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REVIEW

Mechanisms of foam cell formation in atherosclerosis

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Abstract Low-density lipoprotein (LDL) and cholesterol homeostasis in the peripheral blood is maintained by specialized cells, such as macrophages. Macrophages express a variety of scavenger receptors (SR) that interact with lipoproteins, including SR-A1, CD36, and lectin-like oxLDL receptor-1 (LOX-1). These cells also have several cholesterol transporters, including ATP-binding cassette transporter ABCA1, ABCG1, and SR-BI, that are involved in reverse cholesterol transport. Lipids internalized by phagocytosis are transported to late endosomes/lysosomes, where lysosomal acid lipase (LAL) digests cholesteryl esters releasing free cholesterol. Free cholesterol in turn is processed by acetyl-CoA acetyltransferase (ACAT1), an enzyme that transforms cholesterol to cholesteryl esters. The endoplasmic reticulum serves as a depot for maintaining newly synthesized cholesteryl esters that can be processed by neutral cholesterol ester hydrolase (NCEH), which generates free cholesterol that can exit via cholesterol transporters. In atherosclerosis, pro-inflammatory stimuli upregulate expression of scavenger receptors, especially LOX-1, and downregulate expression of cholesterol transporters. ACAT1 is also increased, while NCEH expression is reduced. This results in deposition of free and esterified cholesterol in macrophages and generation of foam cells. Moreover, other cell types, such as endothelial (ECs) and vascular smooth muscle cells (VSMCs), can also become foam cells. In this review, we discuss known pathways of foam cell formation in atherosclerosis.

Keywords Macrophage · Endothelial cell · Smooth muscle cell · oxLDL · Cholesterol · Foam cell · Atherosclerosis

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Introduction

Foam cells play an important role at all stages of atherosclerotic lesion development, from initial lesions to advanced plaques. Macrophages serve as the main source of foam cells after they penetrate the endothelial barrier and accumulate in the arterial intima media in response to the pro-inflammatory activation of endothelial cells (ECs) [1]. A small part of foam cells originates from ECs and vascular smooth muscle cells (VSMCs). ECs can also differentiate to smooth muscle-like cells that can be involved in pro-atherogenic vascular remodeling. In addition, VSMCs can differentiate to macrophages that become foam cells upon lipid uptake [2]. Transformation of VSMCs to macrophage-like cells is regulated by Kruppel-like factor 4 (KLF4), a transcription factor, for which over 800 target genes were found in cholesterol-treated VSMCs [3]. Cholesterol loading of VSMC converts them to a macrophage-appearing state by downregulating the microRNA (miR)-143/145-myocardin axis, a key pathway that is essential for SMC-specific differentiation [4]. Salusin-β, a pro-atherogenic agent, induces foam formation and monocyte adhesion via inducing expression of acetyl-CoA acetyltransferase (ACAT)1 and vascular cell adhesion molecule 1 (VCAM-1) in VSMCs [5].

The main cause of foam cells generation is the excessive influx of modified low-density lipoproteins (LDL) and accumulation of cholesterol esters in intimal macrophages [6]. It should be noted that native (unmodified) LDL that can be found in the peripheral blood of healthy individuals, does not cause accumulation of cholesteryl esters in cultured macrophages, while modified LDL isolated from atherosclerotic patients induces a significant increase of intracellular cholesteryl esters (Fig. 1). In normal conditions, macrophages serve as a major regulator of plasma lipoprotein metabolism and content [7]. These cells express a variety of scavenger receptors (SR), such as SR-A1, CD36, and lectin-like oxLDL receptor-1 (LOX-1) with affinity to oxidized low-density lipoproteins (oxLDL). Additionally, macrophages have an advanced enzymatic machinery, such as acyl coenzyme A:cholesterol acyltransferase-1 (ACAT1), which is essential for formation of cholesterol esters [8]. Cholesteryl esters are hydrolyzed by two enzymes: neutral cholesteryl ester hydrolase 1 (NCEH1) and lysosomal acid lipase (LAL), that generate free fatty acids and cholesterol [9]. Macrophages also express a range of membrane pumps, such as ATP-binding cassette (ABC) transporters ABCA1 and ABCG1 and scavenger receptor SR-BI that are involved in reverse cholesterol transport [7]. Together, these proteins ensure an effective control of LDL and cholesterol content in the peripheral blood under normal conditions.

In atherosclerosis, macrophage-dependent cholesterol handling is deregulated. Due to increased generation of oxLDL, macrophage expression of LOX-1 is significantly upregulated by stimulation of multiple factors such as pro-inflammatory cytokines [9], oxLDL itself, lysophosphatidylcholine (a product of oxLDL degradation) [10], advanced glycation end-products (AGEs) [11], vasopressors [12], and others. Elevated expression of LOX-1 leads to increased lipid uptake by macrophages. By contrast, expression of ABCA1 and ABCG1 is decreased in atherosclerosis, further aggravating intracellular cholesterol accumulation and promoting generation foam cells formation [13].

