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Curcumin as a potential modulator of M1 and M2 macrophages: new insights in atherosclerosis therapy

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Abstract

Accumulation of macrophages within the artery wall is an eminent feature of atherosclerotic plaques. Macrophages are influenced by various plaque microenvironmental stimuli, such as oxidized lipids, cytokines, and senescent erythrocytes, and thereby polarize into two main phenotypes called proinflammatory M1 and anti-inflammatory M2 macrophages. In the hemorrhagic zones of atheroma, upon exposure to iron, sequestration of iron by M1 macrophages results in an uncontrolled proinflammatory phenotype impairing wound healing, while M2 macrophages phagocytose both apoptotic cells and senescent erythrocytes. M1 macrophages are prominent phenotype in the unstable plaques, in which plaque shoulder contains macrophages mainly present markers of M1 phenotype, whereas the fibrous cap encompassing the necrotic lipid core content macrophages expressed markers of both M1 and M2 subtypes. The abovementioned findings suggest macrophage modulation as a potent approach for atherosclerosis therapy. Curcumin is a polyphenol dietary derived from turmeric with numerous pharmacological activities. Recent in vitro and in vivo studies have indicated that curcumin exerted lipid-lowering effects, and also can modulate function of different macrophage subsets in various macrophage-involved diseases. The current review aimed to present role of macrophage subtypes in atherosclerosis development and progression, and to understand effect of curcumin on macrophage polarization and foam cell formation in the atherosclerosis lesions. Overall, we would address important targets for macrophage modulation in atherosclerotic plaques.

Keywords Atherosclerosis · Atherosclerotic plaque · Curcumin · Inflammation · M1 and M2 macrophages

Abbreviations

ABCA1	ATP-binding cassette transporter
aP2	Adipocyte protein
CD163L1	CD163 antigen-like 1
CERP	Cholesterol efflux regulatory protein
COX-2	Cyclooxygenase-2
ERK	Extracellular signal–regulated kinases
FABPs	Fatty acid-binding proteins
JNK	c-Jun N-terminal kinase
iNOS	Inducible nitric-oxide synthase
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
SEPP	Selenoprotein P
GM-CSF	Granulocyte-macrophage colony stimulating factor

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IFN γ	Interferon gamma
IL	Interleukin
LDL-C	Low-density lipoprotein cholesterol
LPS	Lipopolysaccharide
LXR-α	Liver X receptor alpha
M-CSF	Macrophage colony-stimulating factor
NFE2L2	Nuclear factor (erythroid-derived 2)-like 2
Ox-LDL	Oxidized-LDL
SR	Scavenger receptors
TNF	Tumor necrosis factor
LPS	Llipopolysaccharide
PI3K	Phosphoinositide 3-kinase
PPAR-γ	Peroxisome proliferator-activated receptor gamma
RCT	Reverse cholesterol transport
ROS	Reactive oxygen species
S1P	Sphingosine-1-phosphate
Th1	T helper 1
TLRs	Toll-like receptors
TNF-α	Tumor necrosis factor alpha
TGF-β	Transforming growth factor β
VSMCs	Vascular smooth muscle cells

Background

Atherosclerosis is an inflammatory disorder of the vascular system in which accumulation of macrophages within the artery wall contributes to progress of the inflamed atherosclerotic plaques. Macrophages include heterogeneous cell populations posing distinctive functional phenotypes in response to specific signals of the surrounding microenvironments. In the atherosclerotic plaques, various environmental stimuli, such as cholesterol clefts, modified lipoproteins, and cytokines can switch function and subset of macrophages. From a medicinal point of view, understanding the role of specific macrophage phenotypes and their contribution to the composition and progression of atherosclerotic plaque would assist the emersion of novel strategies to delay or halt the development of the disease and its associated pathophysiological consequences. The experimental studies of the efficient natural products can reveal worthwhile hints to discover malicious cellular and molecular targets that pave new therapeutic avenues. In this regard, curcumin, a natural remedy, has been frequently shown to have lipid-lowering effects, and also affect function of different macrophage subsets in various macrophage-involved diseases. Considering the lipid-lowering effect of curcumin, its impact on the vascular macrophage subsets can introduce valuable clues to understand the role of macrophage phenotype modulating in atherosclerosis development. This review presented a comprehensive overview of effector macrophages in atherosclerosis, and also addressed curcumin's effects on the function of two main phenotypes of macrophages, proinflammatory M1 and anti-inflammatory M2 subsets, in the inflamed vascular wall.

