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REVIEW

The role of high-density lipoprotein in the regulation of the immune response: implications for atherosclerosis and autoimmunity

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Summary

Inflammation and immune dysfunction have been increasingly recognized as crucial mechanisms in atherogenesis. Modifications in cell lipid metabolism, plasma dyslipidaemia and particularly low high-density lipoprotein (HDL) levels occur both in atherosclerosis and in autoimmune rheumatic diseases (which are strongly associated with an increased risk of atherosclerosis), suggesting the presence of a crucial link. HDL, the plasma lipoprotein responsible for reverse cholesterol transport, is known for its several protective effects in the context of atherosclerosis. Among these, HDL immunomodulatory effects are possibly the less understood. Through the efflux of cholesterol from plasma cell membranes with the consequent disruption of lipid rafts and the interaction with the cholesterol transporters present in the plasma membrane, HDL affects both the innate and adaptive immune responses. Animal and human studies have demonstrated a predominance of HDL anti-inflammatory effects, despite some pro-inflammatory actions having also been reported. The HDL role on the modulation of the immune response is further suggested by the detection of low levels together with a dysfunctional HDL in patients with autoimmune diseases. Here, we review the current knowledge of the immune mechanisms of atherosclerosis and the modulatory effects HDL may have on them.

KEYWORDS

atherosclerosis, high-density lipoprotein, immune response, lipid metabolism

INTRODUCTION

Cell lipid metabolism has been increasingly recognized to modulate the immune response in atherosclerosis and in autoimmune diseases.[1] It is well established that hyperlipidaemia, especially increased levels of low-density lipoprotein (LDL), is associated with an increased atherosclerosis risk whilst also contributing to the pathogenesis of autoimmune

Abbreviations: ABCA1, adenosine triphosphate binding cassette transporter A1; ABCG1, adenosine triphosphate binding cassette transporter G1; ApoA-I, apolipoprotein A-I; ATF3, activating transcription factor 3; BAFF, B-cell-activating factor; BCR, B-cell receptor; CETP, cholesteryl ester transfer protein; DC, dendritic cell; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; IRF1, interferon regulatory factor 1; JNK, Janus kinase; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; NK, natural killer; LN, lymph node; LPS, lipopolysaccharide; LTA, lipoteichoic acid; LXR, liver X receptor; MCP-1, monocyte chemo-attractant protein 1; NADPH, nicotinamide adenine dinucleotide phosphate; NF-kB, factor nuclear kappa B; NLRP3, NOD-like, LRR-like and pyrin domain-containing protein 3; oxLDL, oxidized low-density lipoprotein; PMN, polymorphonuclear; PON, paraoxonase; PAFAH, platelet-activating factor-acetyl-hydrolase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; RA, rheumatoid arthritis; RCT, reverse cholesterol transport; S1P, sphingosine-1-phosphate; SAA, serum amyloid A; SR-BI, scavenger receptor class B type I; STAT1, signal transducer and activator 1; TACI, transmembrane activator and calcium-modulating cyclophilin ligand interactor; TCR, T-cell receptor; TGF-β, transforming growth factor-β; TNF, tumour necrosis factor; TLR, Toll-like receptor.

diseases.[2] In fact, lipids are an important source of energy along with being membrane components indispensable for cell proliferation and migration, membrane expansion and other functions in the immune cells.[3]

High-density lipoprotein (HDL) is the plasma lipoprotein responsible for reverse cholesterol transport (RCT), which is associated with a protective role in atherosclerosis through reducing the lipid burden of atherosclerotic plaques.[4,5] In addition to its role in cholesterol efflux, other properties are attributed to HDL: inhibits LDL oxidation,[6] ameliorates endothelial function,[7] decreases monocyte adhesion to the endothelium and has anti-thrombotic and anti-inflammatory properties.[8,9] As such, HDL seems to be a crucial link between inflammation, immune activation and atherosclerosis. However, the consequences of the HDL-associated benefits have not been clear in clinical trials. This raises the question of HDL function or quality versus HDL quantity. HDL proteomic studies revealed that variations in protein cargo can greatly influence HDL function. The study of the complex effects of HDL on the immune response in parallel with the increasing knowledge of the HDL constituents and their functions may contribute to better understand the pathogenesis of atherosclerosis in inflammatory diseases and how this lipoprotein relates to it. In order to put into context the different mechanisms involved, we reviewed the current information on HDL immunomodulatory effects and the atherosclerosis immune-associated pathways.