LDL transport through the endothelial barrier

Atherosclerosis and pro-atherogenic conditions such as hypertension, smoking, and diabetes are characterized by increased vascular permeability for LDL [14, 15] and upregulated expression of LOX-1, which is associated with increased endothelial permeability for oxLDL through activation of protein kinase C (PKC) and calcium influx into ECs. In parallel, expression of desmoglein 1 (DSG1) and desmocollin 2 (DSC2) is reduced [16]. DSG1 is a component of desmosomes, which is involved in cell-cell junctional contact formation and is regulated by calcium [17]. Similarly, DSC2, a calcium-binding cadherin-type protein, is also involved in desmosomal intercellular contacts [18]. LOX-1-mediated downregulation of desmosomal cell-cell contacts weakens the endothelial junctions and increases trans-endothelial transfer of oxLDL.

Upregulation of PKC leads to activation of a RhoA/Rho kinase-dependent signaling and phosphorylation of occludin, a key structural component of tight junctions, which weakens the endothelial barrier [19]. PKC stimulation also results in activation of protein phosphatase 1 regulatory subunit 14A (PPP1R14A), an inhibitor of smooth muscle myosin phosphatase, which in turn causes cytoskeletal rearrangement, disruption of cell-cell contacts, and increased permeability [20].

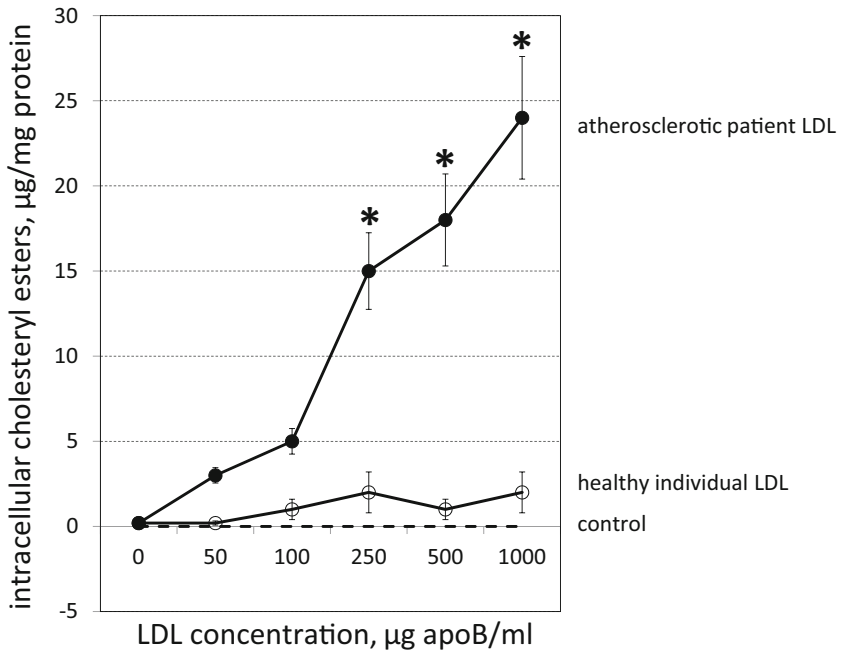

Fig. 1 Effect of LDL isolated from the plasma of individuals without atherosclerosis and patients with carotid atherosclerosis on cholesterol esters in human macrophages. Human monocyte-derived macrophages were incubated in medium 199 containing 10% lipid-deficient serum and LDL for 24 h at 37 °C. Control cells were incubated in the medium without LDL. Data are presented as the mean of three repetitions ± standard deviation. The *asterisk* indicates significant difference from the control, $p < 0.05$

Increased transfer of cholesterol-rich oxLDL into the intima media through the endothelial barrier contributes to lipid accumulation in the intimal macrophages, which is an early event in atheroma formation.

Current consensus favors the inflammatory hypothesis of atherosclerosis induction [21], according to which pro-inflammatory stimuli initiate penetration of monocytes into the intima media followed by sub-endothelial lipid accumulation in the arterial wall. In the intima media, monocytes differentiate predominantly to pro-inflammatory macrophages (the M1 phenotype) that actively take up lipids but cannot effectively empty the lipid excess due to the inhibition of efflux pumps in pro-inflammatory microenvironment [22]. Classical M1 macrophages can be induced by exposure to pro-inflammatory cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α or to pathogenic products such as lipopolysaccharide (LPS), an endotoxin of Gram-negative bacteria, and flagellin, a structural component of bacterial flagellum [23]. In infection or injury, M1 macrophages are mainly involved in inflammatory responses directed by Th1 cells. These macrophages release a variety of inflammatory cytokines and chemokines essential for propagation of inflammation. M1 macrophages also produce high amounts of nitric oxide (NO) and reactive oxygen species (ROS) to destroy a pathogen [24].

M2 (or alternatively polarized) macrophages can be induced by various stimuli and generally possess anti-inflammatory properties. A variety of M2 subtypes was characterized, with the most pro-inflammatory M2a that can be generated under exposure to Th2 cytokines, i.e., interleukin (IL)-4 and IL-13. Typically, M2 macrophages secrete significant amounts of anti-inflammatory IL-10 and transforming growth factor (TGF)-β, contribute to wound healing, phagocytosis of apoptotic cells, tissue remodeling, angiogenesis, and carcinogenesis [25].