Development and progression of atherosclerotic plaque

Atherosclerotic lesions develop upon multifactorial and multistep inflammatory processes starting from the innermost layer of the intima, which includes transendothelial recruitment and activation of the circulating inflammatory cells (including lymphocytes, monocytes, and macrophages), proliferation and migration of vascular smooth-muscle cells (VSMCs) from the medial layer, and accumulation of connective-tissue elements and lipoproteins [1].

The elevated levels of the plasma low-density lipoprotein (LDL) cholesterol (LDL-C) and the subsequent accumulation of oxidized-LDL (ox-LDL) within the intima layer promote the recruitment and retention of monocytes and other immuno-cells in the vessel wall [2]. In the subendothelial space, the recruited monocytes are exposed to the proinflammatory cytokine which differentiate into macrophages [3, 4]. Monocyte-derived macrophages eat lipoprotein particles via scavenger receptors (SRs), such as SR-A, CD36, and toll-like receptors (TLRs) that take up particles posing molecules with pathogen-associated molecular patterns such as ox-LDL particles [5, 6]. If cholesterol derived from the internalized ox-LDL particles cannot be eliminated from the macrophage to an adequate extent, it will accumulate as cholesterol ester or cytosolic cholesterol crystals. Eventually, the macrophage is transformed into a foam cell that is the prototypical cell in atherosclerosis. The macrophage-derived foam cells express inflammatory cytokines (e.g., TNF-α, IL-1, and IL-6), proteases (e.g., metalloproteinases), growth factors (e.g., platelet-derived growth factor and insulin-like growth factor I), and cytotoxic oxygen and nitrogen radical species that can collectively enhance lipid retention, break down the extracellular matrix, and exacerbate inflamed atheroma [3].

A determinant step in atherosclerosis progression is apoptosis of foam cells in the extracellular lipid droplets (lipid core). The apoptotic foam cells are cleared by phagocytes, mostly macrophages, which engulf dead cells in a process called efferocytosis, nullifying further progression of atherosclerosis. If efferocytosis is no longer enough to internalize all dead cells, apoptotic debris will gradually accumulate in the lipid core and form a necrotic core, which promotes further inflammation, necrosis, and thrombosis [7] (Fig. 1).

Over the past decade, the notion that atheroma lesion-resident macrophages are heterogeneous populations has been progressively emerged. Accumulating evidence shows that monocytes and macrophages contain heterogeneous populations that acquire their practical phenotype in response to defined microenvironmental signals and molecules [8, 9].

