The iterative lipid impact on inflammation in atherosclerosis

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Purpose of review
Lipid-mediated atherogenesis is hallmarked by a chronic inflammatory state. Low-density lipoprotein cholesterol (LDL-C), triglyceride rich lipoproteins (TRLs), and lipoprotein(a) (Lp(a)) are causally related to atherosclerosis. Within the paradigm of endothelial activation and subendothelial lipid deposition, these lipoproteins induce numerous pro-inflammatory pathways. In this review, we will outline the effects of lipoproteins on systemic inflammatory pathways in atherosclerosis.

Recent findings
Apolipoprotein B-containing lipoproteins exert a variety of pro-inflammatory effects, ranging from the local artery to systemic immune cell activation. LDL-C, TRLs, and Lp(a) induce endothelial dysfunction with concomitant activation of circulating monocytes through enhanced lipid accumulation. The process of trained immunity of the innate immune system, predominantly induced by LDL-C particles, hallmarks the propagation of the low-grade inflammatory response. In concert, bone marrow activation induces myeloid skewing, further contributing to immune cell mobilization and plaque progression.

Summary
Lipoproteins and inflammation are intertwined in atherogenesis. Elucidating the inflammatory pathways will provide new opportunities for therapeutic agents.

Keywords
atherosclerosis, cardiovascular disease, immune system, inflammation, lipoproteins

INTRODUCTION
Atherosclerosis is a multifactorial process, and lipid accumulation and subsequent inflammation have been shown to play a central permissive role [1]. In the course of further progression of the atherosclerotic lesion, many other inflammatory cells come into play, resulting in a local and systemic chronic low-grade inflammatory state.

Apolipoprotein B (apoB)-containing lipoproteins are causally related with atherosclerotic cardiovascular disease (ASCVD). These comprise low-density lipoprotein (LDL), triglyceride rich lipoproteins (TRLs), very-low-density lipoprotein (VLDL), remnant particles (remnants particles (remnants of VLDL and chylomicrons), lipoprotein(a) (Lp(a)) and intermediate-density lipoprotein (IDL). The number of apoB particles, which mostly are LDL particles, is loglinearly associated with ASCVD risk [2]. Therefore, the number of apoB containing TRLs is similarly associated [3]. In addition, Lp(a) emerges as a third causal and independent risk factor [4]. These lipoproteins promote inflammation by upregulating multiple pathways, both locally and systemically. Many patients continue to suffer from CVD events, despite reaching guideline-recommended lipid target levels. Part of this residual risk is attributed to inflammation, and contemporary studies have shown that this inflammatory residual risk, as defined by C-reactive protein (CRP) plasma levels of 2 mg/L or above, is present in almost half of the patients [5–8]. Therefore, attenuating both lipoproteins and inflammation may be pivotal in further targeting ASCVD.
In this review, we will describe how LDL cholesterol (LDL-C), TRLs, and Lp(a) contribute to the inflammatory state observed at the subendothelial level, within the circulation and in immune cell production in atherogenesis.

**Lipids in endothelial dysfunction: the first step toward an inflammatory environment**

The endothelium constitutes the first-line defense mechanism shielding the subendothelial space from entering of harmful blood-born components. A low or disturbed blood flow pattern can lead to endothelial dysfunction [9,10]. By disintegration of the glycocalyx, the surface layer of the endothelial surface, increased vesicular trafficking and open endothelial junctions, lipoproteins up to 70 nm in diameter are able to migrate and to be retained in the intimal space [11]. Once retained in a highly oxidative environment, the LDL particles are modified by exposure to oxidizing agents and enzymes forming minimally modified LDL (mmLDL). The oxidized form of Lp(a), oxidized Lp(a) [oxLp(a)], is mainly formed within the bloodstream prior to migration.

Within the early process of atherogenesis, the key inflammatory process is monocyte recruitment and accumulation, instigated by endothelial activation. This increased monocyte recruitment is mediated via increased expression of endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin and P-selectin), cytokines (MCP-1 and IL-8) and pro-inflammatory receptors (toll-like receptor 2 [TRL2]) [12–14] on either endothelial cells and/or circulating monocytes.

**Low-density lipoprotein cholesterol**

Subendothelial retained mmLDL contributes to monocyte chemotaxis by its binding and stimulation of endothelial secretion of MCP-1, one of the key chemoattracting proteins for monocytes [15,16]. Other chemokines, including IL-8, are upregulated by mmLDL in human aortic endothelial cells (HAEC) [17]. In addition, the endothelial adhesion molecules E-selectin, P-selectin, ICAM-1 and VCAM-1 are upregulated by mmLDL, contributing to monocyte adhesion [18,19]. In addition, the CD40/CD40L signaling pathway, which plays an important role in atherogenesis including the expression of adhesion molecules, is upregulated by mmLDL [20].