Macrophage M2 polarization is associated with an increase of fatty acid oxidation. However, it is unclear whether this association is a simple correlation only or it directly influences M2 polarization [26]. By contrast, M1 polarization is associated with the activation of fatty acid synthesis that primarily contributes to the inflammatory response and affects cholesterol homeostasis and neutral fat accumulation [27]. Recently, Da Silva et al. (2016) performed an interesting experiment to evaluate how macrophage-derived foam cells respond to M1-polarizing stimuli [28]. Macrophage-colony stimulating factor (M-CSF)-induced macrophages were transformed into foam cells and then exposed to M1-polarizing factors (i.e., LPS + IFN-γ). While normal M-CSF-induced macrophages started to express various pro-inflammatory genes, foam cells exhibited weaker pro-inflammatory activation. In response to M2-polarizing signal (i.e., treatment with IL-4) both normal macrophages and foam cells responded by upregulation of anti-inflammatory genes with equal magnitude [28]. Indeed, in M1-polarizing microenvironments of atherosclerotic lesions, foam cell formation may locally weaken the macrophage-dependent inflammatory component of atherogenesis.

How macrophages can sense and take up lipids

Lipid internalization by macrophages has been reviewed in several previously published works [7, 8, 13, 29]. Briefly, circulating monocytes and resident macrophages can sense circulating lipids through a number of previously described receptors, including CD36, SR-A1, and LOX-1 (Fig. 2) [7].

There are three known isoforms of the SR-A1 receptor, of which two are functionally relevant and can participate in the transfer of oxLDL. The full-length isoform SR-A1 contains a large extracellular domain, the cytosolic domain, and the transmembrane domain (Fig. 3). The extracellular domain consists of α-helical coiled coils, the collagen-like domain, and the C-terminal region enriched by cysteine residues [30]. The second isoform SR-A1.1 is shorter but remains the capacity to recognize ligands due to the presence of the collagen-like domain. On the C-terminus, the third isoform SR-A1.2 contains only four cysteine residues and therefore dysfunctional for lipid transport because lacks the capability to bind any extracellular ligand [31]. This isoform serves as an inhibitor of the first two isoforms thereby downregulating lipid uptake by macrophages [32, 33]. In experimental atherosclerotic rodent models, such as Apolipoprotein E (ApoE)- and LDL receptor (LDLR)-deficient mice, knockout of SR-A1 results in anti-atherogenic effects that primarily inhibit formation of foam cells [34, 35].

Expression of SR-A1 is regulated by the nuclear transcription factor (NF)-κB, which can be stimulated by pro-inflammatory cytokines [36]. SR-A1 expression can be upregulated through stimulation of voltage-dependent K^+ channel Kv1.3, which in turn leads to a higher uptake of oxLDL [37]. Furthermore, inhibition of Kv1.3 by a specific antibody leads to the downregulation of SR-A, LOX-1, and ACAT1, and increased expression of ABCA1 in cultured THP-1 macrophages and human primary macrophage cultures [38], indicative of a possible contribution of potassium influx.

Anti-atherosclerotic and antioxidant messengers, such as polyphenols and curcumin, downregulate SR-A expression. In macrophages of mice deficient for ApoE, curcumin induces ubiquitination and degradation of SR-A1 mediated by calpain, an intracellular protease [39]. Plant polyphenols suppress SR-A1 expression by inhibiting peroxisome proliferator-activated receptor γ (PPARγ), a transcriptional regulator that controls lipid uptake, fatty acid storage, and glucose metabolism [39]. Hydrogen sulfide (H_2S) was shown to downregulate SR-A1 levels in macrophages, but its production is reduced in the vessels of ApoE-deficent mice [40]. In blood vessels, H_2S is synthesized by cystathionine γ-lyase from an aminoacid L-cysteine, accompanied by production of pyruvate and