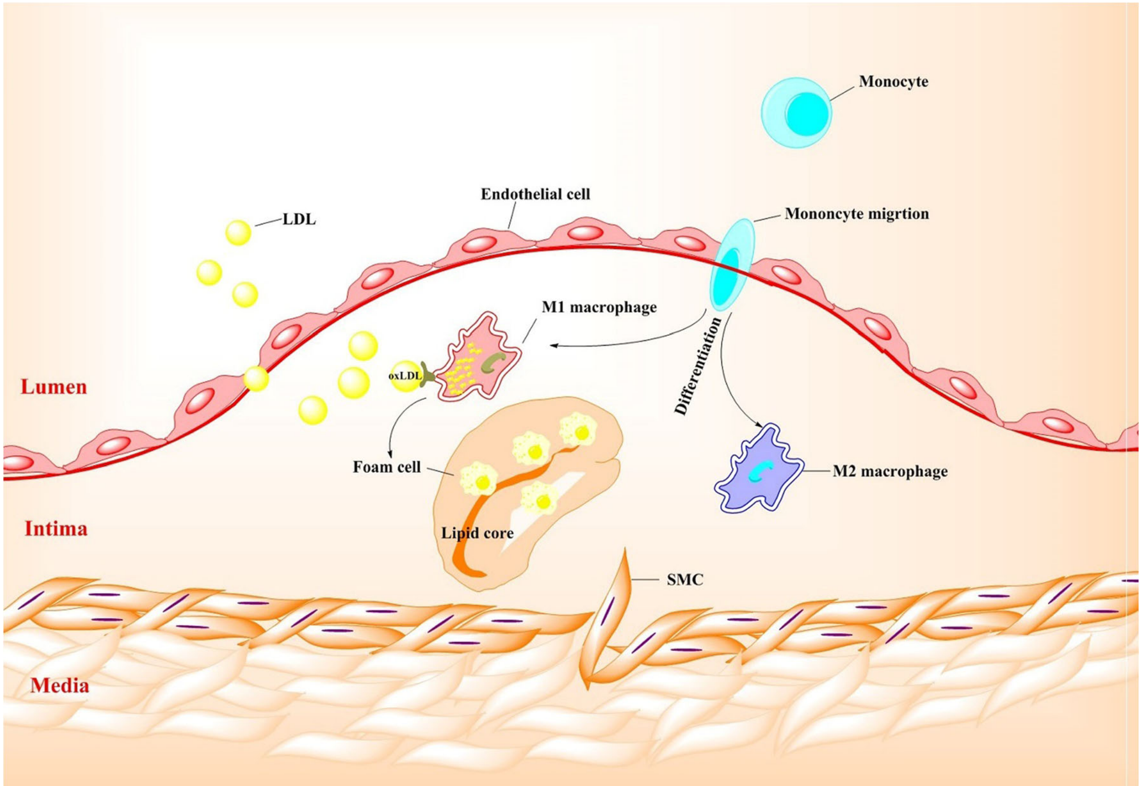

Fig. 1 M1 & M2 macrophages and atherosclerotic lesion. The increased levels of plasma LDL-C and the subsequent accumulation of oxidized-LDL (ox-LDL) within the intima layer promote the recruitment and retention of monocytes in the artery wall. In the subendothelial space, the recruited monocytes differentiate into M1 and M2 macrophages[1–216–173-4](Ross, 1999, Smith et al., 1995). During the plaque progression, smooth-muscle cells (SMCs) proliferate and migrate from media to intima layer. M1 macrophages scavenge oxLDL via scavenger receptors and, eventually, form foam cells that undergo apoptosis and die in the lipid core. M2 macrophages can phagocytose the apoptotic foam cells and counteract their deleterious effects

Further, it has also been known that macrophages resident within the tissue can proliferate independently of monocyte recruitment [10]. Of note, macrophages present in early atherosclerotic plaques are primarily stemmed from recruited monocytes, whereas macrophage proliferation is a superior property of advanced plaques and is affected by microenvironment signals [11]. Correspondingly, differences in phenotypes of resident macrophage can also impact their potential to locally proliferate, which can change the abundance of a given phenotype of macrophages [10, 12].

Macrophage populations and plasticity

Macrophages, in response to the surrounding microenvironment, can polarize to different phenotypes characterized by their expression of markers, the generation of specific factors, and their biological roles [13]. There are two main classes of macrophages known as classically activated (M1) proinflammatory macrophages [14] and alternatively activated (M2) anti-inflammatory macrophages [15].

Proinflammatory M1 macrophages are typically triggered by Th1 (T helper 1) cytokines, such as tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), or by recognition of lipopolysaccharide (LPS). These cells express interleukin (IL) 12 (IL-12) and IL-23 in high levels and IL-10 in low levels [16], and produce the proinflammatory cytokines TNF, IL-1β, and IL-6 [17]. In function, M1 subtypes act to remove pathogens during infection through production of reactive oxygen species (ROS) via activation of the NADPH oxidase system. Activation of M1 macrophage can, therefore, result in ROS-mediated tissue damaged and decline wound healing [14].

To defend against such tissue damage, the induced inflammatory response is modulated by regulatory mechanisms driven by anti-inflammatory M2 macrophages [15]. M2 macrophages have been detected to be in three different subtypes, including M2a subtype promoted by the Th2 cytokines IL-4 and IL-13; M2b macrophages promoted by immune complexes in combination with IL-1β or LPS; and M2c group promoted by IL-10, transforming growth factor-β (TGF-β), and/or glucocorticoids. All M2 subtypes contain an anti-inflammatory cytokine profile characterized by high levels of IL-10 and TGF-β, and low levels of IL-12 [18]. From a functional point of view, M2 macrophages phagocytize and scavenge apoptotic cells and debris [19, 20] and provoke tissue repair and healing [21], thereby contributing to both maintenance of efficient efferocytosis within the atheromatous lesions and resolution of inflammation [22]. Macrophage subpopulations have also been classified based on hemostatic roles of macrophages, including host defense macrophages (M1 class), wound healing macrophages (M2a subclass), and immune regulatory macrophages (M2b/c subclass) [23].

Interestingly, macrophages are plastic cells that can switch from an activated M1 state back to M2 phenotypes, and vice versa, depending on the environmental signals [24, 25]. Therefore, macrophage polarization and plasticity can be orientated by the local cytokine milieu. Hence, in the case of atherosclerosis, not only does plaque composition impact the macrophage phenotype, but macrophage subtypes, due to their intrinsic functions (such as phagocytosis) and aptitude to secrete proinflammatory and anti-inflammatory factors, can also impact plaque structure and progression [26].