HDL, IMMUNE FUNCTION AND ATHEROSCLEROSIS

HDL structure and function

HDL is composed of a cholesterol core enriched with cholesterol esters and triglycerides and a surface lipid bilayer containing free cholesterol, phospholipids and proteins. The HDL structure is modified during its maturation from small to large particles. Being the densest plasma lipoprotein, HDL is highly heterogeneous in size, charge and composition. The different proteins in HDL constitute more than half of its mass and render a high complexity to the HDL structure. The main HDL apolipoprotein is apolipoprotein A-I (ApoA-I), which makes up to approximately 70% of HDL protein. HDL particles also carry enzymes such as paraoxonase (PON), platelet-activating factor-acetyl-hydrolase (PAFAH), lecithin cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP).[10]

HDL mediation of cholesterol efflux is one of the main mechanisms by which HDL modulates the immune response. The lipid organization in the plasma membrane determines the constitution of micro-domains called lipid rafts, rich in glycosphingolipids and cholesterol, that are more ordered and less fluid than the surrounding membrane. Many functional proteins (including B- and T-cell receptors) are predominantly found in lipid rafts, which act as signalling platforms by colocalizing various signalling components.[11]

Cholesterol efflux to HDL occurs at higher rates through the adenosine triphosphate binding cassette transporters A1 (ABCA1) and G1 (ABCG1). The first complexes with ApoA-I to produce preβ-migrating HDL or very-small HDL particles, and the second promotes further lipidation to constitute mature HDL particles. Cholesterol efflux occurs also through the scavenger receptor class B type I (SR-BI) and through aqueous diffusion.[12]

In macrophages, the cholesterol efflux to HDL mediated by ABCA1 and ABCG1 limits the cholesterol availability to constitute lipid rafts, which inhibits Toll-like receptors (TLRs) trafficking mediated by MyD88, an adaptor protein for all TLRs (except TLR3).[13] Activation of MyD88 after TLR ligation induces the factor nuclear kappa B (NF-kB) pathway. Mouse models deficient for ABCA1 and ABCG1 were shown to accumulate cholesterol in peritoneal macrophages and have increased inflammatory responses to TLR agonists.[14] In T cells, the promotion of cholesterol efflux to HDL through ABCA1 and ABCG1 by liver X receptors (LXRs) is associated with a decrease in proliferation.[15] Mouse models of atherosclerosis lacking SR-BI showed an increased expression of pro-inflammatory cytokines, namely interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and IL-1-β.[16] At the cellular level, SR-BI regulates macrophage conversion to the inflammatory M1 form versus the anti-inflammatory M2 phenotype. SR-BI also regulates inflammation mediated by macrophages by reducing NF-kB, P38 and Janus kinase (JNK) signalling.[17] In humans, genomic analysis studies suggest that SR-BI decrease the risk of cardiovascular disease.[18]

Some of the HDL proteins are directly involved in the modulation of the immune response. These include ApoL-1, sphingosine-1-phosphate (S1P), immunoglobulins and components of the complement system. ApoL-1 has microbicidal activity through the formation of pores in the lysosomal membranes with the consequent lysis of trypanosomes, which confers anti-parasitic properties to HDL.[19] S1P involved in several HDL is the main sphingolipid in HDL, and HDL is its principal transporter in plasma.[20] S1P binds to cells through its own cell surface receptors, contributing to immune cell trafficking and endothelial barrier function.[21] ApoM, a negative acute-phase protein, is the carrier of S1P in HDL. S1P is responsible for many of the HDL biological effects that are not related to reverse cholesterol transport.[22] These include immunological effects: inhibition of TNF-α-induced adhesion molecule expression in endothelial cells,[23] induction of long pentraxin 3 [24] and transforming growth factor-β (TGF-β) in endothelial cells,[25] inhibition of TLR2 activation in

macrophages,[26] reduction in pro-inflammatory and increase in anti-inflammatory cytokine production by dendritic cells (DCs),[27] migration of T lymphocytes from lymphoid organs [28] and control of T-cell lineage determination.[29] Acute-phase proteins, such as serum amyloid A (SAA), are also abundant in HDL, reinforcing its role in the immune response.[30]

