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Phenotypic modulation of macrophages in response to plaque lipids

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Abstract

Purpose of review—The accumulation of macrophages in the vascular wall is a hallmark of atherosclerosis. The biological properties of atherosclerotic plaque macrophages determine lesion size, composition and stability. In atherosclerotic plaques, macrophages encounter a microenvironment that is comprised of a variety of lipid oxidation products, each of which has diverse biological effects. In this review, we summarize recent advances in our understanding of the effects of plaque lipids on macrophage phenotypic polarization.

Recent findings—Atherosclerotic lesions in mice and in humans contain various macrophage phenotypes, which play different roles in mediating inflammation, the clearance of dead cells, and possibly resolution. Macrophages alter their phenotype and biological function in response to plaque lipids through the upregulation of specific sets of genes. Interaction of oxidized lipids with pattern recognition receptors and activation of the inflammasome by cholesterol crystals drive macrophages towards an inflammatory M1 phenotype. A new phenotype, Mox, develops when oxidized phospholipids activate stress response genes via Nrf2. Other lipid mediators such as nitrosylated-fatty acids and omega-3 fatty acid-derived products polarize plaque macrophages towards anti-inflammatory and proresolving phenotypes.

Summary—A deeper understanding of how lipids that accumulate in atherosclerotic plaques affect macrophage phenotype and function and thus atherosclerotic lesion development and stability will help to devise novel strategies for intervention.

Keywords

Macrophages; oxidized lipids; atherosclerosis; inflammation

Introduction

Distinguishable macrophage phenotypes, M1 and M2, have been observed in the course of inflammatory reactions [1]. Upon activation by IFNγ and LPS, M1 macrophages secrete inflammatory factors TNFα, IL1β, IL6, and IL12 that incite a Th1 immune response. M1 macrophages also produce reactive oxygen and nitrogen species and upregulate COX2 which leads to the production of eicosanoids. As inflammation proceeds, IL10, IL4, and IL13 alternatively activate macrophages towards an M2 phenotype with anti-inflammatory functionality, including the production of IL10, TGFβ1, and arginase 1 [1]. A macrophage phenotype isolated during the resolution phase of inflammation (Mres) has been characterized by elevated cAMP levels and shares attributes of both M1 and M2 [2]. The development of macrophage phenotypes is under transcriptional control. The NFκB pathway directs activation of M1 while PPARγ directs M2. The recently discovered macrophage

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phenotype, Mox, develops in response to oxidized phospholipids involving the redox-sensitive transcription factor NF-E2-related factor 2 (Nrf2) [3].

Macrophages play a key role in the development of atherosclerotic lesions [4]. The presence of distinguishable macrophage phenotypes in atherosclerotic plaques has been reviewed recently [5;6]. Subpopulations of pro-and anti-inflammatory macrophages were identified in human lesions [7;8] and in advanced atherosclerotic lesions of LDL-R null mice, where the relative abundance of macrophage phenotypes was found to be 40 % M1, 30% Mox, and 20% M2 [3]. However, mechanisms that control macrophage polarization in atherosclerosis are just beginning to be understood.

Priming for phenotypic polarization can occur in circulating monocytes: In mice, a monocyte subset characterized by expression of Ly6C and CCR2 was shown to be readily recruited to atherosclerotic lesions [9;10] where development into M1 macrophages ensued. Interestingly, C-reactive protein was shown to induce polarization of monocytes towards M1 [11]. Studies in humans have shown that treatment with ligands specific for PPARγ primes monocytes to become M2 macrophages in atherosclerotic lesions [8]. Notably, low-intensity exercise by sedentary individuals also primed circulating monocytes towards an M2 phenotype by a mechanism that involved PPARγ [12].

Macrophage phenotypic polarization also occurs in response to changes in the tissue microenvironment: A macrophage phenotype characterized by elevated expression of CD163, a scavenger receptor for hemoglobin-haptoglobin complexes, was shown to develop in response to intraplaque hemorrhage perhaps as part of a mechanism to protect against atherosclerotic lesion destabilization [13]. The importance for controlled heme-catabolism is further underlined by the finding that iron overload induced an unrestrained proinflammatory M1 phenotype [14].

