region of the protein.[79] It is considered that there are two main markers of macrophages that turn into foam cells: scavenger receptor class A (SR-A) and a member of the class B family, CD36.[68] Binding of phospholipids to CD36 on the surface of the macrophage leads to heterodimerization of TLR4/TLR6, which in turn activates IL-1, nuclear factor kappa B (NF-κB), myeloid differentiation factor 88 (MyD88), and toll-like receptor domain-containing adapter-inducing interferon-β (TRIF).[80] It is worth noting that the interaction of oxLDL with CD36 causes TLR2-dependent signaling, provoking pro-inflammatory reactions and apoptosis in macrophages exposed to ER stress.[81] Blocking the binding of USP9X to SR-A1 led to the formation of foam cells and increased atherogenic activity.[79] At the same time, the K27R mutation in SR-A1 lowers the uptake of oxLDL caused by USP9X knockdown.[79]

Cholesterol efflux from foam macrophages, which ensures the removal of excess sterol from atherosclerotic plaques and its subsequent elimination by the liver via bile, is the first and rate-limiting stage of reverse cholesterol transport (RCT).[82,83] This process is critically important for preventing the toxic accumulation of lipids and foam cell formation, since peripheral cells are unable to degrade cholesterol, and efflux is the only way to eliminate its excess.[84] In macrophage foam cells, the main share of active efflux is provided by ATP-dependent transporters ABCA1 and ABCG1, which transfer free cholesterol to lipid-poor ApoA-I and high-density lipoprotein (HDL) particles, initiating and supporting the formation and maturation of HDL and the entire RCT cascade.[83] An additional contribution is made by passive diffusion, as well as by the SR-BI receptor and other pathways. However, under conditions of cholesterol overload, ABCA1-mediated cholesterol removal dominates over other routes. Deficiency or functional impairment of ABCA1/ABCG1 in macrophages dramatically reduces efflux, increases the deposition

of cholesteryl esters, and is accompanied by a marked increase in atherogenesis and inflammatory responses in lesions.[85] Conversely, pharmacological or genetic activation of these transporters, as well as an increased capacity of HDL and ApoA-I to accept cholesterol, enhances macrophage RCT, reduces the number of foam cells, and is considered a promising strategy for atheroprotection.[86]

25-hydroxycholesterol (25-HC) is a product of cholesterol oxidation under the action of cholesterol-25-hydroxylase (Ch25h). Studies have revealed the role of 25-HC in the development of atherosclerosis.[87] The level of 25-HC is associated with macrophage accumulation in atherosclerotic plaques at later stages, as evidenced by increased accumulation of 25-HC along with a higher content of $CD68^{+}$ macrophages. Increased expression of Ch25h in macrophages of human atherosclerotic plaques was also noted, while histological analysis of the aortic root of mice with Ch25h knockout showed a decrease in atherosclerotic lesions, lipid accumulation, and necrotic cores, as well as increased stability of atherosclerotic plaques. In macrophages from $Ch25h^{-/-}Ldlr^{-/-}$ mice treated with LPS, decreased expression of genes associated with pro-inflammatory metabolic pathways (STAT1, IRF3, Tnf, Cxcl10, Il12a, and Ccl5) was observed. The TLR4/p38/NF-κB pathway was also inhibited, while the expression of anti-inflammatory genes (STAT6, STAT3, NFE2L2, SMAD3, Arg1, Mrc1, Mfge8) increased. It is noted that Ch25h knockout stabilized atherosclerotic plaques by increasing efferocytosis. In contrast, 25-HC contributed to the inhibition of SMC migration, making atherosclerotic plaques less stable.

DExH-Box helicase 9 (DHX9) is elevated in peripheral blood mononuclear cells of patients with coronary heart disease, and its expression increases in macrophages treated with oxLDL and IFN-γ.[88] Analysis of the DHX9-knockdown THP-1 monocyte cell line revealed that adhesion to human umbilical vein endothelial cells (HUVECs) using Dil-oxLDL reduced lipid uptake, while quantitative polymerase chain reaction showed reduced expression of IL-6 and TNF-α. Using ChIP and ChIP-re-ChIP under the influence of oxLDL, increased binding of DHX9 and DHX9-p65 to the IL-6 promoter was detected, while DHX9 knockout reduced binding to the promoter. DHX9 may become a potential target in the treatment of atherosclerosis. Using an $ApoE^{-/-}$ mouse model, it was shown that deletion of epsin1/2 led to reduced foam cell formation and preservation of vascular smooth muscle cell (VSMC) and endothelial cell functions.[89]

It is worth noting that M2 macrophages with anti-inflammatory activity are more prone to foam cell formation than M1 macrophages.[90] In addition, cholesterol crystals are found in atherosclerotic plaques and contribute to the differentiation of M1 macrophages.[91] Various forms of cholesteryl esters, as well as lipids from the microenvironment of atherosclerotic plaques, can contribute to macrophage polarization. For example, cholesteryl linoleate induces M1 polarization via a TLR4/NF-κB-dependent mechanism,[92] while cholesteryl 9-oxonanoate enhances TGF-β signaling in promonocytic cells.[93] Conjugated linoleic acid and docosahexaenoic acid induce M2 polarization.[94,95] Sphingosine-1-phosphate also promotes the formation of M2 macrophages but has a pro-atherogenic effect due to interaction with sphingosine-1-phosphate type 2/3 receptors.[96] In experiments in mice, palmitoylethanolamide increases the efferocytic capacity of M2 macrophages while reducing the number of M1 macrophages.[97] In general, the formation and polarization of M2 macrophages contribute to anti-inflammatory and anti-atherogenic effects.

Macrophage localization in atherosclerotic lesions

According to histological classification, there are six types of atherosclerotic lesions (Fig. 3).[9,41,68,76,98-100] Type I, the initial lesion, contains a sufficient amount of atherogenic LDL, which causes an increase in the number of macrophages in the artery intima and contributes to the formation of foam cells.[8] Adaptive intimal thickening is considered a non-atherosclerotic adaptive lesion.[100] non-atherosclerotic lesions. Such changes are adaptive and occur in response to blood flow and do not lead to atherogenesis. Early atherosclerotic lesions include pathological intimal thickening. This condition includes the presence of SMCs with areas where they are absent but enriched with ECM containing proteoglycans and hyaluronic acid.[100] Atherosclerotic lesions of type II are characterized by fatty streaks, layers of foam cells, and lipid droplets inside SMCs of the artery intima, as well as minimal coarse-grained particles and heterogeneous droplets of extracellular lipid. In type II lesions, the lipid composition consists mainly of cholesteryl esters (77%), cholesterol, and phospholipids.[8] Atherosclerotic lesions of type III, also known as preatheroma, are an intermediate type of lesion between type II and type IV lesions and are characterized by adaptive thickening of the artery intima and accumulation of extracellular lipids.[8] Type IV lesions are the first progressive atherosclerotic lesions. Type IV lesions, or atheromas, are characterized by the presence of a lipid core and severe disorganization of the artery intima. Fibroatheromas are divided into early and late stages. In early fibroatheromas, macrophages infiltrate lipid pools, while in late fibroatheromas, a necrotic core covered with a fibrous cap forms.[100] In the next type, type V atherosclerotic lesions, fibrous connective tissue is formed. There are several subtypes of type V: Va is characterized by the presence of connective tissue with a lipid core (fibroatheroma), Vb is characterized by calcification of the lipid core, and Vc is characterized by the absence of a lipid core and reduced lipid content.[9] The final type, type VI atherosclerotic lesions, includes disruption of the integrity of the artery wall, hematomas, hemorrhages, and thrombotic deposits. Type VI is also divided into several subtypes: VIa is characterized by destruction of the artery surface, VIb by the presence of a hematoma or hemorrhage, and VIc by thrombosis. The VIabc type combines all of these features.[9] Atherosclerotic plaques are classified as stable, characterized by calcification and fibrosis, or unstable, prone to rupture and thrombosis.[100] Thin-cap fibroatheroma refers to an unstable plaque with a fibrous cap of less than 65 microns, a large necrotic core, and infiltration by T lymphocytes and macrophages. Unstable plaques may have ruptures, erosions, and calcified nodules. Stable plaques include healed plaque ruptures covered with neointima, chronic total occlusion, and fibrocalcified plaques. The late stages of atherosclerosis can also lead to myocardial infarction.

In atherosclerotic plaques, different types of macrophages are localized in different regions. In humans, both major macrophage types are present throughout atherogenesis: M1 and M2.[76] M1-type macrophages are predominantly located in the shoulder regions of plaques that are prone to rupture and infarction, while