HDL effects on immune modulation can be relevant not only to the pathogenesis of atherosclerosis but also to other inflammatory conditions. Experimental studies showed that low HDL increases the risk of infection. In humans, low HDL levels inversely correlate with the severity of sepsis.[31] However, very high HDL levels were also associated with higher risk of infection in a population study,[32] which is still puzzling. In population cohorts, low HDL levels are associated with increased risk of infection-related hospitalizations,[33] particularly with bacterial infections. It is attributed to the capacity of HDL to decrease the pathogenicity of bacteria by limiting endotoxin toxicity, as HDL is a chelator of lipopolysaccharide (LPS) from Gram-negative and lipoteichoic acid (LTA) from Gram-positive bacteria. The clearance of HDL-LPS complex in mediated by SR-BI.[34] HDL also limits the activation of the innate immune system by the pathogen and modulates the adaptive response.[35] In addition, HDL provides cholesterol for glucocorticoid synthesis after interaction with SR-BI,[36] which can influence the outcome in the context of sepsis.

In autoimmune rheumatic diseases, plasma lipoprotein profiles are commonly altered, with several studies reporting a decrease in HDL plasma concentrations.[37] Low HDL levels are associated with an increased risk of autoimmune disease, both in animal and in human studies. LDLR-/-apoA-I-/- mice showed enlarged peripheral lymph nodes (LNs) and spleens, compared with LDLR-/- mice, and increased proliferation of LN cells that showed an autoimmune phenotype.[38,39] SR-BI-deficient mice developed a systemic autoimmune disorder,[40] which is probably related to the consequent modifications in HDL, which is less capable of inhibiting lymphocyte proliferation.[41,42] In the Copenhagen General Population Study and the Copenhagen City Heart Study, a low HDL level was associated with an increased risk of autoimmune disease. However, in the Copenhagen City Heart Study very high HDL levels were also associated with autoimmune diseases,[32] suggesting that function and not only quantity could be at play.

Low HDL levels are also one of the factors contributing to the high prevalence of atherosclerotic plaques and cardiovascular disease among individuals with autoimmune rheumatic diseases.[43] However, mendelian randomization genetic studies suggest that HDL functionality (mainly related to cholesterol efflux capacity) may be more important than HDL plasma concentration in the pathogenesis of cardiovascular diseases.[44] Several studies in autoimmune rheumatic diseases demonstrated that HDL dysfunction is frequently present.[45-47] In rheumatoid arthritis, HDL-mediated cholesterol efflux is impaired in patients with active disease. In systemic lupus erythematosus, the cholesterol efflux mediated by ABCA1 and ABCG1 is compromised despite not correlating with disease activity.[46] Additionally, HDL from patients with SLE and rheumatoid arthritis (RA) was shown to be pro-inflammatory and associated with increased levels of oxidized LDL (oxLDL).[48] HDL from patients with ankylosing spondylitis and psoriasis also showed to have several functional modifications.[49,50] Interestingly, the HDL functional properties are usually independent from its serum levels and so the role of HDL dysfunction in the pathogenesis of autoimmune rheumatic diseases is still not completely understood. There are many factors leading to modifications in HDL function in the context of inflammation. HDL can be modified by the binding of acute-phase proteins, complement factors and other inflammatory proteins.[48,51] The humoral response against HDL components, associated with increased cardiovascular risk, may also be an important cause of HDL dysfunction.[52,53] In inflammatory conditions, HDL loses antioxidant capacity consequent to a decreased content of PON1 [54] and increased levels of PAFAH.[55,56] This impairment of the antioxidant capacity is associated with an increase in oxLDL levels. A decrease in ApoM also occurs, thus affecting the function of S1P.[57] As a result, dysfunctional HDL loses anti-inflammatory properties and can promote inflammation.[58]

The effects of HDL on inflammation and atherosclerosis

The cholesterol content of plasma membranes is crucial to immune cell function and can be highly influenced by the presence of HDL. Intracellular cholesterol, in the form of oxysterols, is also relevant as it binds to the LXRs (LXRα and LXRβ) and participates in the regulation of various pathways linked to inflammation and immune response.[15] LXRs also promote the expression of the cholesterol transporters ABCA1 and ABCG1.[59]