In addition to interleukins, atherosclerotic plaques contain a plethora of bioactive lipid species that potentially regulate macrophage phenotypic polarization and function. Cholesterol has been observed to crystallize in the core of plaques and induce pro-inflammatory signaling pathways in this form. Sphingolipids can be released from cells or are found associated with HDL. Lysophospholipids and fatty acids can be released from LDL via phospholipases. Prostaglandins and leukotrienes [15] are formed from arachidonic acid and omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are precursors to resolvins and protectins. Moreover, the microenvironment in atherosclerotic lesions is characterized by increased oxidative tissue damage and accumulation of oxidatively modified lipids. Lipoproteins and dying cells are main sources of oxidized lipids. Isoprostanes, which are formed by free radical-induced oxidation of arachidonic acid, are useful biomarkers and potentially modulate inflammation in atherosclerotic plaques [16]. Oxysterols can be present as a byproduct of cholesterol metabolism which can be quite dysfunctional in lipid laden foam cells [17]. Additionally, oxidized phospholipids can be presented on MM-LDL and on the membranes of apoptotic cells and shed as microvesicles and apoptotic blebs.

This review will focus on how bioactive lipids in the plaque microenvironment affect pro- and anti-inflammatory signaling to determine phenotypic polarization and consequently biological function of macrophages in atherosclerosis (Figure 1).

Macrophage phenotypic polarization in response to pro-inflammatory lipid mediators

Oxidatively modified lipids and lipoproteins resemble “danger signals” that are recognized by pattern recognition receptors such as TLR2 and TLR4. Moreover, CD36, a scavenger receptor that binds oxidized LDL, has been shown to act in combination with certain TLR heterodimers, mediating pro-inflammatory effects of oxidized lipoproteins and lipids [18;19]. Accumulating evidence supports a role for toll-like receptors (TLRs) in the pathogenesis of atherosclerosis, and TLR activation in macrophages by lipids induces NFκB-, MAP kinase- and ROS-dependent inflammatory gene expression, producing an M1-like phenotype. In addition, activation of the inflammasome and other stress-response mechanisms result in a pro-inflammatory phenotype in plaque macrophages.

Oxidized lipoproteins

In atherosclerosis, peripheral blood monocytes are recruited to the vessel wall where they differentiate into macrophages and develop into foam cells through the ingestion of lipids [4]. Accumulation of oxidized LDL (oxLDL) in M2 macrophages drives these cells toward a pro-inflammatory state accompanied by downregulation of the anti-inflammatory transcription factor KLF2 [20]. Minimally modified LDL (MM-LDL), was recently shown to activate macrophages via TLR4, inducing recruitment and activation of spleen tyrosine kinase (Syk) and protein kinase C, and to intracellular generation of ROS by NADPH oxidase 2 (gp91phox/Nox2) [21]. Nox2 was required for the expression of inflammatory cytokines including IL-1β and RANTES/CCL5. MM-LDL was shown to activate TLR signaling by inducing a redistribution of CD14, TLR4, and TLR2 in the macrophage membrane [22] and MM-LDL cooperatively activated TLR4 with low-dose LPS [23]. Further evidence for an involvement of TLR4 in mediating effects of modified lipoproteins comes from a study where lipoproteins isolated from zebrafish larvae that had been fed a high fat diet, induced MAP kinase signaling and cell spreading in wild type, but not in TLR4-deficient murine macrophages [24]. Interestingly, phenotypic polarization of macrophages in fish largely resembles that observed in mammalian systems [25].

Oxidized phospholipids

Oxidized phospholipids induce inflammatory gene expression in macrophages and several studies have implied oxidized phospholipids as activators as well as inhibitors of TLR signaling [26–29]. The exact mechanisms of how oxidized phospholipids activate TLRs are not known, but dependent on the experimental system, different combinations of pattern recognition receptor multimers as well as accessory receptors such as CD14 or LBP may be required [30;31].