**Triglyceride rich lipoproteins and remnants**

Triglycerides and TRLs promote endothelial activation by upregulation of both chemo- and adhesion cytokines. The role of TRLs in MCP-1 regulation is not fully elucidated. Although some in vitro studies showed that MCP-1 expression in monocytes and macrophages was downregulated upon TRL incubation, other studies have reported MCP-1 upregulation [21–24]. Chylomicron remnants prime monocytes toward the endothelium by a direct stimulation to secrete IL-8 [21].

Activation of the endothelium was observed in human endothelial cells upon incubation with TRLs, where the mRNA expression of VCAM-1, ICAM-1, P-selectin and E-selectin was increased [25]. Stimulation of isolated human monocytes with lipolysis products of VLDL, particularly free fatty acids, resulted in monocyte adhesion and transmigration with coincides with increased expression of integrin complexes including Mac-1 and VLA-4 (ligand of VCAM-1) [26]. In addition, the expression of pro-inflammatory cytokines TNF-α, IL-1β and IL-8 was increased.

**Lipoprotein(a)**

For Lp(a), it has been shown that, similar to mmLDL, it is able to bind MCP-1 [15]. Also, Lp(a) increases IL-8 expression in macrophages and human endothelial cells respectively [27,28]. Similar findings for several adhesion molecules were found in cultured human endothelial cells, where Lp(a) was demonstrated to stimulate the surface and mRNA expression of ICAM-1, VCAM-1 and E-selectin [29,30]. In addition, a Mac-1 dependent transendothelial migration (TEM) pathway was also shown to be upregulated by Lp(a), activating the pro-inflammatory transcription factor NF-κB [31].

Recently, the OxPL impact on arterial endothelial cells has been examined. Lp(a) stimulated human endothelial cells had a 2-fold increase in monocyte adhesion and a concomitant 5-fold increase in monocyte chemotaxis by its binding and stimulation of endothelial secretion of MCP-1, one of the key chemoattracting proteins for monocytes [15,16]. Other chemokines, including IL-8, are upregulated by mmLDL in human aortic endothelial cells (HAEC) [17]. In addition, the endothelial adhesion molecules E-selectin, P-selectin, ICAM-1 and VCAM-1 are upregulated by mmLDL, contributing to monocyte adhesion [18,19]. In addition, the CD40/CD40L signaling pathway, which plays an important role in atherogenesis including the expression of adhesion molecules, is upregulated by mmLDL [20].

**KEY POINTS**

- LDL-C, TRLs, and Lp(a) induce endothelial activation by upregulating chemokines and adhesion molecules.
- Lipoprotein oxidation and remnant formation potentiate foam cell formation and release of pro-inflammatory cytokines.
- Trained immunity has been proven to be effectuated by LDL-C and Lp(a) particles.
- Designing specific immune system targets raises the opportunity of attenuating the inflammatory component in atherosclerosis.

In this review, we will describe how LDL cholesterol (LDL-C), TRLs, and Lp(a) contributes to the inflammatory state observed at the subendothelial level, within the circulation and in immune cell production in atherogenesis.
increase in TEM compared to unstimulated endothelial cells [32]. This was accompanied by an increased expression of chemokines and cytokines which was linked to enhancement of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB3)–mediated glycolysis. These data illustrate the capacity of Lp(a), and in particular the oxidized phospholipids bound to apo(a), to provoke the activation of the vascular endothelium.

**Plaque development by monocyte foam cell formation and cholesterol deposition**

With endothelial dysfunction, monocytes are primed for adhesion and migration. Whilst retained, monocyte differentiate into macrophages and internalize the various lipoproteins to become foam cells. Subsequently, these macrophages reprogram in a pro-inflammatory phenotype [33].

**Low-density lipoprotein cholesterol**

mmLDL is the main source of lipid accumulation and foam cell formation [34]. One of the adhesion receptors controlling lipid uptake, CD146, intriguingly also has been shown to trigger macrophage retention [35].

Upon stimulation of the activated endothelium and lipid accumulation, macrophages are mainly polarized into two main phenotypes, a pro-inflammatory phenotype mainly characterized by CD11c and CD80/CD86 expression (referred to as classically activated or M1 macrophages) or anti-inflammatory phenotypes which may express CD206 (alternatively activated or M2a-d, M4, Mox, Mhem macrophages) [36]. The pro-inflammatory macrophages aggravate plaque progression as has been observed in murine and human models. These macrophages produce pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α and predominate in unstable plaques [36–38]. Anti-inflammatory macrophages on the other hand, can elicit plaque regression and produce anti-inflammatory cytokines [39].