Lipid metabolism can affect the innate immune response, mainly through modulation of TLR-dependent macrophage and adaptive immune responses, namely T-cell proliferation and differentiation into Th17 and Treg cells.[60] The increase in lipid rafts resultant from cholesterol accumulation in T cells predisposes to higher inflammatory reactivity through the facilitation of TCR contact with costimulatory receptors in lipid rafts.[61] Membrane cholesterol also influences the immune synapse formation through variations in lipid raft abundance and membrane fluidity.[62] In B cells, lipid rafts are thought to promote BCR signalling [63] and membrane cholesterol influences BCR endocytosis.[64]

The increasing number of studies on the HDL immunomodulatory effects shows a wide variety of mechanisms involved. However, the use of different methodologies adds complexity to the analysis of an interpretation of these studies. The available evidence from animal and human studies, frequently contradictory, will be reviewed separately and is summarized in Figure 1.

Immune effects of HDL in animal studies

Mouse studies have shown several anti-inflammatory effects of HDL, mainly on endothelial cells and cells of the innate immune system. Mice overexpressing ApoA-I had lower NF-kB signalling (IL-6, TNF-α, monocyte chemoattractant protein 1 – MCP-1) in endothelial cells, in response to palmitate.[65] However, conflicting results arose from other studies showing no influence of HDL in NF-kB in mouse macrophages [66] or activation of the protein kinase C (PKC)-NK-kB/signal transducer and activator 1 (STAT1) – interferon regulatory factor 1 (IRF1) axis due to cholesterol depletion in the presence of HDL in murine and human primary macrophages.[67] The anti-inflammatory effects of HDL on mouse macrophages seem to be related to a decrease in lipid rafts consequent to the cholesterol efflux from cells, a reduction in reactive oxygen species generation through its antioxidant properties and an inhibition of TLR4 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 translocation into the lipid rafts.[68] Cholesterol accumulation in mouse myeloid cells activates the NOD-like, LRR-like and pyrin domain-containing protein 3 (NLRP3) inflammasome,[69] which is linked to the HDL-induced reduction in polymorphonuclear (PMN) leucocyte infiltration in the atherosclerotic plaque.[70,71] In fact, mice lacking the cholesterol transporters ABCA1 and ABCG1 showed leucocytosis and a myeloproliferative disorder, which resolved after bone marrow transplantation into transgenic mice with high levels of HDL,[72] demonstrating that cholesterol