Moreover, oxidized phospholipids induce the development of the Mox phenotype via activation of Nrf2-dependent gene expression [3]. The unique expression pattern of antioxidative and detoxifying genes in Mox macrophages sharply distinguishes this phenotype from conventional M1 and M2 macrophages and implies specific functions in atherosclerotic lesions. For instance, Mox macrophages demonstrate decreased phagocytotic capacity and reduced migratory properties [3]. In any case, it remains to be shown whether the Mox phenotype plays a beneficial or detrimental role in the development of atherosclerotic lesions.

It was shown that Nrf2-dependent anti-oxidant signaling counteracts LPS-induced inflammation in foam cells [32] via mechanisms that included upregulation of heme-oxygenase-1 (HO-1), a marker for Mox macrophages [3]. However, recent findings point to a role for Nrf2 in mediating inflammatory responses in addition to anti-inflammatory

processes. In support of this concept, it was shown that Nrf2 deficiency was protective in models of experimental atherosclerosis [33–35]. A possible mechanism underlying these seemingly paradoxical findings may involve a role for Nrf2 in activation of the inflammasome [33]. In fact, the proatherogenic activity of Nrf2 may be caused by cholesterol crystals which have been shown to activate the NLRP3 inflammasome in a Nrf2-dependent manner [33].

Cholesterol crystals

Crystallization of cholesterol was thought to be a late event in atherosclerosis and thus would not contribute to the initiating inflammatory events. However, a recent study showed that minute cholesterol crystals can be detected in early lesions after only 2 weeks of HFD feeding in ApoE null mice as well as in human lesions [36]. Engulfed cholesterol crystals were shown to cause damage to the phagolysosome of macrophages, allowing leakage of mediators like cathepsin into the cytoplasm which can activate the NLRP3 inflammasome [36;37]. Inflammasome activation leads to activation of caspase-1 and release of IL-1 and IL-18 and LDL-R null mice transplanted with NLRP3-deficient bone marrow showed decreased atherosclerosis [36]. Together, these findings strongly support a role for inflammasome activation by cholesterol crystals in early atherogenesis.

Oxidized cholesteryl esters

In the core of LDL, cholesterol is found esterified with fatty acids. Cholesteryl esters containing unsaturated acyl chains can be oxidatively modified, leading to the formation of biologically active compounds that activate macrophages [38;39]. Cholesteryl linoleate induces inflammatory signals in macrophages in a MAP kinase pathway-dependent fashion [24;40]. Another cholesteryl ester, 7-ketocholesteryl-9-carboxynonanoate induces NFκB signaling in macrophages [41]. Recent studies have shown that oxidized cholesteryl esters can trigger inflammatory signaling and foam cell formation via pinocytosis by a process that involves TLR4 [21;42]. Clearly, cholesteryl esters are capable of inducing inflammatory signals; however, other cholesteryl esters such as 9-oxononanoyl-cholesterol are able to induce expression of anti-inflammatory mediators such as TGFβ [43].

Oxidized cholesteryl esters and oxidized phospholipids may play an important combined role in the regulation of foam cell formation. Cholesteryl ester hydroperoxides increase expression of the scavenger receptor CD36 by macrophages [44]. Certain oxidized phospholipids that are ligands for CD36 and also the scavenger receptor class B, type 1 (SR-B1) were shown to interfere with SR-B1-mediated selective uptake of cholesteryl esters [45]. A link between phenotypic polarization and foam cell formation was provided by a recent study that showed that activation of αMβ2 integrins prevented alternative macrophage activation and foam cell formation by inhibiting CD36 expression [46].

Oxysterols

Originally believed to be cytotoxic by-products of cholesterol metabolism, recent findings demonstrate that oxysterols, as ligands of liver X receptors (LXR), potently modulate lipid metabolism and inflammation (recently reviewed in [17]). Oxysterols may also have effects on macrophages that are independent of LXR. ORP9 is an oxysterol binding protein that is upregulated in oxLDL-stimulated peripheral blood monocytes [47]. Moreover, treatment of Thp-1 macrophages with 7-keto-cholesterol or a mixture of oxysterols induced expression of MCP-1 [48]. Additionally, oxysterols caused expression of the scavenger receptor CD36 via a GPCR/Src/PLC/PKCδ/ERK-dependent mechanism that resulted in PPARγ upregulation [49].