Conversely, it has been demonstrated that pro-inflammatory macrophages are more prone to mmLDL for the foam cell formation in comparison with anti-inflammatory macrophages [40]. In addition, the degree of LDL oxidation influences the macrophage differentiation; a lower oxidation level was found to shift toward a more inflammatory macrophage phenotype [41]. For both phenotypes however, mmLDL does increase expression of pro-inflammatory cytokines, suggesting an overall pro-inflammatory effect on macrophages [42].

Circulating lipoproteins can serve as a source for intracellular cholesterol crystals [43]. Following an overload of intracellular cholesterol, cholesterol crystals are formed which trigger the NLRP3 inflammasome [44]. NLRP3 plays a central role in inflammation as it induces release of IL-1β and IL-18 and downstream cytokine IL-6. This complex is central in promoting a prolonged inflammatory response in atherogenesis [45]. Regarding endothelial activation, IL-1β has been shown to stimulate ICAM-1, VCAM-1 and MCP-1 [46,47].

Furthermore, it has been demonstrated that mmLDL can activate the NLRP3 inflammasome independently of cholesterol crystals [48]. In macrophages, CD36-dependent absorption of mmLDL resulted in cholesterol crystallization and release of IL-1β.

**Triglyceride rich lipoproteins and remnants**

Lipoprotein lipase (LPL) hydrolyzes TGL, which results in the formation of TRL remnants and fatty acids. Remnants, although larger than LDL particles, are much smaller compared to VLDL and can cross the endothelium. One remnant particle can carry up to 4 times more cholesterol compared to one LDL-C particle, which explains why up to 30% of the postprandial cholesterol load in the apoB fraction is transported by remnant particles. Once migrated into the subendothelial space, remnants have been shown to have a lower preponderance to egress compared to LDL particles, resulting in longer retention [49,50].

Apart from receptor mediated uptake, TRLs may also be taken up by macrophages in a receptor-independent manner suggesting a potent ability of TRLs in enhancing foam cell formation [51,52].

Remnants do not require oxidation or other modifications to be phagocytized by macrophages [53]. These combined characteristics allow TRLs and remnants, despite their lower plasma concentration compared with LDL particles, to potentially contribute more cholesterol to the vessel wall than LDL can [50,54].

In addition to the direct role, TRL also contributes to atherogenesis by the products of lipolysis, such as fatty acids [55]. Upon TLR stimulation, reactive oxygen species (ROS) and pro-inflammatory proteins are produced [56,57]. LPL is not only present on the endothelium but also resides within the atherosclerotic lesions itself, which induces a very pro-atherogenic milieu locally [58].

**Lipoprotein(a)**

In a rabbit model, it was shown that Lp(a) particles do migrate more easily into the subendothelial space compared to LDL particles [59]. This could
Lipids in circulating immune cells

**Lipid loading in circulating monocytes**

In the previous section we described the monocyte activating role of subendothelial cholesterol. However, recent studies have shown that activation of monocytes also takes place in the bloodstream by interacting with lipoproteins. High plasma serum LDL-C levels have a profound effect on circulating monocytes by being able to enrich them with cholesterol. These monocytes are more potent to adhere to and migrate through the endothelium [64,65]. In patients with elevated LDL-C levels, monocytes displayed greater intracellular lipid content as compared to healthy controls with lower LDL-C levels [66]. Furthermore, CCR2 expression, the MCP-1 ligand, was increased which coincided with a 1.6-fold increased migratory capacity.

Monocytes have also been shown to incorporate lipid particles in response to elevated triglyceride levels, especially during the postprandial rise [67,68]. During this hypertriglyceridemia, monocytes internalized TRLs through the LPR-1 receptor. This was accompanied by CD11c and VCAM-1 upregulation, further contributing to monocyte recruitment [64,68]. In addition, fatty acids, produced by local lipolysis, can increase lipid droplet accumulation [69].

**Innate immune system – trained immunity**

The innate immune system has been widely considered to lack immunological memory. However, recent studies suggest that triggering the innate immune system can induce a sustained pro-inflammatory response which is known as ‘trained immunity’ [70,71]. Driven by epigenetic and metabolic reprogramming, it contributes to atherosclerosis by inducing pro-inflammatory cytokines and a monocyte phenotype.