Macrophages in atherosclerotic plaque

The total number of macrophages is lower in asymptomatic than symptomatic plaques, and gradually elevates with severity and progression of plaque [27–29]. Examination of human atherosclerotic plaque has shown the spatial distribution of different macrophage phenotypes. M1 macrophages have been found to be superior in plaques with an unstable phenotype, suggesting that instability of the plaque might be a result of an imbalance between M1 and M2 subtypes. The plaque shoulder, known as one of the most unstable areas within the plaque [30], involves macrophages mainly presenting markers of the M1 phenotype, whereas the fibrous cap encompassing the necrotic lipid core content macrophages expressed markers of both M1 and M2 subtypes [27]. Therefore, M2 macrophages with beneficial effects (plaque-stabilizing and profibrotic) can counterbalance proinflammatory deleterious effects of M1 macrophages within the fibrous cap [31]. To sum up, the M1/M2 ratio can determine the plaque fate, and is influenced by various plaque microenvironment stimuli, including accumulated lipids and their derivatives, cytokines, and growth factors, as well as plaque hemorrhage.

Lipid-mediated macrophage polarization

Accumulation of cholesterol crystals during the early stages of the lesion development were suggested to provoke polarization of the M1 phenotype through activation of IL-1 by inducing the caspase-1-activating NLRP3 inflammasome [32]. Deposited ox-LDL and other oxidized lipoproteins induce M1 polarization, mechanistically, through activation of a TLR4-mediated pathway [33] and inhibition of the transcription factor Kruppel-like factor 2 [34, 35]. Cholesteryl esters, including linoleate and 7-ketocholesteryl-9-carboxynonanoate, can also polarize macrophages to M1 phenotype via activation of the TLR-4 and/or nuclear factor (NF)-κB signaling pathways [36, 37]. Contrarily, a major product of cholesteryl ester oxidation, 9-oxononanoyl cholesterol, induces the polarization of anti-inflammatory macrophage phenotype through increasing secretion of TGF-β [37]. Additionally, conjugated linoleic acids, a set of natural isomers of linoleic acid, were found to promote an anti-inflammatory M2 subtype through increasing the production of IL-10 [38, 39]. Furthermore, macrophage plasticity has also been detected during regression of atherosclerotic plaque [40]. Sphingolipid metabolites, especially sphingosine-1-phosphate (S1P), were known to convert the M1 phenotype to M2 through activation of its receptor, S1P1 [41]. Switching the macrophage phenotype toward an M2-like subtype was also shown to mediated by ω3-polyunsaturated fatty acid derivatives, particularly resolvin D1 [42], an anti-inflammatory and inflammation modulator derived from docosahexaenoic acid [43].

Macrophage polarization in response to plaque cytokines and growth factors

The macrophage phenotype can also be influenced by cytokines and growth factors present in atherosclerotic plaques [44]. IL-4 cytokine, known as a potent inducer of the M2a subtypes [15], could polarize a population of the M2 phenotype resident in neovascularization zones and stable lesion regions away from the lipid core [20, 45]. This population displays high phagocytosis function, but they show reduced cholesterol efflux capacity and decreased lipid accumulation owing to the dropped expression of ABCA1 (ATP-binding cassette transporter also known as the cholesterol efflux regulatory protein (CERP)) and LXR-α (liver X receptor alpha) [20].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) are important growth factors regulating differentiation and polarization of macrophages. As revealed by an in vitro study, GM-CSF and M-CSF allow monocytes to act similarly to the M1 and M2 phenotype, respectively [16, 46]. GM-CSF was found to induce M1 macrophage through promoting the expression of *PPBP* (called C-X-C motif chemokine 7, encoding platelet basic protein), whereas M-CSF induced M2 phenotypes through enhancing the expression of genes such as *CD163L1* (encoding CD163 antigen-like 1 protein), *STAB1* (encoding stabilin 1 protein), and *SEPP1* (encoding selenoprotein P) [47]. During atherosclerosis progression, the ratio of GM-CSF/M-CSF fluctuates in vivo [47, 48]. M-CSF is found to express in both healthy arteries and atherosclerotic lesions [47], whereas the expression of GM-CSF elevates in endothelial cells and smooth muscle cells upon macrophage accumulation and atherosclerosis development [48]. This alteration in the balance between GM-CSF and M-CSF might associate with the raised prevalence of M1 macrophages in progressed plaques.