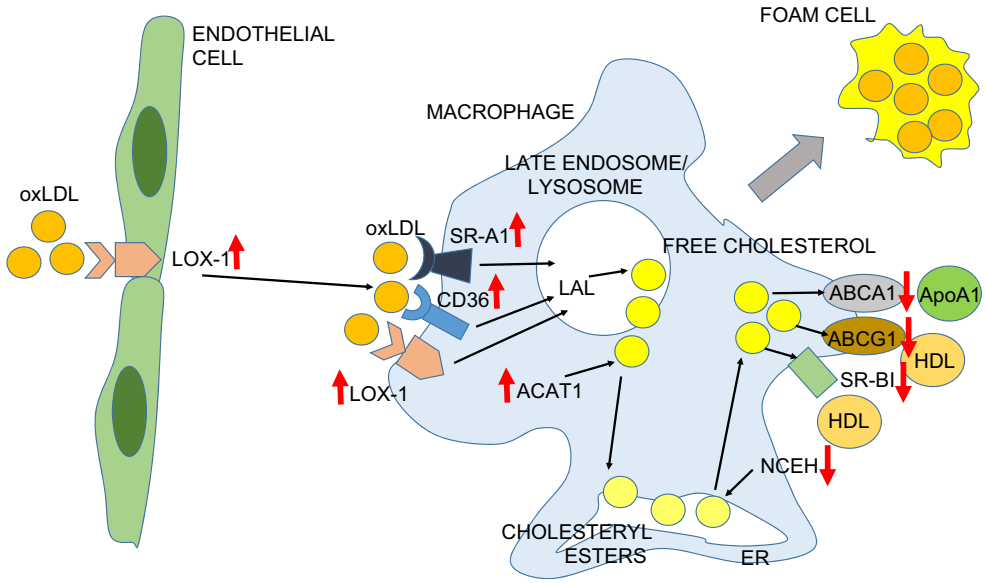

Fig. 2 Mechanisms of lipid handling in macrophages. Endothelial cells have a high surface expression of lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1) capable to bind and transfer oxidized LDL (oxLDL) across the cell to the intima media, which is infiltrated by macrophages in atherosclerosis. Macrophages sense and bind oxLDL with several scavenger receptors (SR) such as SR-A1, CD36, and LOX-1. In late endosomes/lysosomes, lysosomal acid lipase (LAL) degrades cholesteryl esters, which are highly present in LDL particles, to free cholesterol and free fatty acids. In the endoplasmic reticulum (ER), acyl coenzyme A: cholesterol acyltransferase-1 (ACAT1) contributes to formation of cholesteryl esters from free cholesterol. Cholesteryl esters accumulate in the ER. Neutral cholesteryl ester hydrolase (NCEH) processes cholesteryl esters liberating free cholesterol that is transported outside the cells via ATP-binding cassette (ABC) transporters ABCA1 and ABCG1, as well as via SR-BI. Apolipoprotein A-1 (ApoA-1) serves as an acceptor for cholesterol carried by ABCA1. High-density lipoprotein (HDL) accepts cholesterol that is transferred by ABCG1 and SR-BI. In normal conditions, this machinery is tightly regulated ensuring cholesterol homeostasis. In atherosclerosis, the control is deregulated. Expression of scavenger receptors is increased, which leads to elevated uptake of oxLDL. By contrast, expression of cholesterol transporters ABCA1 and ABCG1 is suppressed, which diminishes cholesterol efflux and promotes cholesterol deposition in macrophages. ACAT1 is upregulated while NCEH is downregulated. This leads to accumulation of cholesteryl esters in the cell. Together, these mechanisms lead to excessive lipid deposits and transformation of macrophages to foam cells

ammonium (NH_3). It has been demonstrated that H_2S decreased atherosclerosis plaque size and suppressed aortic expression of intracellular adhesion molecule-1 (ICAM-1) on the endothelial surface [40]. H_2S was also shown to downregulate foam cell formation by reducing SR-A1 activity through the K_{ATP}/Erk ½-dependent signaling mechanism [41].

CD36 belongs to the family B of scavenger receptors. This glycoprotein contains an extracellular domain flanked by two transmembrane domains (Fig. 3) [42, 43]. CD36 has a high affinity to oxLDL mediating its atherogenic role by internalization of the CD36-oxLDL assembly [44]. Higher blood concentrations of soluble CD36 (sCD36) were observed in monocytes of subjects affected by cardiovascular diseases [45, 46] and those who exhibit cardiometabolic risk factors [47–49]. Treatment with statins or suppression of CD36 with low molecular inhibitors leads to reduced uptake of lipids by monocytes/ macrophages and decreased accumulation of oxLDL in the arterial wall [50–53].

Multiple factors are able to regulate expression of CD36 in macrophages. Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) drives circumin-dependent CD36 expression [54]. In monocytes, palmitate activates expression of CD36 by newly induction of ceramide production [55], since ceramides inhibit CD36 expression and reduce oxLDL accumulation in monocytes. Astaxanthin, a plant antioxidant, was found to inhibit formation of oxLDL and to increase high-density lipoprotein (HDL)-cholesterol levels in clinical studies, thereby demonstrating atheroprotective effects [56]. Lipopolysaccharide (LPS), a toxic agent of *Porphyromonas gingivalis*, a main cause of gingivitis, which is associated with atherosclerosis [57], increases CD36 in macrophages through the upregulation of the c-Jun/activator protein-1 (AP-1)-mediated transcription mechanism [58].

Some compounds, like plant antioxidants, including squalene, quercitrin, and kaempferol, inhibit expression of CD36 in macrophages, thus preventing excessive lipid deposits in these cells [59–61]. All those are dietary components that can be considered for nutritional modulation of atherosclerotic disease.

Structurally, LOX1 receptor consists of a short N-terminal domain, transmembrane domain, coiled-coil domain, and C-type lectin-like domain (Fig. 3) [62]. In the C-type lectin-like domain of LOX1, the presence of ten C-terminal basic amino acids is essential for binding oxLDL [63].

