Macrophages in Atherosclerosis Development

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Atherosclerosis is a multifactorial chronic disease that has a prominent inflammatory component. Currently, atherosclerosis is regarded as an active autoimmune process that involves both innate and adaptive immune pathways. One of the drivers of this process is the presence of modified low-density lipoprotein (LDL). For instance, lipoprotein oxidation leads to the formation of oxidation-specific epitopes (OSE) that can be recognized by the immune cells. Macrophage response to OSEs is recognized as a key trigger for initiation and a stimulator of progression of the inflammatory process in the arteries. At the same time, the role of oxidized LDL components is not limited to pro-inflammatory stimulation, but includes immunoregulatory effects that can have protective functions.

Keywords: atherosclerosis ; LDL ; oxidized LDL ; macrophage ; inflammation ; immunomodulation

1. Introduction

The multifactorial nature of atherosclerosis pathogenesis makes studying this disease challenging. According to current view, atherosclerosis can be considered as a chronic inflammatory disease associated with progressive accumulation of lipids and inflammatory cells in the arterial wall. The atherogenic process begins with deposition of low-density lipoprotein (LDL), which is normally present in the blood plasma, in the subendothelial space of the arterial wall. In human arteries, such deposition often occurs at the sites of laminar flow perturbation, where activated or dysfunctional endothelial cells are present [1].

For many years, LDL was known as the main source of lipid accumulation in atherosclerosis, and much of anti-atherosclerotic therapies is aimed at correcting the blood lipid profile to slow down the disease progression.

Inside the arterial wall, oxLDL provides for oxidation-specific epitopes (OSE) that can be recognized by the innate immune system cells as damage-associated molecular patterns (DAMPs) [2]. These early events trigger the immune response, which eventually involves many cellular subtypes of both innate and adaptive immunity [1]. It was shown that macrophages along with T lymphocytes are the major subset of inflammatory cells in atherosclerotic lesions [3]. Moreover, phagocytic macrophages appear to be a major cell type responsible for intracellular lipid accumulation in atherosclerosis. A recent study of the transcriptome of LDL-induced macrophages demonstrated that native LDL and oxLDL changed the expression of different sets of genes [4]. Macrophages internalize oxidized lipoproteins via macropinocytosis, phagocytosis and receptor-mediated uptake. These processes are mediated by two main classes of membrane receptors involved in the sensing of oxLDL: scavenger receptors (SRs) and Toll-like receptors (TLRs), although soluble receptors may also be important for atheroinflammation progression and atherosclerosis complication development [5][6][7].

Macrophages, the key players of the innate immune system, have been identified as one of the cell types that directly respond to the presence of modified atherogenic LDL, including oxLDL. Following oxLDL recognition and internalization, macrophages undergo metabolic and functional reprogramming [4]. This process involves decrease of phagocytic activity, increase of pro-inflammatory cytokines production, and differentiation of macrophages into foam cells. Excessive foam cell formation results in the appearance of fatty streaks, the first grossly visible stage of atherosclerotic lesion. OxLDL was also described as an important driver of pro-inflammatory (also known as M1) macrophage polarization [4]. Pro-inflammatory macrophages interact with T-cells to drive the inflammatory response and atheroma progression, presenting antigens to T cells activating T-helper type-1 (Th1) responses. In turn, Th1 cells stimulate pro-inflammatory activation of macrophages by creating a specific cytokine environment inside the growing plaque.

2. Pathways of Lipid Oxidation and Their Relevance for Atherosclerosis

The presence of activated endothelial vascular cells, neutrophils, macrophages and T and B cells in atherosclerotic plaques, together with the proinflammatory cytokine environment, suggests that atherosclerosis is an active immunopathological process [1]. The hypothesis of oxLDL acting as a trigger of atherosclerosis development originated

from the studies in 1980s–1990s that showed that macrophages treated with oxLDL, but not native LDL, accumulated cholesterol esters [8]. Another study demonstrated the presence of autoantibody response to oxLDL in apolipoprotein E deficient mice [9]. Since then, it has become clear that atherosclerosis is an autoimmune process and oxidized forms of LDL are among most validated autoantigens relevant to atheroinflammation [1].