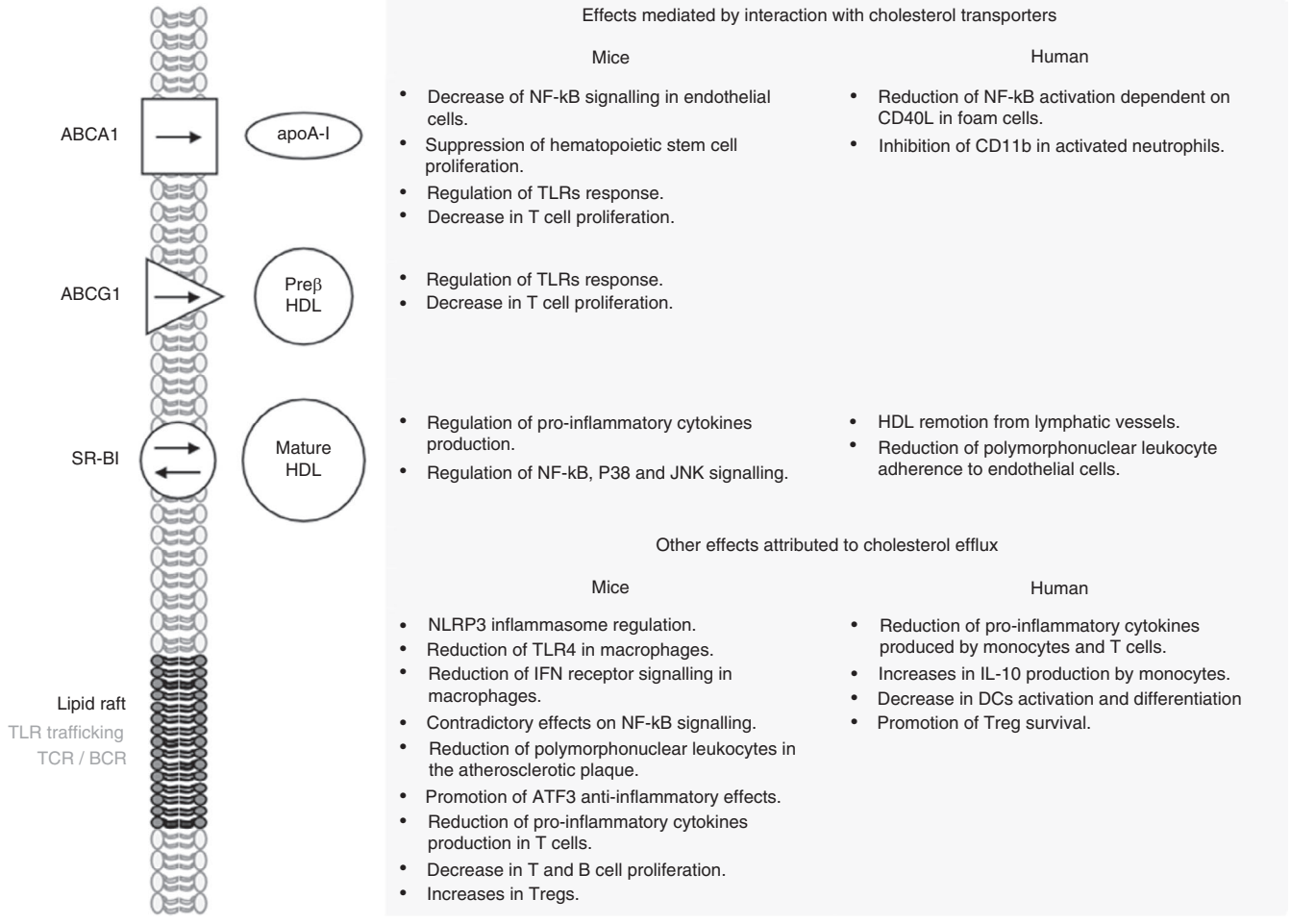

FIGURE 1 HDL immune effects mediated by cholesterol efflux. The different cholesterol efflux pathways may have diverse effects on immune response. However, in many studies the specific involved pathway was not determined. Lipid raft disruption in consequence of cholesterol efflux is related to many of the HDL effects on immune response. DC: dendritic cell. TLR: Toll-like receptor. NLRP3: nucleotide binding domain leucine-rich repeat receptor protein 3. NF-kB: nuclear factor kappa B. JNK: Janus kinase. IFN: interferon. ATF3: activating transcription factor 3

transporters and HDL suppress haematopoietic stem cell proliferation. ABCA1 has additional anti-inflammatory effects (that rely on ApoA-I ligation but are independent of cholesterol efflux) through the activation of the JAK2/STAT3 pathway, which suppresses the production of pro-inflammatory cytokines.[73] HDL was also reported to promote activating transcription factor 3 (ATF3)-mediated anti-inflammatory effects at supra-physiological concentrations in mouse macrophages,[66] but this effect was not observed when treating cells with HDL at physiological concentrations nor in human macrophages.[74] HDL also exerts pro-inflammatory effects in mouse macrophages. Fotakis *et al* verified that the infusion of reconstituted HDL into atherosclerotic mice induces anti-inflammatory effects related to reduced TLR4 levels and reduced interferon (IFN) receptor signalling, and late pro-inflammatory effects due to a modified endoplasmic reticulum stress response in the context of extreme cholesterol depletion.[75] However, in lesion macrophages the anti-inflammatory effects predominate.