The LOX-1 receptor seems to be strictly pro-atherogenic since its expression is very moderate in normal conditions, but becomes markedly upregulated in atherosclerosis accounting

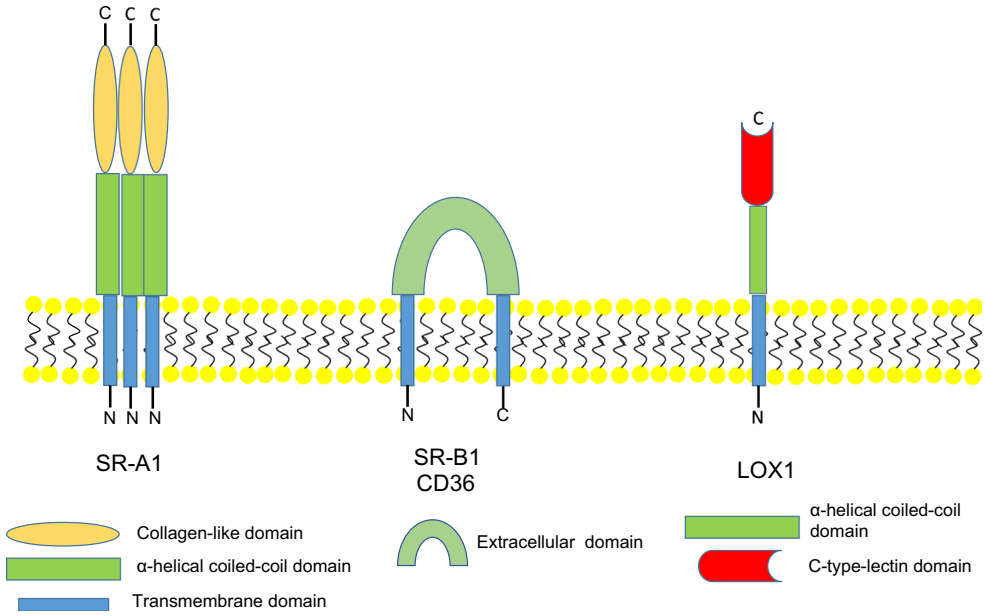

Fig. 3 Schematic representation of a structure of scavenger receptors that are involved in modified LDL uptake in macrophages. SR-A1 is expressed on the surface as a homotrimer

for up to 40% of oxLDL uptake by pro-inflammatory macrophages [64]. Furthermore, this receptor is not expressed in monocytes, but can be upregulated in differentiated macrophages, a fact that indirectly suggests for its pro-atherosclerotic role [65]. LOX-1 is a main receptor for binding oxLDL in ECs [66] and may also be induced in VSMCs, which indicates the possibility for conversion of VSMCs to foam cells in atherogenesis [9]. This receptor can sense moderately modified and not fully oxidized LDL, indicative of a potential contribution of LOX-1 to early atherogenic steps [67].

Inflammatory modulators, such as pro-inflammatory cytokines [9], oxLDL [10], LPS [68], AGEs [58], mitochondrial ROS [69], and others may serve as potent inductors of upregulation of LOX-1 expression in macrophages. In addition, vasopressors such as endothelin-1 and angiotensin II could also activate macrophage LOX-1 expression [12].

A pro-atherogenic role of LOX-1 is supported by the data obtained in atherosclerotic animal models. Genetic deletion or knockdown of LOX-1 in rodent atherosclerotic models led to diminished disease, less plaque progression, and decreased inflammation [67]. By contrast, hyperexpression of LOX-1 in hypercholestemic mice and rabbits caused enhanced disease, increased apoptosis of vascular cells, plaque instability, and atherothrombosis [68–71].

Finally, macrophage receptor with collagenous structure (MARCO) can also be involved in lipid uptake. Like SR-A, MARCO has internal collagen-like domains. It is expressed in macrophages and ECs and is able to interact with oxLDL [72]. It was demonstrated that MARCO is involved in lipid uptake by cultured macrophages induced by treatment with Dalcetrapib, a chemical that targets cholesteryl ester transfer protein [73]. These observations indicate a likely involvement of MARCO in handling influx of lipids by macrophages. However, further studies are needed to evaluate whether MARCO could significantly contribute to the generation of foam cells during atherogenesis.

Cholesterol-handling machinery in macrophages

The formation of cholesteryl esters is crucially involved in transformation of macrophages to foam cells (Fig. 2). Free cholesterol is a substrate for acetyl-CoA acetyltransferase (ACAT1), an enzyme that transforms cholesterol to cholesteryl esters. The newly formed cholesteryl esters reside in the endoplasmic reticulum, and their excessive intracellular accumulation drives foam cell formation. Another enzyme, neutral cholesterol ester hydrolase (NCEH) hydrolyzes cholesteryl esters liberating free cholesterol [74], which is transported outside through the system of membrane cholesterol transporters. The balance between etherification/detherification of cholesterol may therefore define whether macrophages will be converted to foam cells or not.

In ApoE-deficient mice, ACAT1 inhibition by a small inhibitory molecule F-1394 was shown to result a less advanced atherogenesis [75]. However, depletion of ACAT1 specifically in macrophages of LDL receptor-deficient mice has the pro-atherogenic role [76]. F-1394 is a non-specific inhibitor of both of the isoforms ACAT (ACAT1 and ACAT2), the second of which in predominantly expressed by parenchymal liver and intestinal cells [77]. In macrophages, excessive cholesterol uptake can cause formation of highly cytotoxic, pro-inflammatory, and pro-atherosclerotic cholesterol crystals [78].

Ghrelin, a hormone secreted by specialized intestinal cells, suppresses ACAT1 through interaction with growth hormone secretagogue receptor (GHSR) and suppressing PPARγ [79].