Intraplaque hemorrhage and macrophage polarization

Another macrophage-polarizing stimulus in atheroma is intraplaque hemorrhage that accrues after vessel rupture in the areas of neovascularization [49]. During hemorrhage, erythrocytes are released by microvessels, and scavenged by macrophages, causing an elevation in iron content and release of haem associated with accumulated oxidized lipids [50]. Sequestration of iron by M1 macrophages results in an uncontrolled proinflammatory phenotype impairing wound healing [51]. In the hemorrhagic zones, upon exposure to iron, M2 macrophages also greedily phagocytose both apoptotic cells and senescent erythrocytes by elevating ferroportin expression through LXR-α and NFE2L2 (nuclear factor (erythroid-derived 2)-like 2)-dependent mechanisms [20, 52].

Although M1 and M2 macrophages are the major phenotypes within the inflamed atheroma, growing evidence exhibits that the heterogeneous and complex environment of the atherosclerotic plaque can induce other specific and distinct subpopulations of macrophages. Macrophages displayed an M (Hb) phenotype expressing CD163 (scavenger receptor cysteine-rich type 1 protein M130) induced by hemoglobin-haptoglobin complexes, and can produce anti-inflammatory factors [53, 54]. After plaque hemorrhage, M (Hb) macrophages clear hemoglobin-haptoglobin complexes through endocytosis by the CD163 scavenger receptor and may thereby protect from free hemoglobin-mediated oxidative damage. In response to ligation of the hemoglobin-haptoglobin complex by CD163, these macrophages express anti-inflammatory cytokine IL-10 by a mechanism mediated by the phosphoinositide 3-kinase (PI3K)-Akt signaling pathway [55, 56]. M (Hb) macrophages can also inhibit lipid accumulation and foam cell formation through increasing the activity of the LXR-α transcription factor and inducing cholesterol efflux [54].

Effects of curcumin on foam cell formation and atherosclerosis

Curcumin, a natural polyphenol derived from the rhizome of *Curcuma longa* (turmeric), has been shown to exert beneficial effects on numerous cellular functions in cell culture as well as in animal models and human clinical trials [57–63]. Curcumin has recently received a lot of attention for its functions, such as anti-inflammation, immunosuppressive, antioxidant, antiviral and antitumor activity, anticoagulation, and lipid-lowering property [64–68]. The lipid-lowering effect of curcumin has been established in the several lines of investigation, in which curcumin could significantly decrease atherogenic lipids, such as total cholesterol and LDL-C, in dyslipidemia condition in animal models and human subjects (Table 1) [76]. The lipid-lowering effects of curcumin can be responsible for its beneficial effects against conditions in which hyperlipidemia exerts prominent roles, such as development of atherosclerosis [71, 77–80].

As outlined in the last section, macrophages have a central role in atherosclerosis development since they accumulate lipids and inflammatory cytokines leading to formation of foam cells and fatty streaks in the artery wall. Curcumin has

Table 1 The effect of curcumin on serum lipid profile in animal studies and human trials

Study model	Treatment period	Dosage	Lipid parameters				Ref.
			TC	LDL-C	TG	HDL-C	
Hamster	10 weeks	0.05 g/100 g diet	− 19.4%	− 15%	− 25%	16.62%	[69]
Rat	8 weeks	0.1% *w/w* of diet ad libitum	− 34%	− 68%	− 27%	–	[70]
Rat		50 mg/kg/day	− 9.9%	− 2.8%	− 32.2%	1.2%	
		100 mg/kg/day	− 15.7%	− 11.84%	− 25.2%	5.71%	
Mouse	18 weeks	0.02% *w/w*	− 8.3%	− 11.3%	− 13.3%	30.76%	[71]
Human	1 week	500 mg/day 6000 mg/day	− 17% − 5%	– –	− 47% − 15%	– –	[72]
Human	2 months	15 mg three times/day 30 mg three times/day	− 2.10% − 0.20%	− 8.60% − 3.40%	− 18% − 10.3%	11.30% 7.70%	[72]
		60 mg three times/day	− 0.30%	− 15.40%	− 20%	7.70%	
Human	3 months	300 mg/day	− 8.7%	− 11.6%	− 20.1%	3.64%	[73]
Human	8 weeks	500 mg/day	− 11.08%	− 13.06%	− 8%	17.33%	[74]
Human	3 months	1890 mg/day	− 9.86%	− 11.46%	− 28.8%	6.83%	[75]