Lysophospholipids and fatty acids

The action of phospholipases on lipoproteins and membrane phospholipids results in release of lysophospholipids and free fatty acids. A recent study showed that modification of LDL by group V PLA2 results in products that activate macrophages to secrete TNFα and IL6 via NFκB activation in addition to enhancing lipid uptake and foam cell formation [50]. An acidic environment, as would be found in advanced atherosclerotic plaques, enhances the inflammatory activity of lysophosphatidylcholine (lysoPC) and free fatty acids by impairing the ability of albumin to sequester those products [51]. The G-protein coupled receptor G2A mediates the ability of lysoPC to induce signaling and chemotaxis in macrophages [52–54]. Moreover, G2A may be a receptor for oxidized fatty acids [55]. Recently, two splice variants of G2A were described, both of which recognized 9-HODE [56]. Interestingly, deficiency of G2A was shown to promote an inflammatory phenotype in macrophages, resembling an M1 macrophage. This was characterized by increased nuclear translocation of NFκB, and IL6 and IL12 expression, as well as reduced Arginase 1 [57]. Global and myeloid cell-specific G2A deficiency were shown to have profound effects on atherosclerosis development [57–59].

Pro-atherogenic effects have been attributed to saturated fatty acids. Palmitic acid promotes foam cell formation by macrophages by the upregulation of oxLDL receptor 1 (LOX1), possibly by inducing ER stress [60], an effect counteracted by unsaturated fatty acids. Several studies indicate that saturated free fatty acids may be ligands for TLRs 2 and 4, causing NFκB-dependent inflammatory gene expression and thereby contributing to atherosclerosis, inflamed adipose tissue, and insulin resistance [61–63]. Moreover, palmitate and stearate in the presence of high glucose increase expression of TLR2 and TLR4 on monocytes, causing ROS generation and increased NFκB activity [61]. Debate continues as to whether saturated fatty acids directly bind to and activate TLRs [64].

Macrophage phenotypic polarization in response to anti-inflammatory and proresolving lipid mediators

Several lipid mediators that are present in atherosclerotic plaques were shown to polarize macrophages towards anti-inflammatory and proresolving phenotypes. For instance, oxidized lipids were described to have numerous anti-inflammatory effects [65] and omega-3 fatty acid-derived products, resolvins and protectins, have been shown to play important roles in the resolution of inflammation [66].

Polyunsaturated fatty acids and nitro-fatty acids

Unlike saturated fatty acids, polyunsaturated fatty acids (PUFAs) can evoke anti-inflammatory mechanisms in macrophages. What is more, unsaturated fatty acids often counteract inflammatory pathways induced by saturated fatty acids; for example, in macrophages PUFAs suppress palmitic acid-induced increases in LOX1 and FABP expression [66;67]. Conjugated linoleic acid (CLA) has been shown to cause regression of preestablished murine atherosclerotic plaques, accompanied by a decrease in lesion macrophage accumulation and suppressed COX2, cPLA2, MCP1, and MMP9 expression in macrophages [68].

Another class of anti-inflammatory unsaturated fatty acid products are electrophilic nitro-fatty acids which are formed via nitric oxide or nitrite-dependent redox reactions [69]. Nitro-fatty acids have been shown to activate Nrf2 and PPARγ [70–72]. The anti-inflammatory activity of nitro-fatty acids has been shown *in vitro* as well as in a cardiac ischemia reperfusion model *in vivo* [69;73;74]. Recently, it was shown that nitro-fatty acids also exert anti-atherosclerotic effects: subcutaneous injection of nitro-oleic acid resulted in a

significant reduction of lesion formation in apoE null mice without affecting serum lipid levels. Furthermore, atherosclerotic lesions of nitro-oleic-acid-treated mice showed increased collagen content and stability [75].