Protein kinase A (PKA) mediates ACAT1 suppression by incretin hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [80]. Dipeptidylpeptidase 4 (DPP4) is involved in proteolysis of GLP-1 [81]. In diabetic and non-ApoE-deficient mice, vildagliptin and other DPP4 inhibitors possess anti-atherogenic properties by restoring production of both incretin hormones and repairing insulin secretion [82].

In macrophages, insulin upregulates production of ACAT1 through stimulation of CCAAT/enhancer-binding protein α (C/EBPα), a transcriptional stimulator, mediated by the extracellular signal-regulated kinase (Erk)/p38MAP kinase/Jnk mechanism [83]. Leptin, a fat tissue hormone, stimulates ACAT1 expression via Janus-activated kinase 2 (Jak2)/phosphatidylinositide 3-kinase (PI3K)-mediated signaling pathway [84].

As mentioned above, NCEH is a hormone-dependent lipase that is responsible for removal of ester group from cholesteryl and formation of free cholesterol, which is then effluxed from the cell. This enzyme exists as two isoforms, the shortest of which was found in several cell types including macrophages [85]. The longest is present in the testis and other tissues involved in the steroidal biosynthesis where NCEH activity is necessary for generation of free cholesterol followed steroid hormone synthesis [86, 87].

Suppression of NCEH causes advanced atherosclerosis [88]. Overproduction of NCEH increases degradation of cholesterol esters in lipid-overloaded macrophages [89]. However, overproduction of NCEH alone without concomitant downregulation of ACAT1 and activation of reverse cholesterol cannot protect macrophages from transformation to foam cells [88]. Mice overproducing both NCEH and ApoA4 (lipoprotein acceptor of cholesterol) develop diminished disease [90]. In LDL receptor-deficient mice, overproduction of NCEH led to reduced lesion necrotic core, thereby indicating a key role of macrophage-specific expression NCEH in manipulations with cholesterol in atherosclerotic plaque [91].

Another isoform of NCEH, NCEH1, is involved in cholesterol ester catabolism on the membrane of endoplasmic reticulum in macrophages. In ApoE-deficient mice, NCEH1 accelerates disease progression, indicative of an anti-atherosclerotic role of the enzyme [92]. Both NCEH isoforms prevent transformation of macrophages to foam cells [93, 94].

Cholesterol reverse transport is an essential stage in macrophage-mediated plasma lipoprotein metabolism. Cholesterol efflux could be performed by an intensive work of cholesterol transporters, such as ABCA1, ABCG2, and scavenger receptor SRB1 and by passive membrane diffusion (Fig. 2). Mice with deletion of ABCA1 and SR-BI had severe hypocholesterolemia mainly due to HDL atherosclerosis was absent due to the lack of the pro-atherosclerotic lipids [95]. ApoA-1, a main HDL-associated protein, accepts free cholesterol secreted by ABCA1 [96]. However, in LDL receptor-deficient mice, liver overproduction of ABCA1 caused lipid deposits and enhanced disease because of accelerated transport of HDL cholesterol and slowed degradation of LDL rich of cholesterol [95].

In macrophages, ABCA1 seems to play a central role in cholesterol efflux and therefore is regulated by various bioactive molecules. A transcription factor liver X receptor α (LXRα) primes ABCA1 expression [97]. Quercetin upregulates ABCA1 expression through activation of the PPARγ/LXRα axis [98]. Proteasome inhibitors and ApoA-1 increase cholesterol transport from foam cells by suppressing ABCA1 degradation and increasing stability [99, 100].

A number of negative regulators of ABCA1 have been described. Unsaturated free fatty acids (UFA) induce epigenetic silencing of LXR genes, ABCA1 downregulation through PKCδ-dependent phosphorylation, which in turn leads to the degradation of the transporter [101, 102]. IL-12 and IL-18 downregulate expression of ABCA1 via activation of ZNF202, a zinc finger protein and transcriptional repressor [103]. On the other hand, C-X-C motif chemokine 5 (CXCL5) positively regulates ABCA1 production and therefore limits foam cell formation [104]. Among other activators of ABCA1 expression, cAMP, sterols, PPARγ agonists, and other stimulators can be mentioned [105]. In LDL receptor-deficient mice, deletion of ABCG1 had an anti-atherogenic effect [106] or leads to moderate increase in atherosclerotic lesion size [107]. The observed discrepancy in the results may be explained by a secondary role of ABCG1 in cholesterol efflux in macrophages.

Various dietary components are involved in the regulation of ABCG1. Cineole (a eucalyptus monoterpenoid) and extra-virgin olive oil increase ABCG1 expression [108, 109]. Gut microbiota transforms cyanidin-3-O-β-glucoside (Cy-3-G), a berry anthocyanin, to protocatechuic acid (PCA). PCA can in turn stimulate ABCA1/ABCG1 production by downregulating miR-10b, which targets both cholesterol transporters [110].