With respect to the adaptive immune response, the capacity of moue antigen-presenting cells to activate T cells is reduced by HDL and ApoA-I through cholesterol efflux and lipid raft disruption [76] and by inhibiting the production of some inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, MIP-1 and MIP-1β).[77] Increased levels of plasma membrane cholesterol have been reported to promote the inflammatory T helper response.[78] Mouse splenocytes stimulated with TCR or BCR ligands showed a decreased T- and B-cell proliferation rate in the presence of HDL.[40] In another study, ApoA-I was shown to decrease lymph node immune cells and increase Tregs in LDLr -/-, apoA-I -/- mice fed with an atherogenic diet.[39]

Immune effects of HDL in human studies

Studies with human cells showed that HDL and ApoA-I reduce PMN leucocyte adherence to endothelial cells in vitro, through blocking LPS activity and modifying CD11b/CD18 on PMN,[79] and also protect against the neutrophil respiratory burst.[80,81] The ApoA-I inhibitory effect on CD11b of activated neutrophils is mediated through ABCA1, and the HDL effects are mediated by SR-BI. SR-BI assumes a relevant role in cholesterol efflux from macrophages as it mediates anti-inflammatory signalling in macrophages and endothelial cells [82] and mediates the efferocytosis of apoptotic cells.[83] Endothelial cell SR-BI mediates the uptake and transcytosis of HDL in lymphatic vessels to effectively remove cholesterol from the peripheral tissue, thereby raising the possibility that lymphatic SR-BI may also reduce the foam cell formation in atherosclerotic lesions.[84]

HDL- and ApoA-I-mediated cholesterol efflux results in the decrease in lipid raft abundance. In macrophages, the reduction in available lipid rafts correlates with the decrease in CD11b activation. These results are corroborated by the observation that the infusion of reconstituted HDL in patients with peripheral vascular disease attenuates neutrophil activation.[85] There is also a negative correlation between HDL and leucocyte levels in patients with coronary artery disease.[86] However, HDL from healthy young individuals demonstrated to increase the proliferation of stimulated T cells.[87] In fact, the effects of HDL on lymphocyte proliferation are not clarified, with conflicting results arising from different studies. It is very likely that variations in HDL function, concentration and lipid composition can exert different effects. Apart from the effects of HDL on immune cell proliferation, other aspects of the immune response have also been studied in human cells and patients. HDL and ApoA-I inhibit the expression of inflammation markers, increase IL-10 production and promote spreading in primary human monocytes.[88,89] In human macrophages infected with mycobacteria, HDL reduced TNF-α production through the downregulation of TLR2 and the consequent suppression of the NF-kB, p38 and JNK mitogen-activated protein kinase pathways. In these macrophages, HDL also reduced the production of IL-6, IFN-γ and IL-4 in a dose-dependent manner and increased the production of IL-10.[74] ApoA-I inhibited the soluble CD40L-stimulated activation of NF-kB in human THP-1 macrophage-derived foam cells, which seems to depend on the interaction with ABCA1.[90] HDL and ApoA-I also decrease the production of inflammatory cytokines (TNF-α, IL-1β) by human T-cell lines.[91] The interaction between antigen-presenting cells and T cells in human peripheral blood mononuclear cells (PBMCs) was shown to be affected by ApoA-I as it may decrease DC activation and differentiation and reduce the production of IFN-γ by T cells in response to DC interaction.[92] HDL also affects the human DC ability to induce Th1 response upon TLR stimulation.[93] Furthermore, HDL binds stimulated T lymphocytes, through ApoA-I interaction with cell surface factors, and inhibits the contact-mediated activation of monocytes with a consequent lower production of TNF-α and IL-1β.[91]

Regarding the T-cell repertoire, HDL seems to play an essential role in Treg modulation. Tregs differ from other lymphocytes in its metabolic requirements, as they rely mostly on lipids as the source of energy to survive.[94,95] Treg counts increase in the presence of HDL at physiological concentrations, in a dose-dependent manner, with a decrease in the percentage of apoptotic Treg, suggesting that HDL promotes the survival of human Treg. This effect was not seen in other T-cell populations.[96] In a study that showed an increase in the frequency and absolute numbers of Treg in healthy individuals taking statins, the increase in HDL levels showed a positive correlation with the Treg counts.[97]

In summary, both HDL and its main apolipoprotein ApoA-I decrease inflammation mediated by monocytes/

macrophages and neutrophils. The existent studies point TLR signalling and NF-kB pathways as the principal targets in the innate immune system. In the adaptive immune system, HDL affects T-cell proliferation, increases the prevalence of Treg and modulates cytokine production. Overall, the disruption of lipid rafts seems to be crucial to the modulation of the immune response by HDL, bearing in mind that HDL can also exert pro-inflammatory effects under specific circumstances.