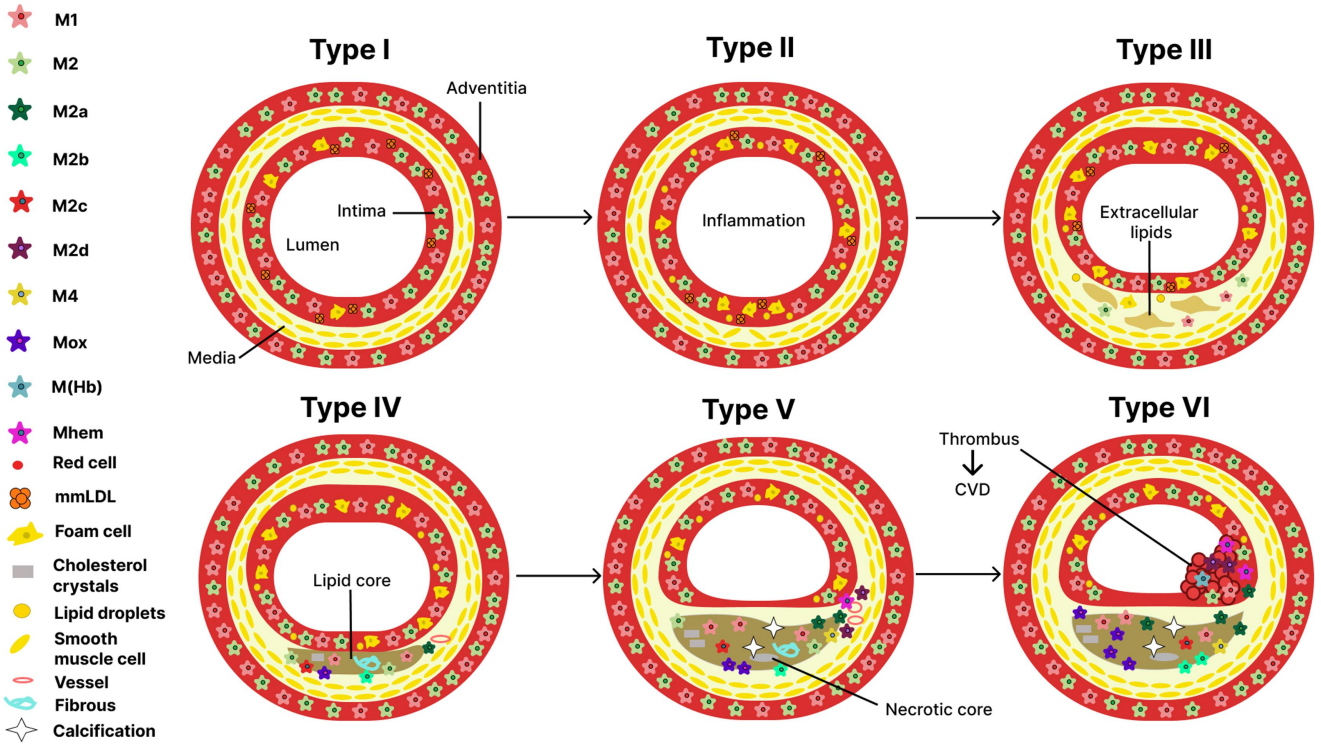

Fig. 3. Localization of macrophage subtypes during different stages of atherosclerotic lesion development. The diagram summarizes the distribution of major macrophage populations, foam cells, modified LDL, cholesterol crystals, smooth muscle cells, calcification and thrombotic changes across type I–VI lesions.[9,41,68,76,100] LDL, low-density lipoprotein; mmLDL, multiply modified LDL; SMC, smooth muscle cell.

M2 macrophages are found in stable plaques and in the vascular adventitia, having migrated from perivascular adipose tissue.[51,101,102] However, the fibrous caps of atherosclerotic plaques contain approximately equal numbers of M1 and M2 macrophages.[101] In type II atherosclerotic plaques, M1 macrophages predominate compared to the initial stages of atherogenesis, while M2 macrophages are more prevalent in regressing plaques or at early stages of atherogenesis.[103] M1 macrophages are predominantly found in lipid-rich regions of plaques, whereas M2 macrophages are located in areas distant from lipid-rich zones.[100] In type IV plaques, M1 macrophages are localized near lipid cores, while M2 macrophages are found in neoangiogenic regions.[76] M2a macrophages, which have increased phagocytic activity, are localized in stable lesions and in zones of neovascularization.[41] M2b macrophages are mostly localized in the artery intima and secrete both pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, and the anti-inflammatory cytokine IL-10. M2c macrophages are also localized in the intima and play a major anti-inflammatory role due to the secretion of IL-10, TGF-β, and pentraxin 3. Mox macrophages have pro-inflammatory activity due to the expression of IL-1β and COX-2 but have low phagocytic activity. M4 macrophages, characterized by atherogenicity and plaque instability, are mainly localized in the adventitia and intima.[40] The role of M4 macrophages is not fully understood, but they may contribute to the instability of atherosclerotic plaques. M4 macrophages are formed in response to exposure to CXCL4.[100] Macrophages M(Hb) and Mhem, which have cardioprotective properties such as reduced production of ROS or increased cholesterol efflux capacity, are mainly localized in areas of hemorrhage or plaque neovascularization.[104] M(Hb) macrophages arise under the action of hemoglobin and its metabolites. M(Hb) macrophages promote angiogenesis and suppress calcification through the CD163/HIF1α/VEGF-A pathway, making plaques less stable.[100] Mhem macrophages inhibit calcification through the synthesis of hyaluronan mediated by the NF-κB pathway. M2d macrophages, located in areas of neovascularization, have antigenic properties and also play an important role in the progression of atherosclerotic plaques.[68] It is worth noting that the stability of atherosclerotic plaques is characterized by the ratio of M1 to M2 macrophages.[99]

Some studies suggest that the transition between M1 and M2 macrophages occurs through the transformation of local cells within the plaque.[105]

It is also worth noting that VSIG4 expressed in M2 macrophages plays an important role in tissue recovery after myocardial infarction.[106] VSIG4 activates the expression of collagen I, collagen III, α-SMA, MMP2, and MMP9. In turn, hypoxia activates HIF1α, which stimulates the expression of VSIG4. After myocardial infarction in ApoE$^{-/-}$ mice, the number of atherosclerotic plaques and CD11b^{+} myeloid cells in the aorta increased.[107] It is worth noting that when bone marrow from mice that experienced myocardial infarction was transplanted into control mice, the area of atherosclerotic lesions increased, along with increased expression of SYK in monocytes and macrophages.

The protein KMT5A methylates histone H4K20, and interaction of KMT5A with CNBP leads to activation of SYK. The latter increases the expression of Il1b, Il6, Mcp1, and TNF-α. Elevated levels of SYK and KMT5A expression were also detected in monocytes of patients with progressive atherosclerosis. Thus, myocardial infarction, through epigenetic mechanisms, contributes to the development of atherosclerosis.

Interaction of macrophages with the ECM

An important role in atherogenesis is played by the interaction of macrophages with the ECM, such as proteoglycans, glycoproteins (fibronectin, thrombospondin, vitronectin, and osteopontin), elastin, and collagens (I, III, IV, and V).[108] One of the functions of the ECM in the early stages of atherosclerosis is the retention of cholesterol inside the artery wall.[109] Proteoglycans responsible for vascular elasticity, having a negative charge, interact with positively charged apoB on LDL particles in the subendothelial space.[110] Macrophage-secreted MMPs, which cleave the ECM, have a substantial impact on the development of atherosclerosis.[109] The concentration of MMPs increases in the presence of macrophages in the lesion, while plaque stability decreases due to the synthesis of inflammatory cytokines and the destruction of plaque structure. However, as the concentration of MMPs decreases, the plaque becomes more stable due to the ECM, which by that time forms a strong fibrous cap.[111] Remodeling of the ECM by MMPs forms plaques with a thin fibrous membrane, which can separate from the endothelium and cause thromboembolism.[112] It is worth noting that the proportion of ECM and MMPs in the atherosclerotic plaque is regulated by and sensitive to inflammatory factors such as TGF-β, TNF-α, and IFN-γ, as well as to tissue metalloproteinase inhibitors. TGF-β produced by endothelial cells increases collagen synthesis, while pro-inflammatory TNF-α and IFN-γ synthesized by macrophages, on the contrary, reduce collagen synthesis.[111]

Atherosclerosis is one of the factors in the development of aneurysms. S-nitrosylation (SNO) is involved in the pathogenesis of various cardiovascular diseases. iNOS is a key source of nitric oxide formation, necessary for the creation of SNO.[113] It was found that in macrophages, SNO-Septin2 increases inflammation and migration of macrophages, degradation of the ECM, and activates the RAC1/NF-κB metabolic pathway. These events provoke an aneurysm but can also occur in atherosclerosis.

Interaction of macrophages with immune cells

Macrophages can interact with other immune cells, both enhancing and reducing the manifestations of atherosclerosis. Macrophages are able to activate T lymphocytes and B cells by presenting oxLDL as an antigen in the major histocompatibility complex.[114] At the initial stages of atherosclerotic plaque formation, in addition to monocytes and macrophages, lymphocytes play an important role.[115] Most T cells express CD3, CD4, and T cell receptors to interact with antigen-presenting macrophages. At the same time, upon interaction with antigen, T cells secrete pro-inflammatory cytokines or differentiate into $CD8^+$ cells. T cells can even trigger cell destruction, which leads to the development of inflammation and atherosclerosis.[114] T helper cells are divided into two subtypes: Th1 and Th2. Although their ratio is regulated by cytokines or antigen-presenting cells, Th1 cells are more common in atherosclerotic lesions.[114] T helper cells (Th1), similar to M1 macrophages, synthesize pro-inflammatory cytokines such as IFN-γ, IL-2, TNF-α, and chemokines, while regulatory T cells (Tregs) and B-1 cells, similar to M2 macrophages, stabilize atherosclerotic plaques, reduce their size, and suppress inflammation.[57] Tregs, which are divided into natural (nTregs) and induced (iTregs), possess an atheroprotective function as they reduce inflammatory reactions or deactivate dendritic cells.[116] B lymphocytes provide humoral immunity by producing antibodies. B lymphocytes are divided into two subtypes, B1 and B2, with different roles in atherogenesis. B1 cells are capable of producing IgM autoantibodies that react with oxidized phospholipids in oxLDL on the macrophage membrane, having an atheroprotective effect.[117] B2 cells, synthesizing IgG and IgE, also contribute to the progression of atherosclerosis.[115] Neutrophils also take part in atherogenesis: they are able to attract monocytes to lesion sites in atherosclerotic plaques, as well as induce the formation of foam cells from macrophages by secreting granular proteins such as α-defensins, azurocidin, and cathepsin G.[118]

Beyond their role in plaque progression, macrophages are now recognized as critical regulators of plaque regression. During regression, macrophages facilitate RCT, a process by which excess cholesterol is effluxed from foam cells via transporters such as ABCA1 and ABCG1 for hepatic elimination. This cholesterol efflux mechanism is essential for reducing plaque lipid content and promoting plaque stabilization. However, the precise molecular pathways governing this process and their potential as therapeutic targets require further investigation.