SR-BI transports cholesterol to HDL. In ApoE-deficient mice, SR-BI overproduction had atheroprotective effect while depletion of SR-BI in macrophages resulted in significant plaque growth thereby indicating the anti-atherogenic role of this scavenger receptor [111]. The described properties of SR-BI could be explained by its capacity to transfer cholesterol in both directions [112]. In initial atherogenic steps, SR-BI acts like SR-A1 supporting lipid and cholesterol uptake in macrophages. In parallel, SR-BI suppresses activity of ABCA1 thereby suggesting competing role of both transporters in regulating cholesterol transfer in macrophages [113].

Multiple dietary substances were shown to influence SR-BI expression. Caffeic and ferulic acids, two main phenolic acids found in coffee, enhance cholesterol efflux in macrophages by activating ABCG1 and SR-BI, i.e., transporters that transfer cholesterol to HDL but not to ApoA-1 [114]. Resveratrol (a polyphenolic compound) and 13-hydroxy linoleic acid increase LXRα and SR-BI by stimulating

PPARγ [115, 116] also stimulate the reverse cholesterol transport from macrophages.

In contrast, pappalysin-1 (PAPPA), a metalloproteinase, which hydrolyzes insulin-like growth factor-binding proteins (IGFBPs) could downregulate all three cholesterol pumps via suppression of the IGF/PI3-K/Akt-dependent stimulation of LXRα [117].

Role of miRNAs in foam cell formation

A pivotal role of aberrant expression of microRNAs (miRNAs), a class of small non-coding regulatory RNAs, in various aspects of atherogenesis including formation of foam cells is established [118, 119]. MiRNAs are involved in post-transcriptional silencing of mRNA targets (through RNA sequestration, cleavage, and decay) and inhibition of translation of mRNA targets. In macrophages, the molecular machinery responsible for cholesterol intake, storage, and efflux is targeted by multiple miRNAs since a proper regulation of this machinery is vital to maintain blood lipid homeostasis. Deregulation of this mechanism may lead to various cardiometabolic abnormalities including atherosclerosis. As formation of foam cells is pro-atherosclerotic, miRNAs whose activity leads to the generation of foam cells could be considered as pro-atherogenic. By contrast, miRNAs, which inhibit foam cell formation, are atheroprotective.

In macrophages, expression of ABCA1 and ACAT1 is regulated by multiple miRNAs, an indicator of a key role of these proteins in cholesterol and phospholipid homeostasis (Table 1). ABCA1 is a major pump involved in the reverse cholesterol transport, and inhibition of this transporter promotes foam cell formation. ACAT1 catalyzes cholesterol esterification, and downregulation of this enzyme attenuates generation of foam cells.

In addition to the direct targeting of lipid-handling machinery components, miRNAs can indirectly influence on this mechanism through the control of pathways or expression of genes involved in the regulation of cholesterol homeostasis. For example, miR-21 [122], miR-133a [126], and miR-223 [132] downregulate LPS-induced lipid accumulation and inflammation by targeting toll-like receptor 4 (TLR4)/nuclear factor (NF)-kB signaling. In human macrophages, miR-216a, which directly targets the 3′ untranslated region of cystathionine γ-lyase (CSE) mRNA, negatively influences ABCA1 expression by suppressing the CSE/H_2S system

Table 1 Effects of miRNAs on foam cell formation

miRNA	Target(s)	Role in foam cell formation	Reference
miR-9	ACAT1	Inhibition	Xu et al. (2013) [120]
miR-19b	ABCA1	Support	Lv et al. (2014) [121]
miR-21	TLR4 signaling	Inhibition	Feng et al. (2014) [122]
miR-26	LXRα	Support	Sun et al. (2012) [83]
miR-33	ABCA1	Support	Zhao et al. (2014) [123]
miR-27a/b	ABCA1, LPL, ACAT1	Support	Zhang et al. (2014) [124]
miR-101	ABCA1	Support	Zhang et al. (2015) [125]
miR-133a	TLR4	Inhibition	Peng et al. (2016) [126]
miR-134	ANGPTL4	Support	Lan et al. (2016) [127]
miR-144	ABCA1	Support	Hu et al. (2014) [128]
miR-150	AdipoR2	Inhibition	Li and Zhang (2016) [129]
miR-155	HBP1	Support	Tian et al. (2014) [130]
miR-216a	CSE	Support	Gong et al. (2016) [131]
miR-223	TLR4 signaling	Inhibition	Wang et al. (2015) [132]
miR-302a	ABCA1	Support	Meiler et al. (2015) [133]
miR-378	ABCG1	Support	Wang et al. (2014) [134]
miR-382-5p	NFIA	Support	Hu et al. (2015) [135]
miR-467b	ACAT1	Inhibition	Wang et al. (2017) [136]
miR-486	HAT1	Support	Liu et al. (2016) [137]
miR-590	LPL	Inhibition	He et al. (2014) [138]

ABCA1 ATP-binding cassette transporter A1; *ABCG1* ATP-binding cassette transporter G1; *ACAT1* acetyl-CoA acetyltransferase, mitochondrial; *AdipoR2* adiponectin receptor 2; *ANGPTL4* angiopoietin-like 4; *CSE* cystathionine γ-lyase; *HAT1* histone acetyltransferase 1, *HBP1* HMG-box transcription factor 1; *LPL* lipoprotein lipase; *LXRα* liver X receptor α; *TLR4* toll-like receptor 4; *NFIA* nuclear factor 1 A-type

[131]. miR-134 was shown to promote cholesterol deposition by suppressing angiopoietin-like 4 (Angptl4), a secreted irreversible inhibitor of lipoprotein lipase (LPL) activity [127]. Overactivation of LPL that is involved in the transformation of very light density lipoprotein (VLDL) to LDL may contribute to atherogenesis [139].