One of the features of atheroinflammation is a high level of protein carbonylation. Covalent adduction of aldehydes to apolipoprotein B in LDL was shown to be strongly implicated in the mechanism of atherogenic modification of LDL [10]. A study on oxLDL lysine and histidine adductome identified Nϵ-(8-carboxyoctanyl)lysine (COL) as a major product of carbonylation in vitro. It was shown to be significantly higher in hyperlipidemic mice and atherosclerosis patients [11]. Moreover, in atherosclerosis patients, multiple MDA-Apo B adducts that resemble autoantigens recognized by antibodies were also described [12].

The subendothelial retention and oxidation of LDL also results in MDA-modifications of surrounding extracellular matrix proteins, including fibronectin, collagen type I-IV and ten ascin-C [13][14], giving rise to new potential antigens. MDA-collagen type IV-specific IgG antibodies were shown to be associated with more severe carotid disease and increased risk of myocardial infarction [15]. It was shown that LDL oxidation in the arterial wall is associated with further modification of surrounding extracellular matrix components through aldehyde formation. Among the modified proteins, fibronectin, collagen type I and III and tenascin-C were named [13]. The study reported the presence of autoantibodies to these modified proteins in human plasma, highlighting the immunogenic properties of such modifications.

3. Receptor-Mediated Uptake and Effects of Oxidation-Specific Epitopes

3.1. Interaction with CD36

Formed as a result of oxidative modification of protein and lipid moieties of LDL, OSEs can be recognized by the immune system, since they resemble the markers of oxidative stress and tissue damage. Moreover, some of the known OSEs resemble the molecular patterns of bacterial cells [16]. It was shown that OSEs were present not only on oxLDL, but also on apoptotic cells, apoptotic blebs and cellular debris. Similarly to other described damage-associated molecular patterns, OSEs are sensed by a number of pattern recognition receptors (PRRs) widely expressed on the innate immune system cells [16]. OSE sensing by PRRs mediates sterile inflammation or clearance and neutralization of OSE-exposing targets depending on the context and the receptor involved (**Table 1**). Macrophages are the main population of immune cells responsible for OSE sensing and clearance.

Table 1. Recognition of OSEs by PRRs.

PRR	OSE	Effect	Cells
Scavenger receptors			
SR-A1,2	MDA	Uptake	Macrophages, mast, dendritic, endothelial, smooth muscle cells
SR-B1	PC-OxPL	Uptake	Monocytes/macrophages, hepatocytes, adipocytes
SRECI/II	OxLDL	Uptake	Endothelial cells, macrophages, CD8+ cells
SR-PSOX	Ox-PS	Uptake Foam cell formation	Macrophages, smooth muscle, dendritic, and endothelial cells, and B-cells and T cells
LOX-1	MDA 4-HNE	Monocyte adhesion Uptake Inflammation	Endothelial and smooth muscle cells, macrophages, platelets
CD36	PC-OxPL	Uptake Inflammation	Macrophages, platelets, adipocytes, epithelial and endothelial cells
	OxPS	Uptake Inflammation	
	CEP	Uptake Inflammation	
TLRs			
TLRs 4-6	PC-OxPL	Inflammation	Monocytes/macrophages, dendritic cells, mast cells, B cells