Role of macrophages in atherosclerotic plaque regression

Macrophages serve as the primary regulators of lesion remodeling during atherosclerotic plaque regression. Their role shifts from supporting chronic inflammation to actively resolving it through three mechanisms: phenotype switching, enhanced clearance of debris (via efferocytosis), and active migration from the lesion.[45,119]

The most critical change during regression is the shift in macrophage phenotype from a pro-inflammatory state to a pro-resolving state. During this process, pro-inflammatory M1 macrophages, which dominate progressing plaques, are replaced by or converted into anti-inflammatory M2 macrophages.[103,119] M2 macrophages begin to secrete cytokines such as IL-10 and TGF-β, helping to suppress inflammation and promote tissue repair.[103,119] This type of anti-inflammatory macrophage (M2) also stimulates collagen production, leading to thickening of the fibrous cap, which makes the plaque less prone to rupture and therefore more stable.[103,119,120]

Efferocytosis is the process by which macrophages remove apoptotic cells and cellular debris.[121] In growing lesions, efferocytosis is often defective, which can lead to the formation of an unstable necrotic core. During regression, certain macrophage subtypes (such as M2) recover their ability to efficiently digest dead cells and their components. This leads to effective shrinkage of the necrotic core and prevents the release of toxic cellular compounds from dead cells into the vessel wall.[119,121]

Atherosclerotic plaque regression is accompanied by a

noticeable decrease in the total number of macrophages within the lesion.[119] At this stage, macrophages can actively leave the lesion and migrate to regional lymph nodes. This process is associated with the expression of the chemokine receptor CCR7 by macrophages. At the same time, a decrease in the recruitment of new monocytes from the bloodstream to the lesion occurs.[45]

M2 macrophages also support the removal of lipid accumulations associated with atherosclerosis development and progression.[122] This occurs mainly through the upregulation of the expression of the transporters ABCA1 and ABCG1.

Macrophages and cytokines in atherosclerosis

In the context of atherosclerosis, cytokines are involved in the initiation and progression of the disease through several mechanisms—inflammation, endothelial dysfunction, and lipid metabolism. Some cytokines contribute to inflammation in the artery wall, which leads to the involvement of immune cells and activation of endothelial cells. This inflammatory reaction contributes to the development of atherosclerotic plaques. Cytokines may also induce endothelial dysfunction by disrupting normal endothelial function and promoting leukocyte adhesion to the arterial wall. This process is an early event in the development of atherosclerosis. Cytokines may affect lipid metabolism in the arterial wall, contributing to the absorption of cholesterol by macrophages and the formation of foam cells, a key component of atherosclerotic plaques.

Under significant influence of pro-inflammatory cytokines, monocytes differentiate into macrophages.[22,23] Th2 cytokines (for example, anti-inflammatory IL-4, IL-10, IL-13) lead to the polarization of macrophages attributed to the M2 phenotype, exhibiting an anti-atherosclerotic effect.[39,45,123-126] While IL-4 and IL-13 induce STAT6 activation, IL-10 activates STAT3, which activates macrophage polarization to the M2 phenotype.[123,125] Due to IL-4, both monocyte-derived and tissue-resident macrophages undergo induction.[127] IL-4 also induces MMP-12, MMP-25, and a tissue type 3 MMP inhibitor in macrophages.[128] IL-6 is involved in destabilization of atherosclerotic plaques.[129]

Some cytokines, namely IL–1β and TNF-α, contribute to the calcification of atherosclerotic plaques.[130,131] Pro-inflammatory cytokines TNF-α and oncostatin M can contribute to further mineralization in plaque lesions due to their ability to induce osteogenic transdifferentiation of VSMCs.[132,133] Various chemokines, including IL-1β, TNF-α, and GM-CSF, can modulate MMPs by using various prostaglandin-dependent and independent mechanisms.[134] GM-CSF and M-CSF induce polarization of M1 and M2 macrophages, respectively.[135]

IL-1β has an important role in plaque stabilization, and it also inhibits the transition of SMCs into an osteochondrocyte-like phenotype. There was a regression of atherosclerotic lesions and a decrease in the area of the necrotic core in ApoE$^{-/-}$ mice, which were switched from a Western diet (WD) to a standard laboratory diet (SLD). After switching to SLD, the number of pro-inflammatory macrophage markers F4/80$^+$, CD11b$^+$, CX3CR1$^+$, CD45$^+$, CD86$^+$, CD124$^+$, CD184$^+$, CD206$^+$, CD140b$^+$, and RUNX2$^+$ decreased, as did the number of cells with inflammatory markers and osteochondrocytes IL-6$^+$, CD44$^+$, CD140a$^+$, CD140b$^+$, RUNX2$^+$, IFN-γ$^+$, TRPV4$^+$, OCT3/4$^+$, and LY6A$^+$.[136] On the contrary, when antibodies to IL-1β were added to SLD mice, an atherogenic effect occurred in the form of an increase in the area of atherosclerotic lesions, necrotic plaque core, intraplaque hemorrhage, and a decrease in the amount of collagen, which led to destabilization of the atherosclerotic plaque. Also, when IL-1β was added, there was an increase in the expression of KLF4$^+$, LY6A$^+$, CD206$^+$, CD34$^+$, and CD140A$^+$, an increase in the expression of markers of cluster 3, including cells of SMC origin: CD200$^+$, IL-6$^+$, NG2$^+$, S100B$^+$, IFN-γ$^+$, and desmin$^+$, and an increase in the expression of markers of osteochondrocytes from the 5-SMC cluster of origin: TRPV4$^+$, S100B$^+$, RUNX2$^+$, OCT3/4$^+$, KLF4$^+$, CD200$^+$, CX3CR1$^+$, IFN-γ$^+$, NG2$^+$, desmin$^+$, CD184$^+$, CD34$^+$, and CD117$^+$.

Due to the production of pro-inflammatory cytokines IL-6 and TNF-α and a number of other factors by M4 macrophages, this subtype of macrophages is associated with atherogenicity and instability of atherosclerotic plaques.[40,137] Also, pro-inflammatory cytokines TNF and IFN-γ contribute to the polarization of M1 macrophages, and even more to the accumulation of pro-inflammatory cytokines.[138] Through the cytokine CXCL-4, macrophages are induced toward the M4 phenotype.[40] The supply of IL-13, which enhances the anti-inflammatory polarization of M2 macrophages, reduces the development of atherosclerosis in mice.[139]

The rs671 aldehyde dehydrogenase 2 (ALDH2) polymorphism is associated with cardiovascular diseases in Asian populations.[140] Peripheral blood mononuclear cells carrying the rs671 (AA) ALDH2 mutation were isolated from patients. The macrophages showed increased expression of pro-inflammatory genes (iNOS, CXCL-10, TNF-α, IL-6, IL-1β) and decreased expression of anti-inflammatory genes (TGF-β, IL-10, Arg1). Also, in the group with the AA mutation genotype, compared with the GG control group, there was an increase in the number of pro-inflammatory macrophages (CD68$^+$CD86$^+$) and a simultaneous decrease in the number of anti-inflammatory ones (CD68$^+$CD163$^+$). In the ALDH2$^{-/-}$ApoE$^{-/-}$ mouse line with the HFD, an increase in the area of atherosclerotic plaques, pro-inflammatory polarization of macrophages, and levels of cGAS, STING, p-TBK1, and p-IRF3 were observed. It was found that ALDH2 promotes the regulation of the cGAS-STING pathway: ALDH2 prevents the interaction of USP14 and cGAS, which leads to accelerated degradation of cGAS by polyubiquitination. ALDH2 is involved in metabolic pathways associated with macrophage polarization and inflammatory reactions. ALDH2 deficiency and the rs671 mutation contribute to the activation of pro-inflammatory polarization of macrophages and increased inflammatory processes.

Branched-chain amino acids (BCAAs) promote the synthesis of pro-inflammatory cytokines. Increased levels of BCAA and branched-chain alpha-keto acids (BCKAs) are seen in monocytes in patients with coronary heart disease.[141] Increased BCAA levels correlate with a decrease in BCKDHA, BCAT2, and PP2Cm, which are the key enzymes of BCAA catabolism. The addition of BCAA to RAW 264.7 macrophages or BCKDHA knockout leads to the accumulation of BCAA and BCKA, an increase in the number of CD11C$^+$ cells, and activates the expression of pro-inflammatory cytokines such as IL-1β and TNF-α. BCAA is also able to initiate the TLR4/NF-κB pathways, increasing the levels of TLR4, p-p65, and nuclear p65 and reducing the level of cytoplasmic IκBα, thereby activating CD11C$^+$ cells. BCAA

activates HMGB1 synthesis by macrophages, but HMGB1 knockout suppresses the TLR4/NF-κB pathway and reduces the expression of IL-1β, TNF-α, and iNOS. BCAA in macrophages also increases the amount of nuclear H2O2; this leads to oxidative stress, as indicated by the markers malondialdehyde and 8-OHdG.

ANGPTL3 expression enhances the processes of atherogenesis, promoting the expression of pro-inflammatory cytokines. ANGPTL3 was detected in human atherosclerotic plaques by immunohistochemical staining.[142] In the Ldlr$^{-/-}$ and ApoE$^{-/-}$ mouse line with the ANGPTL3 gene transfected for overexpression, an increased size of atherosclerotic plaques was detected, in which the number of CD68^{+} macrophages and α-SMA^{+} SMCs increased, and the content of cholesterol in blood plasma increased. ANGPTL3 increased phosphorylation of 45 proteins and 48 sites involved in lipid metabolism and IL-17 signaling pathways in THP-1 cells. Phosphorylation of Akt led to increased TLR4 expression and activation of NF-κB. ANGPTL3 also led to an increase in the expression of iNOS, the synthesis of pro-inflammatory cytokines eotaxin, GRO-α, IL-1β, IL-27, M-CSF, MIG, MIP-α, and TNF-α, while the expression of arginase 1 decreased.