been found to modulate the expression of lipid transporter genes, CD36/FAT and FABP4/aP2, and decrease lipid accumulation in macrophages. Besides the LDLR, two major lipid transport proteins, the CD36 scavenger receptor/fatty acid transporter (FAT) and adipocyte fatty acid-binding protein 4 (FABP4/aP2), are involved in the lipid uptake by macrophages. The aP2 (adipocyte protein 2) is an adipocyte isoform of fatty acid-binding proteins (FABPs), which coordinate cholesterol trafficking and inflammatory activity in macrophages. The high levels of aP2 are produced in both mouse and human atherosclerotic lesions, and aP2$^{-/-}$ macrophages show decreased capacity for foam cell formation [81]. The aP2 intensifies foam cell formation through changing the lipid composition in macrophages, leading to an increase in the activity of PPAR-γ (peroxisome proliferator-activated receptor gamma), resulting in enhanced CD36 expression and consequently elevated uptake of ox-LDL. It also increases inflammation in macrophages through elevating the activity of IκB kinase and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), leading to the increase in the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) and over-production of inflammatory cytokines [81–84]. There have been some studies that reveal debatable results about the modulatory effects of curcumin on the expression of lipid transporters and lipid accumulation in macrophages. Interestingly, curcumin has been shown to elevate levels of the fatty acid transport proteins, CD36 and aP2, and lipid contents in cultured THP-1 macrophages, whereas it decreased them in peritoneal macrophages of curcumin-supplemented Ldlr$^{-/-}$ mice, suggesting that curcumin uptake and metabolism in in vivo condition is different and may play a role in lipid homeostasis [85–88]. Curcumin was also found to inhibit atherogenesis through suppression of aP2 and CD36 expression in aortic macrophages of Ldlr $^{-/-}$ mice fed with high-fat diet, which was coordinated with the reduced expression of IL-6 and MCP-1 [77]. Such discrepancy in the results can be somewhat justified by a hypothesis in which the lipid-lowering effect of curcumin results in a reduced exposure of peritoneal macrophages to serum lipids, which in turn downregulates the expression of CD36 and aP2 with consequent decreased lipid accumulation in these cells [85].

These findings is further supported by another study that showed curcumin could prevent cholesterol accumulation and subsequent foam cell formation and, thereby, reduce the thickness of atherosclerotic lesions in aortic roots of apoE$^{-/-}$ mice. In mechanism, curcumin was found to inhibit foam cell formation and atherosclerotic plaque progression through enhancing RCT (reverse cholesterol transport)-mediated cholesterol efflux via upregulating the protein expression of ABCA1, and through reducing cholesterol influx via downregulating the protein expression of SR-A in aortic foam cells. An additional molecular study revealed that curcumin reduced ox-LDL-induced cholesterol accumulation via inhibiting the SR-A protein expression through upregulating the ubiquitin proteasome pathway, and enhancing ABCA1-dependent cholesterol efflux via the LXR-mediated pathway, in J774.A1-derived foam cells [78]. Therefore, curcumin can inhibit foam cell formation through modifying the expression of lipid transporters and preventing the accumulation of serum lipids in atherosclerotic resident macrophages (Fig. 2 and Table 2).