IMMUNE MECHANISMS OF ATHEROSCLEROSIS

Atherosclerosis, a leading cause of mortality worldwide, is a chronic inflammatory disease of large- and medium-sized arteries with an important immunological component.[98] For many years, it was believed that atherosclerosis was simply due to passive accumulation of cholesterol in the vessel wall. In fact, endothelial dysfunction and inflammation are early pro-atherogenic processes and it is becoming increasingly clear that innate and adaptive immune responses play important roles in atherogenesis. The atherosclerotic plaque is characterized by an accumulation of lipids in the artery wall, together with infiltration of immune cells and the formation of a fibrous cap by vascular smooth muscle cells. However, the interaction between lipid mediators and the immune system in the context of atherosclerosis is not completely understood.

One of the most well-known interactions between lipoproteins and the immune response is the activation of the innate immunity through the detection of danger signals, such as oxLDL, by sensor proteins in the cytoplasm of innate immune cells.[99] These sensor proteins are constituents of inflammasomes that are responsible for a rapid inflammatory response through the cleavage of IL-1β and IL-18 into the pro-inflammatory active forms. NLRP3 is the inflammasome associated with chronic inflammation in atherosclerosis [100] and is also activated by the TLR4 downstream signalling. [101] In a normal artery wall, resident DCs promote tolerization to antigen by silencing T cells. However, danger signals may activate DCs, leading to a switch from tolerance to the activation of adaptive immunity. In fact, DCs are clustered in arterial branch points, where they colocalize with T cells and macrophages.[102] Macrophages assume a relevant role in the development of the atherosclerotic lesions through the uptake of oxLDL, mainly by SRs, and then transforming themselves into foam cells.[103] OxLDL also binds to TLR2 and TLR4, activating the inflammasome and inducing the excretion of pro-inflammatory cytokines.[104] During inflammation, oxLDL can be internalized by macrophages independently of SRs, and macrophages can polarize to a M1 phenotype, with the suppression of the lipid sensors LXR and peroxisome proliferator-activated receptor (PPAR).[105] These mechanisms perpetuate the inflammatory response in the vessel wall, with the consequent activation of a type 1 T helper (Th1) response,[106] which often become chronic.[107]

In the atherosclerotic lesions of mouse models, there is a macrophage/T-cell ratio of approximately 4:1 to 10:1.[108] Most T cells in those atherosclerotic plaques are CD4+, and the remaining are CD8+ T cells. The CD4+ T cells predominantly have a Th1 profile that activate macrophages and increase pro-inflammatory cytokines, such as IFN-γ, TNF-α and IL-2. IFN-γ, the main pro-inflammatory cytokine involved, increases the expression of other inflammatory cytokines, such as IL-1.[109] Th2, Th17, regulatory T cells (Treg) and natural killer (NK) T cells are also present, but whilst the Th1 profile is associated with atherosclerosis progression, the role of the other T-cell subsets is less clear. In fact, the role of Th2 cells is controversial [110-112] and the Th17 impact seems to be context-dependent: if IL-17 expression is accompanied by high levels of IFN-γ, it is atherogenic, but in the presence of IL-10, it is protective.[113]

Tregs are a subset of CD4+ T cells that protect against atherogenesis through the inhibition of pro-inflammatory T cells [114] and the suppression of macrophages and endothelial cell activation. The principal inhibitory cytokines secreted by Treg are IL-10 and TGF-β.[115] Hypercholesterolaemia was shown to impair Treg, but not the effector T-cell accumulation in lesions, thus contributing to the decrease in Treg:Th1 cell ratios in atherosclerotic lesions.[116,117] A negative correlation between Treg and Th17 cells was also found in patients with unstable carotid artery lesions.[118] Additionally, Tregs from patients with acute coronary syndrome were shown to have a reduced suppressive function.[119]