In oxLDL-treated THP-1 macrophages, miR-150-dependent inhibition of adiponectin receptor 2 (AdipoR) was observed to lead to the activation of genes responsible for cholesterol efflux and hence to the suppression of foam cell formation [129]. Increased levels of miR-155 were shown to promote conversion of macrophages to foam cells by targeting HMG-box transcription factor 1 (HBP1) [130]. In human acute monocytic leukemia macrophage-derived foam cells, Hu et al. (2015) found that the long non-coding RNA RP5-833A20.1 and miR-382-5p cooperate in the downregulation of nuclear factor 1 A-type (NFIA), a regulatory protein whose overexpression prevents intracellular lipid deposition and has anti-inflammatory and anti-atherogenic effects [135]. Finally, miR-486 controls ABCA1 expression epigenetically by targeting histone acetyltransferase 1, an epigenetic regulator that promotes ABCA1 production by acetylation of the lysines 5 and 12 of histone H4 at the promoter of the ABCA1 gene [137].

In summary, miRNAs play a significant role in the regulation of cholesterol homeostasis by promoting or inhibiting intracellular lipid deposition and formation of foam cells [140]. Thus, miRNAs may represent a promising therapeutic target to improve reverse cholesterol transport and prevent generation of foam cells in atherosclerosis.

Conclusions

Atherosclerosis is associated with profound disturbances of cholesterol metabolism. In particular, cellular cholesterol uptake is increased in atherosclerosis, while cholesterol efflux is downregulated. Increased cholesterol uptake can be explained by upregulation of oxLDL-bearing scavenger receptors expression, especially LOX-1. Moreover, the expression of cholesterol pumps that are involved in cholesterol efflux is inhibited. This may result in cholesterol deposition in macrophages and formation of foam cells. Another main imbalance observed in atherosclerosis is upregulation of ACAT1 (i.e., cholesterol esterification) and downregulation of NCEH (i.e., formation of free cholesterol), which results in the accumulation of cholesterol esters within the cell and further transformation of macrophages to foam cells.

Until recently, monocyte-derived macrophages were considered as a major source of plaque foam cells. However, Dubland and Francis (2016) found that VSMCs could substantially (up to 50% in humans and at least 1/3 in mice) contribute to a population foam cells [141]. Intracellular cholesterol accumulation leads to inhibition of SMC gene expression and induction of pro-inflammatory and macrophage markers. Foam cells originated from VSMCs have a selective loss of ABCA1. This interesting topic must be further explored to improve the understanding of new roles of VSMCs in atherosclerosis.

A standard therapy that is widely used to treat cardiovascular diseases is reducing plasma LDL cholesterol levels with lipid-lowering agents. However, over 50% of treated patients did not achieve the beneficial effects of this therapy. To prevent intracellular lipid accumulation by enhancing cholesterol efflux and targeting lipid-metabolizing enzyme is a promising approach that can significantly improve the efficiency of anti-atherosclerotic therapy. One of these strategies involves HDL-targeted therapy by optimization HDL cholesterol levels and function in the blood to promote the removal of circulating cholesterol and to prevent or mitigate atherosclerotic inflammation [142]. HDL-targeted therapy assumes implication of HDL-mimetics such as reconstituted HDL, apolipoprotein (Apo) A-IMilano, ApoA-I mimetic peptides, or full-length ApoA-I, which provide an option to enhance cholesterol efflux through the ABCA1 transporter and to act as an anti-atherosclerotic agent by enhancing the biological functions of HDL without elevating HDL cholesterol levels. HDL-mimetics were highly effective in animal models [143]. CER-001, a recombinant human ApoA-1-based HDL mimetic, developed by company Cerenis Therapeutic Holding SA (Labège, France) is evaluated in three clinical trials (NCT01515241, NCT01201837, and NCT01412034) to treat homozygous familial hypecholesteroemia, hypo-alphalipoproteinaemia, and acute coronary syndrome.

Earlier on, CER-001 showed profound anti-atherogenic effects in LDLR-deficient [144] and apoE-deficient [145] mice by promoting cholesterol efflux and inducing atherosclerosis regression. In hypercholesteroemic patients, this preparation led to the significant increase of reverse cholesterol transport and decrease in carotid mean vessel wall area and carotid artery wall thickness [146–148]. In atherosclerotic patients, implementation of CER-001 was well tolerated, targeted plaque regions, and caused enhancement of cholesterol efflux and increase of serum apoA-I levels [149–151]. Thus, preclinical and clinical testing of CER-001 showed beneficial effects of HDL-therapy on the carotid wall thickness, prevention of coronary plaque burden, and plaque size and morphology. Indeed, targeting of cholesterol efflux with apoA-I mimetics may serve as a good example of efficient anti-atherosclerotic therapy.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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