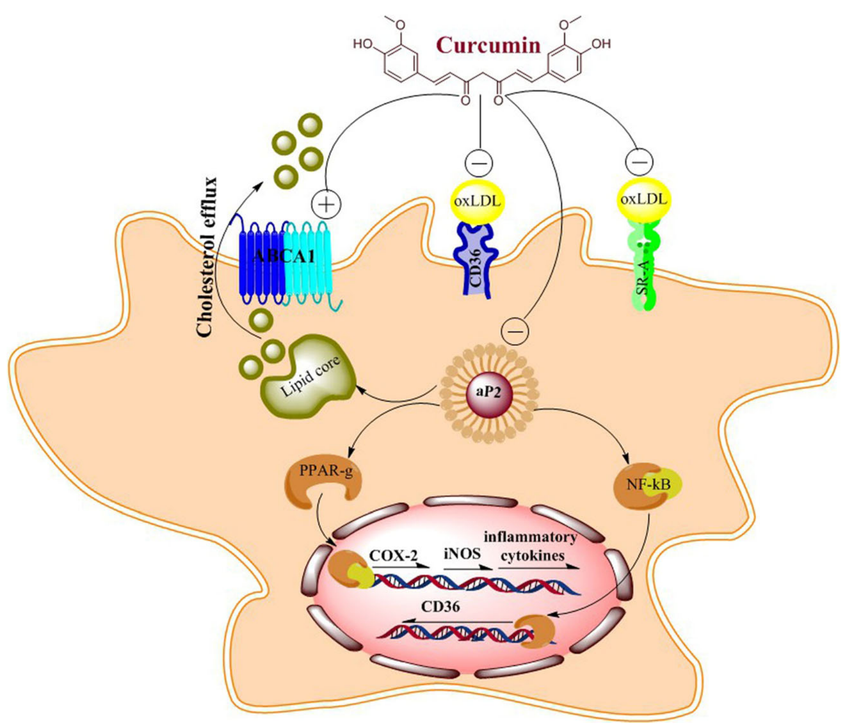

Fig. 2 Effect of curcumin on the foam cell formation. Curcumin inhibits scavenger receptors, such as CD36 and SR-A, and enhances ABCA1-mediated cholesterol efflux. Curcumin also inhibit aP2 and, thereby, decreases expression of CD36, iNOS, and inflammatory cytokines. Consequently, curcumin decrease lipid accumulation in macrophages and suppresses foam cell formation

Table 2 The effect of curcumin on the cytokine profile, polarization, and markers of macrophages

Dose	Cell line	Findings	Ref.
30 μm	THP-1 cell-derived macrophages	-Reduction of TLR4 expression -Inhibition of MAPK/NF-κB pathways -Modulation of macrophage polarization through TLR4-mediated signaling pathway	[89]
50 μm	RAW264.7	Inhibition of ligand-independent TLR4 dimerization and LPS-induced IRF3	[90]
50 μM	RAW264.7	Blocking activation of JNK, NF-κB, and MAPK	[91]
0–30 μM	RAW264.7	Inhibition of TNF-α, IL-6, and IL-12B expression	[89]
25 μmol/L	RAW264.7	-Reducing the expression of M1 macrophage markers, such as iNOS, IL-6, IL-1b, and MCP-1 -Upregulating the expression of PPAR-γ and IκBα	[92]
25 μmol/L	RAW264.7	-Increasing the expression of M2 markers, including KLF4, FIZZ1, and MGL1 -Changing the morphology of the M0 macrophage toward M2 phenotype	[93]
6.25 and 12.5 μM	RAW264.7	Inducing the expression of M1 cytokines, such as IL-1b, IL-6, and TNF-α	[87]
6.25–2.5 μmol/L	RAW264.7	Increasing expression of CD36, ABCA1, and PPAR-γ in ox-LDL-induced M1 macrophages	[87]
6.25–50 μmol/L	Raw264.7	Promoting the translocation of GATA3 into the nucleus contribute to the secretion of IL-4 and IL-13 induced	[94]
6.25–25 nM	RAW 264.7	-Reducing the percentage of M1 macrophages -Increasing percentage of M2 macrophage	[95]

Modulatory effect of curcumin on macrophage polarization

Macrophages corresponding to M1 and M2 types were described as the fundamental contributors in atherosclerotic lesions [96]. As previously mentioned, M1 macrophages are enriched in progressing plaques, and M2 macrophages are present in regressing plaques, where they were involved in tissue repair and remodeling [45, 96, 97]. A growing body of evidence has shown the modulatory effect of curcumin on macrophage polarization, mainly through TLR4/MAPK (*mitogen-activated protein kinase*)/NF-κB signaling pathways. In the inflammatory condition, TLR4 is activated and, consequently, stimulates intracellular signaling cascades, including MAPK and NF-κB transducers, by which the expression of inflammatory cytokines, such as TNF-α, IL-6, and IL-12, becomes upregulated [98].