The role of B cells in atherosclerosis is related to both the humoral and the modulation of cellular responses with anti-atherogenic and pro-atherogenic effects. B1 cells produce naturally occurring IgM antibodies directed to oxidation-specific epitopes that neutralize them and limit endothelial activation and foam cell formation. In contrast, B2 cells produce IgG antibodies that are pro-atherogenic through the formation of immune complexes (e.g. with oxLDL) and promotion of macrophage inflammatory responses.[120] IgE antibodies are also pro-atherogenic by stimulating macrophages and mast cells.[121] The role of IgA in atherosclerosis is less understood, but it was reported to have a positive correlation between IgA antibodies and cardiovascular disease.[122] Additionally, B cells can produce pro-atherogenic and anti-atherogenic cytokines.[123,124] Studies on B-cell-mediated regulation of immune responses showed that B-cell depletion decreases T-cell activation. However, blocking the B-cell-activating factor (BAFF) seems to worsen atherosclerosis in mouse models, as the ligation to its main receptor (BAFFR) leads to B2 cell differentiation and increases IgG levels in mice. Interestingly, the ligation of BAFF to its alternative receptor (TACI) decreases the TLR9-interferon regulatory

factor responses in macrophages, which explains its anti-atherogenic net effect.[125] Indeed, the pharmacologic CD20 blockade showed to be atheroprotective, partly because of a selective depletion of IgG-producing B cells with an incomplete depletion of IgM-producing B cells and partly through an increase in BAFF levels.[126]

The reported mechanisms were observed mainly in studies using mouse models. In humans, cells in atherosclerotic plaques also express TLR family members. However, the role of TLRs in the pathogenesis of atherosclerosis seems to be different among human studies: in one study, loss-of-function mutations in the TLR4 gene decreased cardiovascular disease, but subsequent studies did not show a protective effect of a hyporesponsive TLR4 allele.[127] The role of the different immune cells in atherosclerosis may also vary between mice and humans. In the human atherosclerotic plaque, polymorphonuclear leucocytes are fewer than in mice; DCs increase in atherosclerotic lesions, both in mice and in humans [128]; T cells in the human atherosclerotic plaque predominantly exhibit a Th1 cell-associated cytokine secretion pattern, although with less degree of polarization than in mice.[129] The role of deregulated immune response in the pathogenesis of human atherosclerosis is also evident in inflammatory and autoimmune diseases in which atherogenesis is accelerated. Several infections have been implicated as triggers to inflammation in the pathogenesis of atherosclerosis. Some of the implicated infectious agents are Epstein–Barr virus, herpes simplex virus, cytomegalovirus, *Helicobacter pylori* and *Chlamydia pneumoniae*.[130] Chronic infectious diseases, such as periodontitis or bronchitis, also accelerate atherosclerosis. In patients with autoimmune rheumatic diseases, accelerated atherosclerosis and cardiovascular events are an important cause of morbidity and mortality. The autoimmune rheumatic diseases most commonly associated with atherosclerosis progression are rheumatoid arthritis, SLE and Sjogren's syndrome, although many other diseases have also demonstrated an increase in atherosclerosis. Antibodies against oxLDL were reported in higher titres in the serum of patients with autoimmune rheumatic diseases, in comparison with controls.[131] Other autoantibodies have also been implicated in the pathogenesis of atherosclerosis in the context of autoimmune rheumatic diseases, such as anti-cardiolipin and ant-2GPI in the context of SLE.

Chronic inflammation, with immune cell infiltration of the vessel, is one of the main contributors to atherosclerosis. In addition to cellular immunity, humoral immunity with antibodies directed to HDL epitopes is also implicated in the pathogenesis of atherosclerosis.

CONCLUSIONS

HDL effects in the regulation of the immune response are complex and probably context-dependent, protecting from excessive inflammation without compromising the immune response to pathogens. HDL functionality is thus far beyond reverse cholesterol transport, with an effect in the immune system that is closely related to the lipid metabolism ongoing in the immune cells. The knowledge of atherosclerosis-associated immune mechanisms in parallel with the knowledge of lipid metabolism and the HDL impact on the immune response may show a different perspective into the underlying pathways present in this complex disease. Among the studied HDL immunomodulatory effects, the decrease in monocytes/macrophages and neutrophil activation, modulation of cytokine production and promotion of Treg population counteract some of the immune mechanisms thought to be implicated in atherosclerosis. The effects of HDL on the Treg population also suggest a role for HDL in the regulation of immune tolerance mechanisms, which deserve to be investigated in the context of autoimmune diseases. This will hopefully give more clues towards improving the treatment of both the atherosclerotic cardiovascular disease and the autoimmune diseases with an increased risk of atherosclerosis.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

M.F.N. conducted the literature search and wrote the paper. J.B. and J.D.A. reviewed the paper.

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