Omega-3 fatty acids and resolvins

Omega-3 fatty acids have long been known to have anti-atherogenic effects. A recent study of carotid endarterectomy patients who consumed omega-3-polyunsaturated fatty acid capsules for 21 days leading up to surgery had more stable plaques that were less inflamed with fewer T cells and fewer foam cells [76]. Macrophages in atherosclerotic plaques of obese/LDL-$R^{-/-}$ mice showed defective phagocytosis of apoptotic cells that was reversed by supplementation of omega-3 fatty acids EPA and DHA [77]. Moreover, action of COX-2 on omega-3-fatty acids was shown to produce potent anti-inflammatory products [78].

Macrophages themselves can produce a class of DHA-derived anti-inflammatory and proresolving products, the maresins (macrophage mediator in resolving inflammation) [79]. Lipoxin A4, aspirin-triggered lipoxin A4, resolvin E1/D1/D2, and maresin 1 all enhance phagocytosis of apoptotic neutrophils by macrophages, and they activate macrophages in a way that does not cause the induction of inflammatory cytokines [80]. Effects of these mediators in atherosclerotic plaques have been implied [81;82]. Peripheral artery disease (PAD) patients had significantly lower plasma levels of aspirin-triggered lipoxin than healthy volunteers. Further investigation showed that aspirin-triggered lipoxin and resolvin E1 likely effect the migration of vascular smooth muscle cells in PAD [81].

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P) has been shown to induce an anti-inflammatory phenotype in macrophages via S1P receptor 1 [83]. Additionally, some anti-atherogenic effects of high-density lipoproteins are mediated by S1P via S1P receptor 1 (S1PR1) [84]. However, recent evidence suggests that other S1P receptors (S1PR2) may mediate proatherogenic effects. ApoE/S1PR2 null mice have smaller plaques, decreased macrophage density, and decreased proinflammatory cytokines. ApoE/S1P2 null macrophages show decreased activity of ROCK/NFκB, reduced cytokine expression, and decreased oxLDL uptake [85;86].

Open questions: Functional consequences of lipid-induced macrophage phenotypic polarization in plaques

With so many bioactive lipids present in atherosclerotic plaques, it is important to more clearly define their effects on plaque macrophages. Moreover, elucidating the time course of the appearance and action of different lipid mediators will help us better understand the progress of atherosclerosis as well as the mechanisms that are involved in resolution.

Beyond the development of different capacities to regulate inflammation, little is known about functional properties resulting from macrophage phenotypic polarization. What are the migratory properties and phagocytotic capacities of the different phenotypes? In the context of atherosclerosis, it is important to further elucidate the capabilities of different macrophage phenotypes to form foam cells. How might phenotypic polarization alter reverse cholesterol transport and lipid metabolism? Future studies will shed more light on these important properties of different macrophage phenotypes that are present in atherosclerotic lesions.

Conclusions/future outlook, therapeutic potential

The plaque environment contains many different lipid mediators that drive macrophage phenotypic polarizaion. Some lipids activate the inflammasome or act via pattern

recognition receptors to induce inflammatory programs in macrophages or enhance the formation of foam cells. Other lipids incite stress responses in macrophages that enhance antioxidant and detoxifying actions. Yet other lipids such as S1P and oxysterols have both inflammatory and anti-inflammatory effects.

The relative abundance of various macrophage phenotypes may determine the outcome of an inflammatory reaction [5]. Chronic inflammation in atherosclerosis resembles an unresolved inflammatory response where M1 and Mox macrophages outnumber M2 macrophages [3;87]. Shifting the balance from pro-inflammatory towards anti-inflammatory, possibly “proresolving”, macrophages could be a therapeutic strategy to initiate resolution in atherosclerotic plaques and in chronically inflamed tissues in general. In support of this hypothesis, it was shown that during plaque regression, induced by increased HDL or decreased serum cholesterol levels, macrophages switch their phenotype into the anti-inflammatory M2 type [88;89].