PRR	OSE	Effect	Cells
TLR4	OxCE	Inflammation Foam cell formation	Monocytes/macrophages, dendritic cells, mast cells, B cells
	OxPE	Inflammation Foam cell formation	
	4-HNE	Inflammation	
TLRs 2-6	CEP	Inflammation Thrombosis	Monocytes/macrophages, dendritic cells, mast cells, B cells, platelets
	OxPL	Angiogenesis ER stress	
TLR9	CEP	Promotion of platelet hyperreactivity and thrombosis	Platelets
Complement			
CFH	MDA	Neutralization Opsonization	
C3a	MDA	Complement activation	
CRP	PC-OxPL	Enhanced efferocytosis	
Other PRRs			
MFG-E8	OxPS	Enhanced efferocytosis	
	OxPE	Enhanced efferocytosis	
Annexin A5	OxCL	Neutralization	
CD16	MDA	Inflammation	Macrophages

Abbreviations: 4-HNE, 4-hydroxynonenal; CEP, 2-(ω-carboxyethyl) pyrrole; CFH, complement factor H; CRP, C-reactive protein; ER, endoplasmic reticulum; LOX1, lectin-like oxidized LDL receptor 1; MDA, malondialdehyde; MFG-E8, milk fat globule-epidermal growth factor 8; OSE, oxidation- specific epitope; OxCE, oxidized cholesterol esters; OxCL, oxidized cardiolipin; OxPE, oxidized phosphatidylethanolamine; OxPL, oxidized phospholipid; OxPS, oxidized phosphatidylserine; PC-OxPL, phosphocholine (PC)-containing OxPL; PRR, pattern recognition receptor; SR, scavenger receptor; TLR, Toll-like receptor.

Among the scavenger receptors, CD36, which is the main contributor to oxLDL influx, is currently best characterized. CD36 is a pattern recognition receptor that binds polyanionic ligands that can be present both on pathogens and host cells, including thrombospondin-1, oxPLs, hexarelin, fibrillar Aβ amyloid peptides and long-chain fatty acids [17]. Genetic deletion or chemical blockade of CD36 in atherosclerosis-susceptible murine models were shown to be protective against the pathology development [18][19][20]. In addition to oxLDL recognition and transport, CD36 also has signaling functions (**Figure 2**). In macrophages, interaction between CD36 and oxLDL induces the phosphorylation of Lyn and the subsequent activation of the Jun kinases (JNK) 1 and 2. Signaling mediated by CD36 activates nuclear factor kappa beta (NFkB) and pro-inflammatory cytokine response that recruits the immune cells and promotes their infiltration in the arterial intima [17].

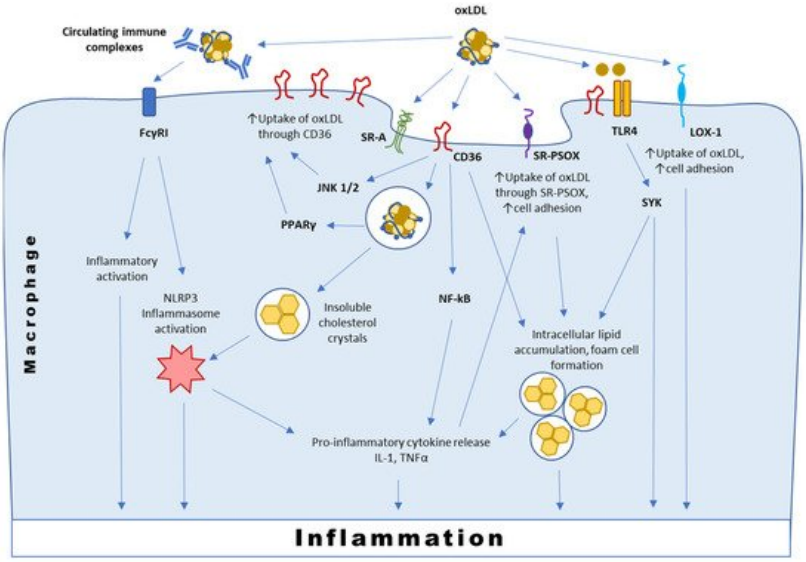

Figure 2. Simplified presentation of interaction of oxLDL with macrophage membrane receptors.