The effect of mitochondria and mitochondrial mutations

At present, atherosclerosis is being widely studied at both cellular and molecular levels. Mitochondrial mutations in the cells of arterial walls and blood may be significantly associated with the development of cardiovascular diseases caused by oxidative stress, including atherosclerosis.[143] Mutations of mitochondrial DNA can negatively affect the processes of oxidative phosphorylation, transcription, and metabolism, and lead to increased oxidative stress and inflammatory processes, consequently resulting in mitochondrial diseases.[144]

Pathological processes leading to the formation of atherosclerotic plaques can be caused by mitochondrial mutations in the genes encoding the subunits of the electron transport chain, such as cytochrome B and NADH dehydrogenase subunits 1, 2, 5, and 6, as well as rRNA12S, and the UUR and CUN recognition codons of tRNA-Leu.[145] Recent studies in C57BL/6J ApoE$^{-/-}$ mice have revealed a correlation between mitochondrial DNA mutations and the occurrence of atherosclerosis.[146] In subsequent studies, the most common mutations in mitochondrial DNA genes associated with the development of cardiovascular diseases were identified: G12315A (gene MT-TL2), G13513A (gene MT-ND5), C3256T (gene MT-TL1), and G15059A (gene MT-CYB).[147] Later, in 2020, the list of mitochondrial mutations associated with atherosclerosis was expanded to include del562G, m.1555A>G, m.14459G>A, and m.14846G>A.[143] Previously, a link was shown between mtDNA variants, including haplogroups and heteroplasmy, and the development of atherosclerosis.[148-150] It was also shown that atherosclerotic mutations of mitochondrial DNA G12315A, G14459A, and G15059A are associated with patient age.[151]

Some mitochondrial DNA mutations, such as m.A1811G, m.G9477A, m.G14459A, m.A1555G, and m.G12315A, may be responsible for inducing inflammatory processes in macrophages.[152] In addition to mitochondrial mutations, an important factor in the development of atherosclerosis is the number of mtDNA copies (mtDNA-CN). This parameter reflects the number of mitochondrial DNA copies per cell. It was found that a reduction in mtDNA-CN contributes to the development of atherosclerosis through the production of pro-inflammatory cytokines TNF-α and IL-1β in monocytes.[153] Thus, mitochondrial DNA mutations and mtDNA copy number can serve as important markers in the diagnosis of atherosclerosis, as well as potential targets in the treatment of this disease.

Pathological processes in atherosclerosis also affect mitochondria and contribute to atherogenesis. Immunofluorescence staining of human carotid artery tissues and mouse aorta revealed a correlation between the coexpression of VCAM-1 with TOM20 and oxidative DNA damage marker 8-OHdG.[154] The expression of VCAM-1, TOM20, and 8-OHdG also positively correlates with the size of the necrotic core in atherosclerotic plaques. Macrophages with VCAM-1 knockout show reduced activity of respiratory complexes III and IV, as well as reduced expression of complexes II and III. Macrophages expressing VCAM-1 and treated with oxLDL (compared to knockout macrophages) show increased oxygen consumption rate, mitochondrial volume and membrane potential, enhanced mtDNA synthesis, and accelerated consumption of Krebs cycle metabolites. Enhanced mtDNA synthesis due to increased expression of Cmpk2, Pgc1a, and Polg activates the STING pathway, leading to the synthesis of IL-6 and TNF-α and promoting atherogenesis. In addition, VCAM-1 suppresses the expression of the Fkor and Lyz1 genes, which also enhances atherogenesis, resulting in an increased area of atherosclerotic plaques and necrotic cores.

It was found that exposure of macrophages to cholesterol crystals significantly increases the expression of key glycolytic markers such as GLUT1, hexokinase 2, GAPDH, HIF1α, and PFKFB3. In addition, the expression levels of CXCL9 and CXCL10 mRNAs (characteristic of M1 macrophages) increased, while the expression levels of MRC1 and CCL13 mRNAs (characteristic of M2 macrophages) decreased.[155] Ndufs4 deficiency leads to a pro-inflammatory process in macrophages.[156] In studies of mitochondrial dysfunction in macrophages, recovery after myocardial infarction involved macrophages treated with LPS, leading to a transition from oxidative metabolism to glycolysis, which is characteristic of the pro-inflammatory phenotype in atherosclerotic plaques. Macrophages with knockout of the Ndufs4 protein of mitochondrial complex I, or those treated with LPS, have increased levels of mitochondrial reactive oxygen species (mtROS), leading to oxidative stress and further inducing inflammatory processes. In the mKO macrophage line with NDUFS4 knockout, mitochondrial respiration is reduced both at the basal level and upon FCCP stimulation. The metabolism of macrophages with Ndufs4 knockout mimics that of control macrophages treated with LPS.

Under the influence of oxLDL on wild-type bone marrow-derived macrophages (BMDMs), ERK5 S496A is phosphorylated and NRF2 K518 undergoes SUMOylation.[157] This, in turn, increases mtROS levels and leads to decreased oxidative phosphorylation in macrophages and increased glycolysis. These processes contribute to senescence-associated secretory phenotype (SASP) and mitochondrial dysfunction. In macrophages from ERK5 S496A KI mice, these processes were attenuated.

The effect of BCAA on the mitochondria of RAW 264.7 macrophages was also demonstrated. Using two photofluorogenic

probes, it was found that BCAA increases mtH2O2 levels, leading to the formation of BCAA-activated pro-inflammatory macrophages. At the same time, the addition of mitochondria-targeted catalase removes mtH2O2, ultimately reducing $CD11C^{+}$ cells and lowering the expression of IL-1β, TNF-α, and iNOS.[141]

MCT4 deficiency improves mitochondrial function and activates oxidative phosphorylation (OXPHOS) in macrophage mitochondria, increasing the expression of genes for Krebs cycle enzymes while reducing glycolysis and the expression of glycolytic enzymes.[158] MCT4 Mct4mKOApoeKO knockout mice showed decreased atherosclerotic plaques and inflammation, along with increased collagen content, leading to a slowing of atherosclerosis.

Macrophage senescence and atherosclerosis

Aging is one of the major factors in the development of atherosclerosis. Atherosclerotic plaques contain aging cells, but the mechanism of macrophage aging has not yet been fully studied. Aging of vascular walls can be accompanied by pathophysiological consequences such as stroke, coronary heart disease, vascular rupture, and atherogenesis.[159] Activated macrophages are known to produce pro-inflammatory cytokines, chemokines, and proteases, leading to the development of atherosclerosis.[160] However, the role of aging macrophages in atherogenesis is poorly understood. Studies have found that BRD4, belonging to the bromodomain and extra-terminal proteins, is involved in macrophage aging and also induces the formation of SASP, leading to the development of atherosclerosis.[161] In atherosclerosis, as well as in other diseases associated with aging, macrophage dysfunction contributes to abnormal neovascular proliferation.[162] BRD4 is the main factor regulating the expression of inflammatory genes, including the co-activation of NF-κB-dependent pro-inflammatory genes when interacting with acetylated REL.[163]

It is assumed that macrophage aging is induced by oxidative stress caused by oxLDL.[164] Studies have shown that oxLDL induces macrophage aging, manifested by increased activity of SA-β-gal and increased expression of aging-associated proteins p53, p21, and p16 (Fig. 4).[164,165] Macrophages that absorb excessive amounts of LDL undergo aging, increase production of ROS, and secrete pro-inflammatory cytokines due to changes in lysosomal pH caused by LDL oxidation.[166] When macrophages were incubated in the presence of oxLDL, NOX4 expression and ROS production were increased, promoting macrophage death.[167] These processes cause macrophage death, formation of necrotic nuclei, and further development of atherosclerotic plaques.

Phosphorylation of ERK5 S496 promotes the progression of atherosclerosis and also promotes SASP in macrophages. SASP is characterized by a cellular state in which, despite aging processes caused by the expression of p53 and SA-β-gal, aggressive proliferative properties driven by Ki67 expression are observed. It was found that the effect of oxLDL on wild-type BMDMs increases the number of mtROS while reducing the levels of antioxidants such as TRX1 and HO1, as well as increasing the expression of aging markers p16, p21, and p53 and the number of SA-β-gal-positive cells. It also reduces efferocytosis and increases TNF-α expression and NF-κB activation. However, these manifestations are absent in ERK5 S496A knock-in mouse models with a mutation that prevents phosphorylation. It was also found that phosphorylation of ERK5 S496 under the influence of oxLDL activates AHR and induces SUMOylation of NRF2, which leads to SASP in macrophages.[157]

In addition to increased oxidative stress, apoptosis and autophagy processes play an important role in aging, which is also induced by increased accumulation of oxLDL.[168] Increased expression of Bcl-2, Bax, Bak, caspase-9, and caspase-3, as well as an increase in the number of TUNEL-positive cells, indicates the induction of apoptosis in LDL-absorbing macrophages.[164] In contrast, reduced expression of Beclin1 and LC3 and a smaller number of autophagosomes indicate suppression of autophagy, leading to increased ROS production and lipid accumulation, which in turn leads to apoptosis, mitochondrial dysfunction, and ultimately macrophage aging.[169]

Interestingly, it was recently found that inhibition of nicotinamide N-methyltransferase expression led to a decrease in atherosclerotic lesion formation in mouse models, while decreased expression of the nicotinamide adenine dinucleotide (NAD)-degrading enzyme CD38 in macrophages reduced atherosclerosis development and macrophage proliferation.[170] NAD is considered an important agent potentially capable of affecting different age-related conditions,[171-173] including mitochondrial function.[174] Instability of NAD and difficulties with its cellular uptake make it hard to apply therapeutically in SASP of cells, including macrophage polarization.[175] NAD and its precursors are currently under intense preclinical and clinical studies for the treatment of cardiovascular and other diseases.[173,176-178]

Possible approaches for atherosclerosis therapy targeting macrophages

It was shown that the effects of hyperlipidemia on the vessel walls should not be seen as the sole reason for atherosclerosis development. According to the data obtained, cholesterol-lowering statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors prevent atherosclerosis progression and promote plaque regression. PCSK9 is one of the main factors leading to an increase in cholesterol and LDL, as it binds to LDLR, mediating its degradation.[179] Therefore, PCSK9 is currently one of the main targets for the treatment of atherosclerosis. A vaccine, PCSK9-NP, was developed based on PCSK9. In the development of the vaccine, the catalytic domain of human PCSK9 was modified with the D374Y mutation, which enhanced its function. The modified domain was bound to 24-domain ferritin nanoparticles (NPs). The vaccine caused a high titer of IgG antibodies to the PCSK9 catalytic domain in BALB/c mice and dogs. The vaccine helped reduce blood levels of total cholesterol and LDL-C and also reduced the area of atherosclerotic lesions, increased collagen synthesis, and contributed to plaque stability. The content of macrophages in atherosclerotic plaques was determined using immunofluorescence. PCSK9-NP contributed to a decrease in the area of pro-inflammatory macrophages ($F4/80^{+}$ cells), reducing the inflammatory response in plaques.