In atherosclerosis, this phenomenon has been observed for both mmLDL and Lp(a) on a cellular level [62,72,73]. Brief exposure of isolated human monocytes to mmLDL induced prolonged expression of pro-inflammatory proteins including IL-6, IL-18 and MCP-1 [72]. In two recent studies, mmLDL priming of human monocytes and endothelium cells promoted metabolic reprogramming and epigenetic modifications to increase an innate immune cell phenotype, characterized by increased production of pro-inflammatory cytokines such as TNF-α and IL-6 [74,75*].

The relevance of lipid-induced trained immunity was shown in a murine model [76]. LDL-receptor knock-out mice received a Western-type diet which resulted in monocyte activation as measured by CD86 expression. Mice were subsequently fed with a chow diet and after four weeks, monocytes were still found to be activated.

In line with these results are the observations of a study conducted in patients with high Lp(a) levels [62]. In these patients, isolated monocytes showed increased production of TNF-α and IL-6 upon TLR stimulation which persisted up to 7 days ex vivo and was particularly effectuated by OxPLs carried on Lp(a).

**Adaptive immune system**

As shown in human and murine studies, T-cell are the predominant leukocyte cells in plaque lesions [77,78]. A wide variety of T-cell subsets modulate the inflammatory response by producing either atherogenic (IL-17, IFN-γ and TNF-α) or atheroprotective (IL-10) cytokines [79]. Distinct roles for pro-atherosclerotic Th1 cells and anti-atherogenic regulatory T (Treg) cells have been observed [80*]. T-cells are activated by peptides presenting on all nucleated cells or antigen-presenting cells (APC) [81]. Peptide epitopes of mmLDL and apoB are the main driver of a T-cell mediated response [80*]. T-cells derived from human atherosclerotic plaques are capable of recognizing mmLDL presented by APCs [82]. ApoB peptides were shown to be another recognizing signal in murine and human cells, mainly in Tregs [83]. This indicates LDL as a self-antigen and a potential driver of an autoimmune response. However, whether lipoproteins have an overall stimulating or attenuating inflammatory effect remains to be elucidated.

**Increased production of immune cells**

**Bone marrow**

Despite significant immune cell signaling and deposition at the local level of the endothelium, a
substantial role in atherogenesis is attributable to a systemic pro-inflammatory state [84–86].

In experimental models, acute events such as stroke and myocardial infarction elicit elevated monocyte and other immune cell levels [85,87]. Accordingly, in humans, an acute myocardial infarction can induce both bone marrow and remote atherosclerotic activity [84].

However, since the circulation of immune cell ranges up to only a few days, a pro-atherogenic effect of elevated monocytes implies persistent systemic immune cell mobilization. Support for this notion has been found in mice, where after induction of myocardial infarction, an increased monocyte recruitment from bone marrow niches persisted for several months [85].

In addition, increased production and mobilization of immune cells in bone marrow sites are associated with the progression rate of atherosclerosis [88–90]. It is also established that circulating monocyte levels are an independent risk factor for ASCVD [91].

In regard to dyslipidemia, hypercholesterolemia in mice promotes mobilization of bone marrow monocytes by induction of extramedullary hematopoeisis [92–94]. Both mmLDL and LDL are able to stimulate myeloid proliferation [95,96].

CONCLUSION AND CLINICAL IMPLICATIONS

Lipids and inflammation are key components in atherogenesis [97,98]. Here, we show the profound effects of dyslipidemia on a plethora of inflammatory pathways. Initiating at prone endothelial sites, the immune response extends from atherosclerotic plaques to a systemic response.

Although effective lipid lowering therapies significantly lower the ASCVD burden, current therapies do not attenuate the residual inflammatory risk. In posthoc analyses of the FOURIER trial, it was shown that patients with a pro-inflammatory phenotype, characterized by high CRP levels, were at increased risk for future ASCVD events compared to participants with normal CRP levels, despite having achieved their LDL target levels [99]. In large clinical trials it has been shown that anti-inflammatory agents lower the risk for CVD. In the Canakinumab Anti-inflammatory Thrombosis Outcome study (CANTOS) trial, the monoclonal antibody directed against IL-β canakinumab significantly lowered major adverse cardiovascular events [100]. This beneficial effect came at a price of increased risk for (fatal) infections and canakinumab has not been further developed for widespread use. In contrast, the LoDoCo2 trial which investigated colchicine in patients with chronic coronary disease, showed a beneficial effect without an increase in fatal infections [101**].

Despite its challenges, targeting inflammation appears to be successful in reducing CVD risk. By combining lipid-lowering and anti-inflammatory therapy, specific modulation should benefit patients with a residual inflammatory risk in the future.

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