Among compounds or treatment strategies that can either prime circulating monocytes or induce the transition of a pro-inflammatory macrophage into M2 macrophages are thiazolidinediones (TZDs) [8], adiponectin [90], FK 506 (tacrolimus) [91], the S1P analogue FTY 720 [92], cordycepin (a component of cordyceps militaris) and adenosine [93], inhibition of CD40-CD40 ligand signaling [94], as well as exercise [12]. Some studies suggest that LXR ligands, conjugated linoleic acid, and PUFAs could switch macrophages into an anti-inflammatory, possibly pro-resolving phenotype. Drugs commonly taken by patients suffering from cardiovascular disease include aspirin and statins which modify COX2 via acetylation or S-nitrosylation, respectively, and this process drives the generation of aspirin-triggered lipoxins, namely 15-epi-LXA4, which may establish and carry forward the resolution of inflammation [80;95].

Macrophage phenotypic polarization and its connection to plaque lipids is an important aspect of lesion development and progression. A better understanding of the complex microenvironment and the multiple biological processes in atherosclerotic lesions that control macrophage function will lead to novel treatment strategies.

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Key points

- Macrophages in atherosclerotic lesions change their phenotype and function in response to plaque lipids.
- The plaque microenvironment determines the relative abundance of pro-inflammatory M1, various forms of M2 and the newly identified Mox macrophage phenotypes.
- Changing lesion macrophages into a pro-resolving phenotype may be a promising strategy to attain plaque regression.

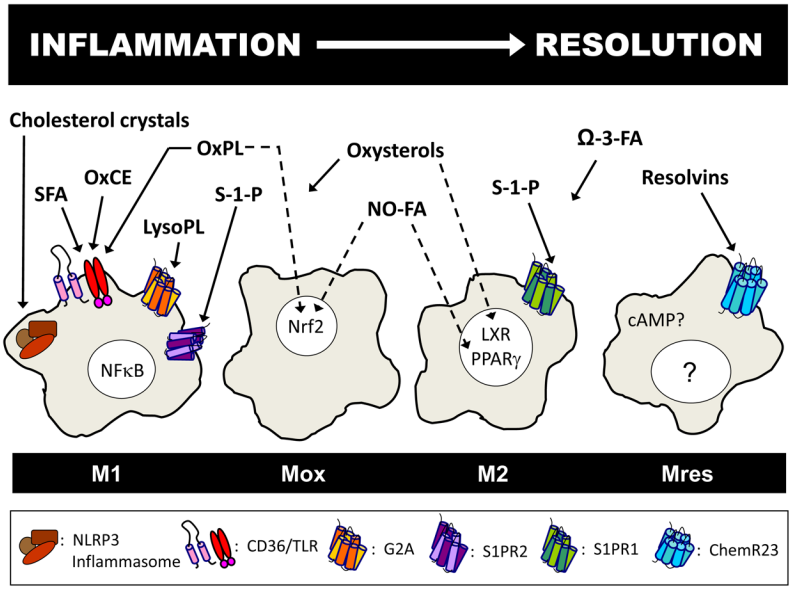

Figure 1.

Modulation of macrophage phenotype and function occurs during the progression and resolution of inflammation. In atherosclerosis, phenotypic polarization of macrophages is affected by bioactive plaque lipids. In a simple model, saturated fatty acids (SFA), oxidized cholesteryl esters (OxCE), and oxidized phospholipids (OxPL) induce inflammatory gene expression via scavenger receptor CD36, toll-like receptors (TLR), and NFκB activation, as seen in M1 macrophages. Crystallized cholesterol activates the NLRP3 inflammasome to sustain inflammation, and lysophospholipids (LysoPL) act on the G-protein coupled receptor G2A. Some macrophages are transformed by oxidized lipid signaling via Nrf2 into Mox macrophages. Other bioactive lipids such as nitrosylated fatty acids (NO-FA), sphingosine-1-phosphate (S1P), and oxysterols activate PPARγ, sphingosine-1-phosphate receptors, and liver X receptors (LXR), respectively, to modulate towards an anti-inflammatory M2 phenotype. However, oxysterols can also induce an inflammatory response, as can activation of S1P receptor 2. Omega-3 fatty acids and resolvins have anti-inflammatory or proresolving effects. Increase in cAMP or activation of the G protein-coupled receptor, ChemR23, may drive macrophages toward a resolving phenotype, Mres.