However, lipid-lowering therapy failed to completely reduce the incidence of cardiovascular diseases and mortality caused by atherosclerosis. Many patients had cardiac diseases even when lower cholesterol levels were achieved. This suggests that factors other than LDL-C also contribute to the progression of

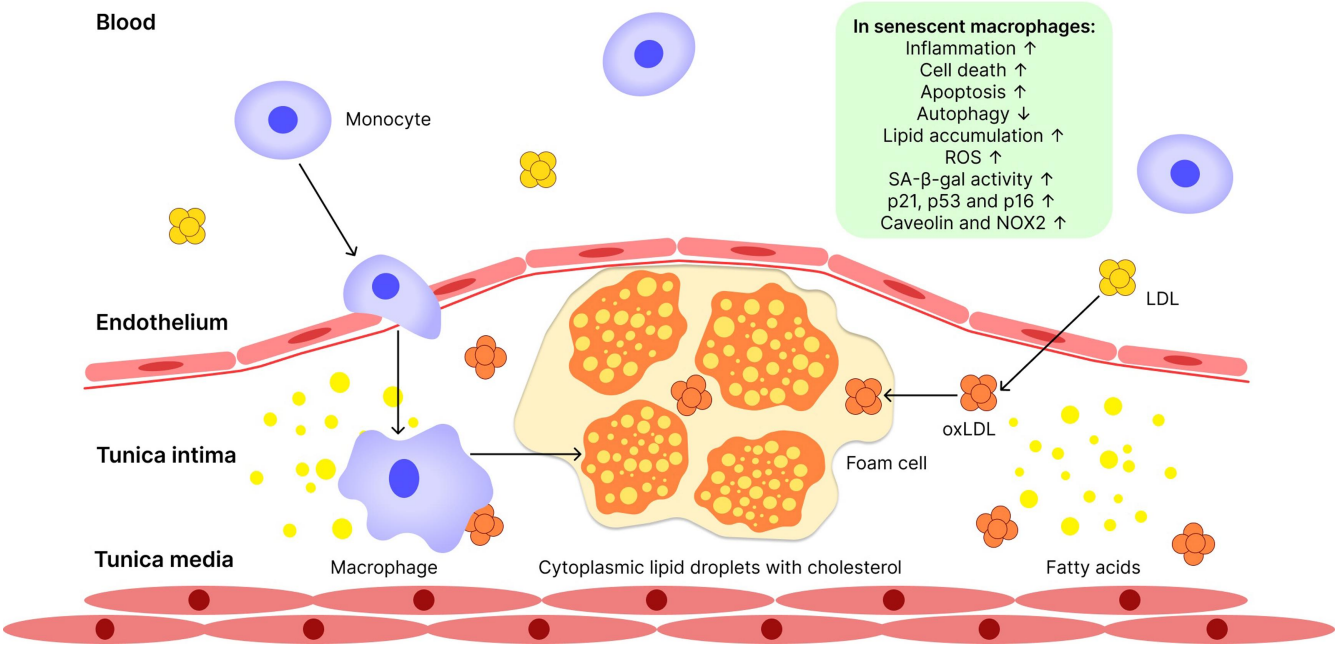

Fig. 4. Senescence of macrophages. The processes leading to the senescence of macrophages begin with the infiltration of monocytes from the bloodstream through endothelial cells into the intima of the artery and the formation of macrophages. LDL penetrates through the endothelium into the intima of the artery, where it is oxidized to form oxidized LDL (oxLDL). Macrophages absorb oxLDL, which leads to the formation of foam cells with cytoplasmic lipid droplets containing large amounts of cholesterol. The absorption of oxLDL by macrophages mainly leads to macrophage senescence: the formation of reactive oxygen species (ROS) increases, leading to inflammatory processes, cell death, decreased autophagy, and increased apoptosis in macrophages. The expression of caveolin-1, NOX2, p16, p21, and p53 also increases.[164,165] ↑, increased; ↓, decreased. LDL, low-density lipoprotein; NOX2, NADPH oxidase 2; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-galactosidase.

atherosclerosis.[180] In this case, inflammation caused by macrophages contributes to the residual risk of atherosclerosis. That is why macrophages are currently among the most important targets for therapy of local atherosclerotic lesions using various therapeutic strategies (Fig. 5).[99,181,182]

One of the approaches in the treatment of atherosclerosis is to reduce the inflammatory activity of macrophages by lowering the levels of pro-inflammatory cytokines and chemokines.

HDAC3 promotes the activation of pro-inflammatory gene expression in M1 macrophages.[183] In one published study, a PROteolysis TArgeting Chimera (PROTAC) was developed to degrade the HDAC3 protein, representing a potential drug for targeted repolarization of macrophages. The study used the THP-1 cell line, which can transform into an M1-like phenotype with the addition of LPS/IFN-γ and an M2-like phenotype with the addition of IL-4. Degradation of HDAC3 by PROTAC P7 in M1 macrophages increased the expression of anti-inflammatory IL-10 by more than 10-fold and reduced the expression of pro-inflammatory IL-12b and iNOS genes compared to the control group. When PROTAC P7 was applied to primary macrophages, the levels of pro-inflammatory cytokines TNF-α and IL-6 decreased. PROTAC P7 also promotes the polarization of macrophages from the M1 phenotype to M0/M2-like phenotypes by reducing the expression of CD68 and CD80 markers of M1 macrophages and increasing CD206 markers characteristic of M2 macrophages.

NPs consisting of gliclazide, an anti-inflammasome agent encapsulated in a polylactide glycolide copolymer (PLGA), or PLGA coated with a monocyte membrane (nanoghosts, NGs), were synthesized in the study. After treatment of monocytes with NG and NP formulations containing gliclazide, TNF-α levels decreased by 9.6 and 8.2 times, respectively, compared with monocytes treated with LPS. Moreover, after treatment with NG monocytes, the expression levels of C1, C3, C8, C9, NOS, MyD88, NLRP3, IL-1β, and IL-18 were significantly reduced. NPs and NGs with gliclazide contributed to the polarization of M1 macrophages into M2 macrophages, as indicated by an increased CD163/CD68 ratio. Histological analysis of the aorta after exposure to NG and NP showed a decrease in the area of atherosclerotic plaques and a reduction in the number of macrophages. These NPs may become an effective drug for targeted polarization of macrophages.[184]

In a study of the effect of Acod1 gene deficiency, which is involved in itaconate synthesis, in Acod1fl/fl LysMcre mice, the following patterns were observed.[185] In the Acod1fl/fl LysMcre mouse line, compared with the wild type, after 10 weeks of hypercholesterolemia, there was an almost twofold increase in the area of atherosclerotic lesions in the aortic root and brachiocephalic artery, and an almost threefold increase in the size of the necrotic core of the atherosclerotic plaque in the aortic root. In Acod1$^{-/-}$ mice, a predominance of M1 macrophages and a reduced number of M2 macrophages were found in atherosclerotic plaques. It was found that treatment with 4-octyl itaconate (OI) helps reduce inflammatory activity and atherogenesis. Treatment

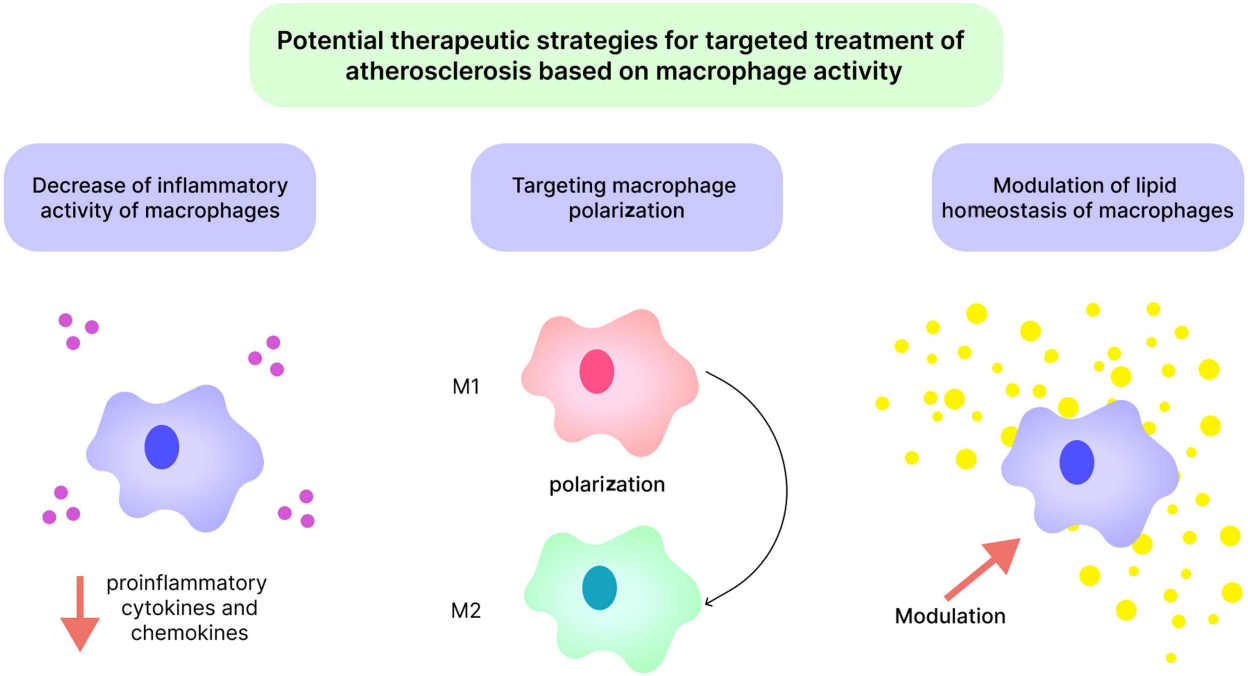

Fig. 5. Possible approaches to atherosclerosis therapy targeting macrophages. Currently, several types of therapeutic approaches are used in the treatment of atherosclerosis through macrophages: reduction of their inflammatory activity in order to curb inflammatory processes in the intima of the artery; targeted polarization of macrophages, which allows macrophages to be converted from a pro-inflammatory to an anti-inflammatory type; and therapy by modulating lipid homeostasis in macrophages.[99,181,182]