3.2. Interaction with SR-PSOX

SR-PSOX, identical to chemokine CXCL16, was also found to be involved in atherogenesis [21]. It is expressed as a transmembrane protein, but due to proteolytic cleavage, the extracellular domain is released and may circulate as a soluble chemokine important for T cell migration. SR-PSOX was shown to be a specific scavenger receptor for oxLDL, as well as adhesion molecule used by monocytes and T cells [22]. SR-PSOX-mediated uptake of oxLDL was shown to be important for foam cell formation [23].

3.3. Interaction with Immunoglobulins and TLRs

A large fraction of circulating modified LDL can be bound by specific antibodies, forming immune complexes. Autoantibodies can develop to various types of modified LDL, including oxLDL [24]. Presence of circulating immune complexes containing modified LDL has long been known as a risk factor of atherosclerosis progression [24][25]. A large study that included patients with type 1 diabetes revealed the strong predictive value of cholesterol and ApoB contents (used as surrogate markers of modified LDL) of circulating immune complexes for carotid intima-media thickness progression [25].

3.4. Interaction with LOX-1 and Other Scavenger Receptors

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is responsible for sensing 4-HNE and MDA. It is primarily expressed by macrophages, endothelial and smooth muscle cells [26]. LOX-1 expression is very low in normal physiological state but is upregulated in vascular endothelium of human atherosclerotic plaques and ischemic tissues. Once activated, it stimulates the expression of adhesion and remodeling molecules, pro-inflammatory signaling pathways and proangiogenic proteins. Studies in Watanabe-heritable hyperlipidemic rabbits revealed that LOX-1 upregulation may in fact precede the atherosclerotic lesion formation. The role of such upregulation in early pathogenesis of atherosclerosis may be connected with endothelium activation and monocyte adhesion [27]. LOX-1 activation was described as a potential mechanism linking atherosclerosis with metabolic syndrome and cancer [26].

3.5. Interaction with Soluble Factors and Chaperons

OSE can also be sensed by soluble factors: Complement factor H (CFH), C3a, C-reactive protein (CRP), Annexin A5 and others, including innate natural antibodies [9]. These interactions may lead to complement activation as well as opsonization and enhanced efferocytosis of OSE-bearing targets. CFH is the major inhibitor of the alternative pathway of complement activation that was recently shown to bind to and prevent the proinflammatory effects of MDA epitopes [28]. CRP-oxLDL interaction triggers complement activation and enhances binding of oxLDL-antibody complexes to Fcγ receptors expressed on macrophages. CRP and modified LDL are colocalized in early atherosclerotic lesions of humans with coronary artery disease [5]. Expression of CRP is a characteristic feature of M1 pro-inflammatory macrophages [29]. In atherosclerotic plaques, CRP participates in a positive feedback loop with oxLDL, whereby increased levels of oxLDL induce endothelial cells and macrophages to express CRP, which may in turn increase the expression of LOX-1 to promote the uptake of atherogenic LDL into cells [30]. Involvement of complement in the pathogenesis of atherosclerosis is being actively studied and was recently discussed elsewhere [6][7].

4. Anti-Inflammatory and Immunoregulatory Functions of oxLDL

Synthetic oxPL analogs, lecinoxoids, have been studied in atherosclerosis models. VB-201, a small-molecule lecinoxoid, exhibited up to 90% inhibition of monocyte chemotaxis in vitro [31]. It was found to bind directly to TLR-2 and CD14, restricting TLR2/TLR4 signaling, and has been protective in apoe$^{-/-}$ mice and in a rabbit model without affecting cholesterol or triglyceride levels [32][31].

OxPE generated by 12/15-LO is a key factor in the process known as efferocytosis. Efferocytosis is clearance of apoptotic cells by professional and non-professional phagocytes, and macrophages are the main mediators of apoptotic cells clearance in atherosclerotic plaques [33]. Such clearance is important in the context of atherosclerotic plaque, since apoptotic and necrotic cell death contributes to the plaque development, forming a necrotic core in the interior of advanced plaques. In particular, the pro-apoptotic role of high concentrations of oxLDL has been described in early studies, and much effort has been invested in studying that connection [34].