An in vitro study indicated that curcumin not only could inhibit polarization of RAW264.7 cells (M0) to M1 phenotypes but also switched M1 or M0 macrophages to the M2 phenotype, contributing to the downregulation of the expression of M1 markers including iNOS, IL-1β, IL-6, and MCP-1 [93]. Mechanistically, curcumin could suppress M1 inflammatory phenotype through activation of IκBα in M0 macrophages and promote polarization of M1 or M0 phenotypes to M2 macrophages through activation of PPAR-γ [93] known as a regulator of cholesterol homeostasis and the inflammatory response in atherosclerotic lesion macrophages [45]. It has been shown that curcumin is a natural agonist of PPAR-γ, inducing polarization of macrophages to the M2 phenotype [92]. In addition, the NF-κB-mediated effect of curcumin on macrophage polarization was also reported by another study which showed that curcumin decreased the expression of M1 inflammatory cytokines through inhibition of the NF-κB signal pathway by activation of IκBα and deactivation of p65 [99]. Consistent with these works, another study showed that curcumin was capable of switching M1 macrophages to an M2 phenotype through inhibition of TLR4-mediated MAPK/NF-κB pathways via downregulating TLR4 and inhibiting phosphorylation of NF-κB and some MAPks, such as ERK (extracellular signal–regulated kinases), JNK (c-Jun N-terminal kinase), and p38. These effects were indicated to be associated with reduction of TNF-α, IL-6, and IL-12B protein and mRNA levels in M1 macrophages [89]. The effect of curcumin on the MAPK pathway in inflammatory macrophages is also found in another study which demonstrated that curcumin inhibits inflammation signaling in THP-1 cell-derived macrophages through attenuating the activation of ERK, JNK, and p38 transducers [100]. Further, it was demonstrated that curcumin dose-dependently suppressed the production of monocyte chemoattractant protein-1 (MCP-1) induced by ox-LDL in macrophages via JNK and NF-κB transducers [66]. These findings are underscored by another study showing the attenuating effect of curcumin on the expression and activity of TLR4 and downstream transducers in the inflammatory macrophages [101, 102], as well as the expression of inflammatory cytokines in M1 macrophages, such as IL-6, IL-1b, MCP-1, and TNF-α, involved in atherosclerosis pathogenesis [87, 99, 103, 104]. It is further supported by molecular studies which demonstrated curcumin as an antagonist that blocks the enzyme activity of TLR4, JNK, and NF-κB [90, 91]. Based on the aforementioned evidence, TLR4/MAPK/NF-κB transducers are important determinants of macrophage polarization, in which inhibition of TLR4-mediated pathways shifts macrophage polarization toward M2 phenotypes and suppresses M1 macrophages. To sum up, curcumin can be a potent macrophage modulator, switching the proinflammatory M1 cells to an M2 phenotype through regulating TLR4-mediated signaling cascades. Evidence of the modulatory effect of curcumin is more fortified by studies that evaluated the effect of curcumin on cholesterol hemostasis in M1 macrophages induced by oxLDL. It was revealed that curcumin enhanced the handling capacity of harmful lipids in M1 macrophages through increasing the expression of PPAR-γ, CD36, and ABCA1 by which cholesterol efflux is improved and, consequently, foam cell formation is diminished [77, 85, 87].

It is important to take into account these findings in a broader context. Particularly, previous experimental and epidemiological studies have revealed that the function of TLR4/MAPK/NF-κB pathways is contributed to the initiation and progression of atherosclerosis [105, 106], while TLR4 deficiency is associated with attenuation in atherosclerosis development [107, 108]. Therefore, TLR4/MAPK/NF-κB signaling pathways can be plausible candidates for macrophage switching as a valuable approach for targeted atherosclerosis therapy. Hence, curcumin can be a potent tool to modify macrophage polarization in favor of atherosclerosis therapy.

Conclusions

A growing body of experimental evidence elucidates that curcumin not only prevents foam cell formation but also modulates macrophage polarization. Upon hyperlipidemia, aortic macrophages uptake excessive serum lipids, resulting in overexpression of lipid transporters, such as CD38, aP2, and SR-A, and the hampered RCT-mediated efflux in these cells. Curcumin can alleviate high levels of serum lipids and consequently modulate lipid transport and trafficking in macrophages and thereby impede foam cell formation. Curcumin can also modulate polarization and plasticity of macrophages in favor of mitigating the atherosclerotic lesion, in which polarization of M0 macrophages to the proinflammatory M1 phenotype is prevented, and M0 and the polarized M1 macrophages shift toward anti-inflammatory M2 phenotypes. Curcumin exerts its modulatory effect through influencing the TLR4/MAPK/NF-κB pathways, showing the importance of these pathways in macrophage polarization, particularly in atherosclerotic lesions. Therefore, findings of the present review illustrate TLR4 as a valuable target to modulate or inhibit hostile macrophages in atherosclerotic lesions. Hence, curcumin as a potential modulator of macrophages and foam cells can assist current lipid-lowering agents to prevent or ameliorate the development of inflamed atherosclerotic lesions. However, additional molecular studies and proof-of-concept experiments are necessary to acquire wider knowledge about the exact role of these molecular pathways in macrophage modulation inside the atherosclerotic plaque.

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Compliance with ethical standards

Conflict of interest The authors have no direct conflict of interests related to the content of this review.

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