with OI in the wild-type atherosclerotic aorta reduces the expression of pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, CCL2, CCL3, CCL5, CXCL1, CXCL2, and CXCL10, while increasing the levels of anti-inflammatory cytokines IL-4, IL-10, and TGF-β1. OI also helps reduce oxidative stress, inhibits glycolysis, restores OXPHOS, activates Nrf2, and increases the expression levels of Hmox1 and Nqo1, enhancing the antioxidant response. Another study also notes the role of IRG1 in the development of atherosclerosis.[186] It was observed that IRG1 deficiency in IRG1$^{-/-}$LDLR$^{-/-}$ mice leads to the accumulation of lipids and macrophages in atherosclerotic plaques. IRG1 encodes an enzyme involved in the synthesis of itaconate. Administration of 4-OI to mice with atherosclerotic lesions reduces the number of macrophages in plaques, as well as the area of the necrotic core, lowers IL-1β levels, suppresses the formation of the NLRP3 inflammasome and neutrophil extracellular traps, and increases the levels of anti-inflammatory markers NRF2 and IL-10.

CD147 is expressed in progressive atherosclerotic lesions and plaques.[187] In the CD147M-KO (myeloid cell-deficient) ApoE$^{-/-}$ knockout mouse line, plaques became more stable. The area of atherosclerotic plaques decreased by 46%, the necrotic core also decreased, lipid accumulation was reduced, and collagen synthesis increased compared to the control mouse line. CD147 promotes the proliferation of M1 macrophages by increasing the production of nitric oxide and ROS, increasing the expression of TNF-α and IL-6, and lowering IL-10 levels. The proliferation of M1 macrophages occurs due to activation of the IκB–IRF5 signaling pathway, as well as suppression of GAS6, which additionally leads to a decrease in the efferocytosis capacity of macrophages. CD147 may become a target in the treatment of atherosclerosis. HAb18 has anti-atherogenic properties: in the aorta, there is a decrease in the size of atherosclerotic lesions and the necrotic core by 42% and 64%, respectively. HAb18 suppresses the expression of pro-inflammatory cytokines iNOS, IL-6, MCP-1, and TNF-α, reduces IRF5 expression, increases the level of the anti-inflammatory cytokine IL-10, enhances efferocytosis efficiency, reduces the number of pro-inflammatory M1 macrophages (CD68$^+$ iNOS$^+$), and increases the number of anti-inflammatory M2 macrophages (CD68$^+$CD206$^+$). Thus, the antibody to CD147, HAb18, contributes to the reduction of atherosclerotic plaques and increases their stability.

Micheliolide (MCL) is an active metabolite of parthenolide and may be a potential agent in the treatment of atherosclerosis.[188] ApoE$^{-/-}$ mice treated with a WD with MCL demonstrated slowed atherosclerosis progression: a decrease in the size of atherosclerotic plaques, increased collagen synthesis due to decreased IL-1β, IL-18, and TNF-α levels, and increased IL-4 and IL-10 levels. MCL inhibits oxLDL-mediated ferroptosis in macrophages through increased GPX4 and xCT expression, activation of nuclear NRF2 translocation, and KEAP1/NRF2 dissociation via binding of MCL to Arg483 of KEAP1.

ANGPTL4 may become a potential target in the treatment of

atherosclerosis. When ANGPTL4 was exposed to macrophages isolated from BMDMs of ApoE$^{-/-}$ mice, there was a decrease in the expression of such pro-inflammatory markers as Tnfrsf11b, Tlr4, Ccl2, and Nos2 and a simultaneous increase in the expression of the anti-inflammatory marker IL-10.[189] The Oil Red O analysis also showed a decrease in the formation of foam cells from macrophages due to their reduced oxLDL uptake compared with the control group. The effect of ANGPTL4 on the aorta also showed a decrease in the number of pro-inflammatory macrophages CD11b$^+$F4/80$^+$, CD80$^+$, as well as a decrease in the area of macrophages CD68$^+$ and Mac2$^+$. ANGPTL4 makes atherosclerotic plaques more stable by inhibiting the transition of SMCs into macrophage-like cells. Stable plaques are characterized by a smaller necrotic nucleus and an enlarged fibrous covering. Inhibition is caused by a decrease in ROS due to suppression of TNF-α-induced NOX1, which leads to suppression of KLF4.

Targeted activation of macrophage polarization from the pro-inflammatory to the anti-inflammatory type is one of the promising therapeutic strategies. As already mentioned, M1 macrophages mediate inflammation, while M2 macrophages reduce it.[5,182] Thus, it is suggested that the polarization of macrophages from the M1 phenotype to the M2 phenotype may contribute to the stabilization and regression of atherosclerosis. Most of all, this can be helped by the reliability of macrophages, which consists in the possibility and reverence from M1 to M2.[190]

The microenvironment of atherosclerotic plaques induces their polarization into two main phenotypes. It was shown that anti-inflammatory humoral factors such as HDL, apoE, adiponectin, and angiotensin-converting enzyme (ACE) stimulate the polarization of M2, while inflammatory factors such as activin A and C-reactive protein inhibit the transformation from M1, M2.[191,192]

Geniposide is one of the potential drugs for targeted polarization of macrophages.[193] In a study on an ApoE$^{-/-}$ mouse line treated with a WD diet, a decrease in the expression of iNOS, IL-6, IL-1β, TNF-α genes associated with pro-inflammatory M1 macrophages and an increase in the expression of genes associated with anti-inflammatory M2 macrophages was noted in the aorta: Arg1, IL-4, IL-10, TGFβ. After applying geniposide, western blotting confirmed a decrease in iNOS levels and an increase in Arg1 levels, and using immunofluorescence of the aortic root, an increase in the CD68$^+$iNOS$^+$ area and a decrease in the CD68$^+$Arg1$^+$ area were detected. In addition, cytometric analysis detected a decrease in the level of cytokines IFN-γ, IL-6, TNF-α and an increase in the level of cytokines IL-4, IL-10 in the blood serum. In addition, geniposide increases the expression of CXCL14 in perivascular adipose tissue and 3T3-L1 adipocytes, which leads to M2 polarization of macrophages. The authors noted that CXCL14 participates in metabolic changes in adipose tissue, stabilization of atherosclerotic plaques, and the polarization of macrophages. To evaluate the effect of CXCL14 on macrophage polarization, an *in vitro* experiment was performed: the recombinant CXCL14 protein and the RAW 264.7 macrophage cell line were used; LPS/IFN-γ macrophages were treated to induce the M1 phenotype, and IL-4 was added to induce the M2 phenotype. Using flow cytometry, it was found that CXCL14 reduces the number of F4/80$^+$CD80$^+$ cells and increases the number of F4/80$^+$CD206$^+$ cells, inhibiting the polarization of M1 macrophages and enhancing the polarization of M2 macrophages, respectively.

M2 macrophage membrane-coated nanoparticles (MELT), consisting of PLGA NPs, are loaded with the PROTEC agent dTRIM24 and then coated with an M2-type macrophage membrane.[4] MELT is one of the promising drugs for targeted polarization of macrophages. M1 macrophages are the target for MELT. After MELT treatment of macrophages, a dose-dependent decrease in the expression of the iNOS gene, a characteristic marker of M1 macrophages, and a dose-dependent increase in the expression of the Arg1 gene, a marker of M2 macrophages, were detected with reverse-transcription quantitative polymerase chain reaction. Thus, MELT promotes the polarization of macrophages from M1 to M2. Fluorescence-activated cell sorting analysis after MELT treatment revealed an increase in F4/80$^+$CD206$^+$ M2 macrophage cells and a simultaneous decrease in F4/80$^+$CD80$^+$ M1 macrophage cells. Oil Red O staining of the aortic root of the ApoE$^{-/-}$ mouse line after exposure to MELT confirmed a decrease in the area of atherosclerotic lesions.

Monocarboxylate transporter 4 (MCT 4), predominantly expressed in macrophages, is associated with the processes of histone acetylation outflow and atherosclerosis.[158] A significant increase in MCT4 was observed in human atherosclerotic plaques and in the ApoE KO mouse line on HFD. MCT4 deficiency reduced the accumulation of cholesterol, the formation of foam cells, inflammatory processes, and endothelial dysfunction, and promotes the polarization of M2 macrophages due to the accumulation of lactate. MCT4 deficiency inhibits the processes of atherogenesis due to epigenetic mechanisms: MCT4 deficiency increases H3K18 lactylation and p300 binding to H3K18la, which leads to the expression of genes associated with repair. The use of pharmacological inhibitors of MCT4—VB124 and PROTAC MD-43—leads to suppression of the progression of atherosclerosis and increased lactylation of H3K18.

HDL can contribute to improving the efficiency of ATF3 and STAT6 action. These enzymes promote macrophage migration and convert M1-polarized macrophages to the M2 phenotype.[194] Also, HDL and ApoA1 are important factors in protecting against atherogenesis.[195] It was found that in a line of mice with ApoA1 KO/KO LDLR KO/KO knockout treated for 10 weeks with HFD, an increase in the size of atherosclerotic plaques was observed, while in those with overexpression of the hApoA1TG/TGLDLRKO/KO line, atherosclerotic plaques were significantly smaller compared with the control line ApoA1 WT/WT LDLR KO/KO. Immunofluorescence staining was used to discover the increased level of phosphorylated necroptosis mediators RIPK3 and MLKL in atherosclerotic plaques of ApoA1 knockout mice. The study also noted the atheroprotective role of HDL in protecting against necroptosis through activation of SR-B1, PDZK1, and the PI3K/Akt signaling pathway.