The outcomes of effective efferocytosis are prevention of secondary necrosis, termination of inflammatory responses, promotion of self-tolerance and activation of resolving pathways. When efferocytosis is impaired, these functions are compromised, leading to increased inflammation [33]. Efferocytosis is usually effective in early atherosclerotic lesions, restricting the progression of atheroinflammation, but was shown to be impaired at advanced stages, leading to the accumulation of secondarily necrotic cells in the necrotic core of atherosclerotic plaques [35].

5. OxLDL as a Macrophage Polarization Signal

In the plaque environment, macrophages are exposed to various signals and stimuli, including cytokines, modified lipids, senescent erythrocytes and hypoxia, that influence their transcriptional program and functional phenotype [4]. As a consequence, intraplaque macrophages undergo polarization to distinct subtypes playing opposite roles in atherosclerosis pathology. The early classification of macrophages to M1 (proinflammatory) and M2 (anti-inflammatory) phenotypes is currently regarded as oversimplified and outdated, but can still be useful, especially for interpreting the results of in vitro studies [36].

In atherosclerotic plaques, oxLDL is one of the key signals for macrophage polarization, which mostly promotes M1 phenotype [4]. Cholesterol crystals are responsible for the activation of NLRP3 infammasome [37], resulting in the release of IL-1 family cytokines, considered to be M1-polarizing factors. Cholesteryl esters (including 7-ketocholestery l-9 carboxynonanoate) induce M1 polarization by activating the TLR4 and nuclear factor (NF) κB signaling pathways. Intracellular accumulation of oxLDL was also shown to drive macrophage polarization towards M1 phenotype through inhibition of the transcription factor Kruppel-like factor 2 [4]. Advanced glycation end products (AGEs) were also described as M1-polarizing signals [38]. AGEs are irreversible products of the nonenzymatic glycation and oxidation of proteins, lipids and nucleic acids that activate RAGE (Receptor of AGE) signaling.

Conversely, certain lipids and their derivatives may serve as M2 macrophage polarization signals. Among such agents are 9-oxononanoyl-cholesterol, a major cholesteryl ester oxidation product [14], and resolvin D1 [4].

A hallmark of atherosclerotic lesions is the formation of lipid-loaden macrophages, known as foam cells. Enhanced uptake of oxLDL mediated by scavenger receptors is a prerequisite for foam cell differentiation, but conflicting evidence exists regarding the roles of individual scavenger receptors in foam cell formation [39].

In addition to lipid uptake, foam cell formation can be influenced by levels of lipid biosynthesis and efflux with PPARs and LXRs, playing key role in these processes. LXR-α regulate transcription of ABCA1 and ABCG1, which are involved in cholesterol efflux to apoA1 and HDL, respectively.

6. Conclusions

Lipid and lipoprotein oxidation is a common pathophysiological response to oxidative stress and hyperlipidemia. Oxidized lipids and lipoproteins act as DAMPs and are sensed by a number of pattern recognition receptors. Macrophage response to oxLDL species plays an important role in atherosclerotic lesion initiation and progression. At the early stages of lesion development, it is involved in monocyte adhesion and accumulation in the vascular wall and foam cell formation. Progression of the lesion is accompanied by M1 macrophage polarization, continuous inflammatory response, involvement of the T and B cells and deficient apoptotic cells clearance, all of which can be influenced by oxLDL recognition. It is important to understand the complexity of oxLDL effects on various cell types other than macrophages,

such as endothelial cells, smooth muscle and lymphocytes. Unravelling the pathways of innate and adaptive immune responses to oxLDL may highlight new possibilities for atherosclerosis prevention and treatment.

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