IL-19 promotes the polarization of macrophages by activating KLF4, Arg1, and PPARγ via STAT6.[196] The plasma protein Callistatin has an anti-inflammatory effect and can inhibit the polarization of macrophages into the M1 phenotype, induced by a decrease in the expression of markers of this phenotype (iNOS and MCP-1), and stimulate the polarization of M2 macrophages through the activation of IL-10 and ARG-1.[181]

Thioredoxin-1 promotes the polarization of macrophages toward an anti-inflammatory M2 phenotype and antagonizes

atherosclerosis.[197]

Inhibition of miR-33 has been shown to promote macrophage autophagy and shift macrophages toward an anti-inflammatory M2 phenotype through an AMP-activated protein kinase CC.[198]

Rupture of atherosclerotic plaques leads to arterial thrombosis. It was found that rats with coronary microembolization had increased miR-34a-5p expression.[199] Increased expression of miR-34a-5p leads to increased polarization of macrophages from M0 to M1, and also enhances the NF-κB pathway, which leads to the progression of inflammatory processes. In addition, miR-34a-5p promotes inflammation in HUVECs. PLT-exo exosomes isolated from platelets reduce the above-mentioned negative effects of miR-34a-5p by inhibiting it.

The study developed the cerium-macrophage exosomes (Ce-Exo) nanocomplex based on the lysosomes of RAW264.7 macrophages and CeO_2 NPs as a promising method for the treatment of atherosclerosis.[200] Ce-Exo has cytoprotective properties, protecting HUVECs by inhibiting apoptosis and reducing DNA damage caused by TNF-α through decreased expression of γH2AX. Ce-Exo promoted the polarization of M1 macrophages to M2 and reduced the number of $CD86^+$ macrophages, as well as ROS levels and iNOS expression in RAW264.7 macrophages treated with LPS. Ce-Exo in $ApoE^{-/-}$ mice reduced the number of atherosclerotic plaques and blood lipid levels, remodeled the immune microenvironment, restored endothelial function, and promoted the inhibition of atherosclerosis.

Another method in the treatment of atherosclerosis is to change lipid metabolism and homeostasis in macrophages.

Currently, the strategy of liver X-receptor antagonists is being discontinued. However, in a relatively recent study, NPs carrying the LXR T0901317 (T1317) agonist were used to increase cholesterol efflux from macrophages *in vitro* and in mice with ApoE deficiency. As part of the study, they induced regression of atherosclerotic plaques in mice.[98]

Hydroxytyrosol is one of the promising drugs for modulating lipid homeostasis. It was found that hydroxytyrosol in foam cells obtained from THP-1 exposed to oxLDL is able to reduce the number of lipid droplets in the cytoplasm, the total level of cholesterol and its esters, as well as decrease the accumulation of lipids. A decrease in lipid accumulation occurs due to the effect of hydroxytyrosol on the CD36 receptor gene involved in oxLDL uptake. Activation of RCT occurs due to an increase in the expression of LXRα and ABCA1. Hydroxytyrosol, through activation of PPARγ, increases the expression of ABCA1 through LXRα, activating the PPARγ/LXRα/ABCA1 pathway, which prevents the formation of foam cells. In addition to modulating lipid homeostasis, hydroxytyrosol shows an anti-inflammatory effect by reducing the expression of TNF-α and IL-1β in endothelial cells, as well as ICAM-1 and VCAM-1, which inhibits monocyte adhesion. The antioxidant effect of hydroxytyrosol is observed due to a decrease in ROS, which provides lower oxidative stress and thereby reduces foam cell formation.[201]

Trem2 is a macrophage receptor that plays a role in macrophage differentiation and the functioning of foam cells in atherosclerotic plaques. Macrophages isolated from wild-type C57Bl/6 or $Trem2^{-/-}$ mice pretreated with cholesterol solution showed that macrophages isolated from the knockout line of mice had a reduced ability to absorb oxLDL. $TREM2^{-/-}$ macrophages formed foam cells less efficiently compared with control macrophages in HFD. In addition, a decrease in the number of atherosclerotic plaques was observed in the Them2DMF mouse line in the aortic arch and sinus. TREM2 knockout in macrophages reduces the proliferation of foam cells due to an increase in $CD68^+$ after TAM-HFD feeding for six and eight weeks. Thus, Trem2 deficiency may become a potential therapeutic target. When exposed to the AL002a agonist TREM2, $LDLR^{-/-}$ mice treated with HFD showed an increase in the area of atherosclerotic plaques and total plaque load due to an increase in the number and proliferation of macrophages ($CD68^+$ $Ki67^+$).[202] However, at the same time, there was a decrease in the area of the necrotic nucleus and an increase in the area of the fibrous cap and collagen expression, which made atherosclerotic plaques more stable. It was found that AL002a promotes the reprogramming of foam macrophages due to the secretion by foam macrophages of products of genes associated with lipid metabolism (Lgals3, Fabp5, Trem2), those associated with OXPHOS (Atp5c1, Atp5e, and Uqcrh), and with the synthesis of collagen (Col1a1, Col2a1). The Trem2 agonist enhanced the activation of Syk, which led to increased oxLDL uptake, increased viability, increased proliferation, and improved basal and ATP-associated oxygen consumption rate in the mitochondria of macrophages. TGF-β under the influence of AL002a reduced fibroblast proliferation and increased SMC collagen synthesis. AL002a can be used in the treatment of atherosclerosis to stabilize atherosclerotic plaques in order to reduce the risk of their rupture. Treatment of $LDLR^{-/-}$ mice with another Trem2 agonist also reduced the size of the necrotic nucleus; however, there was no significant change in the overall size of the plaques.[62] 4D9 agonistic antibody enhances the processes of efferocytosis and improves the survival and functioning of macrophages, as well as mitochondrial function. 4D9, as well as AL002a, can potentially be used for therapeutic purposes.

EEDL is an ethanol extract of Danlou tablets that includes gallic acid, puerarin, daidzin, paeoniflorin, calycosin-7-O-glucoside, ferulic acid, naringin, salvianolic acid B, cryptotanshinone, and tanshinone IIA.[203] Using Oil Red O staining, it was found that incubation of RAW264.7 macrophages in the presence of EEDL and oxLDL dose-dependently increases cholesterol efflux to ApoA1. EEDL also promotes LXR translocation, increases the expression of ABCA1 and ABCG1, CYP7A1, ABCA1, ABCG1, ABCG5, and ABCG8, and decreases CD36 expression, which has a positive effect on cholesterol efflux and reduction of its accumulation. EEDL contributes to the change in lipid homeostasis of macrophages.

The study revealed the role of macrophage ACE in the development of atherosclerosis.[204] The atherosclerotic lesion of the aorta of the ACE 10/10PCSK9 mouse line was 25.0% compared with the WT PCSK9 mouse line, in which the atherosclerotic lesion covered 44.7%. ACE 10/10PCSK9 mice also showed a greater number of M2 $CD11b^+F4/80^+CD206$ macrophages, as well as increased expression of IL-10, CD36, Ym-1, and arginase-1. ACE 10/10PCSK9 macrophages increased the expression of PPARα due to increased β-oxidation of lipids, which led to increased efferocytosis processes. In addition, ACE 10/10PCSK9 macrophages showed an increase in cholesterol

Table 1. Possible approaches to target atherosclerosis via macrophages

Target	Approach/Agent	Mechanism of action	Key effect
PCSK9	Vaccine (PCSK9-nanoparticles (NP))	Induces high-titer IgG antibodies against the PCSK9 catalytic domain; prevents LDLR degradation[179]	Reduces total cholesterol and LDL-C; decreases atherosclerotic lesion area[179,180]; increases plaque stability (collagen synthesis); reduces pro-inflammatory macrophages[179]
HDAC3	PROTAC (PROTAC P7)	Degrades HDAC3 protein in M1 macrophages[183]	Repolarizes macrophages from M1 to M0/M2-like phenotype; increases anti-inflammatory IL-10; reduces pro-inflammatory IL-12b, iNOS, TNF-α, and IL-6[183]
Inflammasome (NLRP3)	NP and nanoghosts (NG) with Gliclazide (GL)	Delivers anti-inflammasome agent (GL) to monocytes/macrophages[184]	Reduces TNF-α, C1, C3, C8, C9, NOS, MyD88, NLRP3, IL-1β, IL-18; polarizes M1 to M2 macrophages (increases CD163/CD68 ratio); decreases plaque area and macrophage numbers[184]
IRG1/Itaconate	4-octyl itaconate (OI)	Synthetic itaconate derivative; activates Nrf2; inhibits glycolysis; restores OXPHOS[185,186]	Reduces pro-inflammatory cytokines (IL-1β, IL-6, IL-12, etc.); increases anti-inflammatory cytokines (IL-4, IL-10, TGF-β1); reduces macrophage numbers and necrotic core area; suppresses NLRP3 inflammasome and NETs[185,186]
CD147	Antibody (HAb18)	Blocks CD147, suppressing the IK-IRF5 signaling pathway[187]	Reduces atherosclerotic lesion size and necrotic core; decreases pro-inflammatory M1 macrophages (iNOS, IL-6, TNF-α); increases anti-inflammatory M2 macrophages (IL-10); improves efferocytosis[187]
KEAP1/NRF2	Micheliolide (MCL)	Binds to KEAP1 (Arg483), promoting NRF2 nuclear translocation[188]	Slows atherosclerosis; decreases IL-1β, IL-18, TNF-α; increases IL-4, IL-10; inhibits oxLDL-mediated ferroptosis in macrophages via increased GPX4 and xCT[188]
ANGPTL4	ANGPTL4 (protein treatment)	Reduces ROS via suppression of TNF-α-induced NOX1; inhibits KLF[45,182,189]	Reduces pro-inflammatory markers (Tnfrsf11b, Tlr4, Ccl2, Nos2); increases anti-inflammatory IL-10; decreases foam cell formation; inhibits SMC-to-macrophage-like cell transition; stabilizes plaque[5,182,189]
CXCL14	Geniposide	Increases expression of CXCL14 in PVAT and adipocytes[193]	Promotes M2 macrophage polarization (increases CD206, Arg1, IL-4, IL-10); inhibits M1 polarization (decreases iNOS, IL-6, TNF-α); stabilizes atherosclerotic plaques[193]
Macrophage phenotype (M1)	MELT (M2 macrophage membrane-coated nanoparticles with dTRIM24)	Nanoparticles coated with M2 membrane target M1 macrophages; deliver PROTAC agent dTRIM24[4]	Polarizes macrophages from M1 to M2[190]; decreases iNOS (M1 marker); increases Arg1 (M2 marker); reduces atherosclerotic lesion area[4]
MCT4	Pharmacological inhibitors (VB124) and PROTAC (MD-43)	Inhibits or degrades MCT4, leading to lactate accumulation and increased H3K18 lactylation[158]	Reduces cholesterol accumulation and foam cell formation; promotes M2 macrophage polarization; suppresses atherogenesis via epigenetic mechanisms[158]
HDL/ApoA1	HDL and ApoA1 (overexpression)	Activates SR-B1, PDZK1, and PI3K/Akt signaling pathway; promotes ATF3	Protects against necroptosis (reduces RIPK3 and MLKL); reduces atherosclerotic plaque

Table 1. Possible approaches to target atherosclerosis via macrophages (*continued*)

Target	Approach/Agent	Mechanism of action	Key effect
		and STAT6 action[190,194,195]	size; promotes macrophage migration and M2 polarization[190,194,195]
miR-34a-5p	PLT-exo exo-somes (from platelets)	Inhibits miR-34a-5p, which otherwise activates the NF-κB pathway[199]	Reduces M1 polarization; reduces inflammation in HUVECs; inhibits progression of inflammatory process-es[199]
Macrophages (general)	Ce-Exo (CeO2 nanoparticles + macrophage lysosomes)	Nanocomplex with cytopro-tective properties[200]	Protects endothelial cells (HUVECs); promotes M1-to-M2 polarization; reduces ROS, iNOS, and $CD86^+$ mac-rophages; decreases plaque area and blood lipid levels[200]
LXRα/Cho-lesterol ef-flux	Nanoparticles with LXR ago-nist (T0901317)	Delivers LXR agonist to increase cholesterol efflux from macrophages[98,201]	Increases reverse cholesterol transport; induces regression of ath-erosclerotic plaques[98,201]
PPARγ/LXRα/ABCA1	Hydroxytyro-sol (HT)	Activates the PPARγ/LXRα/ABCA1 pathway; reduces CD36 expression[201]	Reduces lipid accumulation and foam cell formation; decreases total choles-terol and its esters[196,201]; anti-inflammatory (reduces TNF-α, IL-1β, ICAM-1, VCAM-1)[181,201]; antioxidant (reduces ROS)[201]
Trem2	Agonists (AL002a, 4D9)	Activates Trem2, enhancing Syk signaling, efferocytosis, and mitochondrial function[62,202]	Increases plaque stability (increases fibrous cap, collagen, reduces necrotic core); reprograms foam cell metabolism (increases OXPHOS, collagen synthesis); however, can increase overall plaque area and macrophage proliferation[62,202]
Lipid homeostasis	Ethanol extract of Danlou tablets (EEDL)	Promotes LXR translocation; increases ABCA1, ABCG1, CYP7A1; decreases CD36 expression[203]	Increases cholesterol efflux to ApoA1; reduces lipid accumulation; modulates lipid homeostasis in macrophages[203]
Angiotensin converting enzyme (ACE)	ACE (increased expression)	Increases PPARα expres-sion, leading to increased β-oxidation; increases ABCA1 and ABCG1; decreases CD36[204]	Reduces atherosclerotic lesion area; increases M2 macrophages (CD206, IL-10, Arginase-1); improves efferocytosis and cholesterol export[204]
P2Y6R	Antagonist (TPP)	Inhibits P2Y6R and its signaling pathways (calcium, STIM1/ORAI); reduces SRA and PLCβ expression[205]	Reduces plaque size and lipid deposits; inhibits foam cell formation; re-duces NLRP3 inflammasome activation and pro-inflammatory cytokines (IL-1β, TNF-α, IL-6)[205]

ABCA1, ATP-binding cassette transporter A1; ANGPTL4, angiopoietin-like 4; ApoA1, apolipoprotein A-I; CXCL14, C-X-C motif chemokine ligand 14; GPX4, glutathione peroxidase 4; HAb18, anti-CD147 monoclonal antibody HAb18; HDAC3, histone deacetylase 3; HDL, high-density lipoprotein; HUVECs, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule 1; IgG, immunoglobulin G; IL, interleukin; iNOS, inducible nitric oxide synthase; IRG1, immune-responsive gene 1; KLF4, Krüppel-like factor 4; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; MELT, M2 macrophage membrane-coated dTRIM24-loaded nanoparticles; MLKL, mixed lineage kinase domain-like pseudokinase; NETs, neutrophil extracellular traps; NLRP3, NLR family pyrin domain-containing 3; NOX1, NADPH oxidase 1; Nrf2, nuclear factor erythroid 2-related factor 2; ORAI, calcium release-activated calcium channel protein; oxLDL, oxidized low-density lipoprotein; OXPHOS, oxidative phosphorylation; P2Y6R, P2Y purinergic receptor 6; PCSK9, proprotein convertase subtilisin/kexin type 9;PLCβ, phospholipase C beta; PLT-exo, platelet-derived exosomes; PPARγ, peroxisome proliferator-activated receptor gamma; PROTAC, proteolysis-targeting chimera; ROS,reactive oxygen species; SMC, smooth muscle cell; SR-A, scavenger receptor class A; STIM1, stromal interaction molecule 1; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1; xCT,cystine/glutamate antiporter.

export due to increased expression of ABCA1 and ABCG1 and a decrease in CD36 expression. Increased ACE expression may be one of the potential concepts in the treatment of atherosclerosis.

Increased expression of P2Y6R is seen in atherosclerotic plaques and blood of patients with atherosclerosis.[205] The LDLR$^{-/-}$ P2Y6Rfl/fl LysMcre knockout mouse line is characterized by a decrease in the size of atherosclerotic plaques and lipid deposits. In macrophages with a P2Y6R deletion, SR-A expression and PLCβ expression decrease, suppressing the calcium signaling pathway and inhibiting the interaction of STIM1 and ORAI, which inhibits lipid uptake and, as a result, the formation of foam cells. In addition, P2Y6R deletion plays a role in the inflammatory response, and in macrophages it reduces the expression of NLRP3, ASC, caspase-1, and IL-1β. Thus, P2Y6 is an important link in foam cell formation, calcium signaling pathways, and inflammatory processes. TPP—a P2Y6R antagonist—inhibits the activity of P2Y6R and its signaling pathways, reducing the formation of atherosclerotic plaques and foam cells in them. TPP also promotes an atheroprotective effect by reducing the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6.

The possible approaches to treat atherosclerosis mentioned in this section are summarized in Table 1.[4,5,45,62,98,158,179-190,193-196,199-205]

Limitations

Although this review integrates multidimensional studies, the functions of some macrophage subtypes, such as M4 and Mox, remain controversial, and most mechanistic studies are based on animal models; therefore, the effectiveness and safety of clinical translation need to be verified. Most mechanisms of atherosclerosis development have been studied in mouse models, which do not fully replicate human pathology, especially considering the differences in monocyte/macrophage markers between species. This raises doubts about the direct translation of preclinical data into clinical practice. Additionally, the complex relationship between mitochondrial dysfunction, cellular senescence, and inflammation in macrophages is not completely understood. Senescent macrophages that release pro-inflammatory cytokines and proteases can contribute to chronic inflammation and plaque instability, but the mechanisms that govern this process and their synergy with mitochondrial disorders require further study.

Future directions

Future research should focus on identifying specific and validated markers of macrophage subpopulations, which will allow for the development of more accurate therapeutic strategies. We should mention the potential of targeted gene therapy, which has shown promising results for the treatment of different diseases.[207-209] It is necessary to conduct in-depth studies of the synergistic regulatory networks that link mitochondrial dysfunction, ER homeostasis disruption, and cellular senescence. Of particular interest is the clinical evaluation of combined approaches that target multiple pathogenic mechanisms simultaneously, such as inhibiting inflammation in combination with enhancing cholesterol efflux and/or the application of senolytics, drugs targeting senescent cells. Only such multilayered strategies based on a deep understanding of macrophage biology can ensure effective and safe clinical translation and open new horizons in the prevention and treatment of atherosclerosis.

Conclusions

This narrative review summarizes the central role of macrophages in atherosclerosis, including monocyte recruitment, foam cell formation, plaque progression, extracellular matrix remodeling, inflammatory signaling, plaque instability, and potential plaque regression. Macrophage plasticity is a key feature of atherogenesis, but macrophage phenotypes should be interpreted as dynamic and context dependent rather than as fixed categories.

Current evidence suggests that macrophage-targeted strategies may offer therapeutic potential through three main approaches: reducing inflammatory activity, modulating macrophage polarization, and improving lipid homeostasis and cholesterol efflux. However, most of these approaches remain preclinical, and their safety, efficacy, and translational relevance require further validation.

Important gaps remain, particularly regarding subtype-specific macrophage biomarkers, the functional overlap among macrophage states, and the interaction between mitochondrial dysfunction, cellular senescence, and inflammation. Future studies should clarify these mechanisms and evaluate whether combined macrophage-targeted strategies can be translated into safe and effective interventions for atherosclerosis and its cardiovascular complications.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Original idea of the manuscript (EB), writing of the manuscript (EB, DG, EG, AG, EP, VK, AO), editing of the manuscript (EB, DB, TD, YL, AV, IB), and figure creation (DG, EG). All authors have approved the final version and publication of the manuscript.

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