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Review · **Open Access** ·

High density lipoproteins and atherosclerosis: emerging aspects

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Abstract

High density lipoproteins (HDL) promote the efflux of excess cholesterol from peripheral tissues to the liver for excretion. This ability is responsible for the most relevant anti-atherogenic effect of HDL. The ability of HDL to promote cholesterol efflux results also in the modulation of a series of responses in the immune cells involved in atherosclerosis, including monocyte-macrophages, B and T lymphocytes. Furthermore, during inflammation, the composition of this class of lipoproteins varies to a large extent, thus promoting the formation of dysfunctional HDL. The aim of this review is to discuss the emerging role of HDL in modulating the activity of immune cells and immune-inflammatory mediators during atherogenesis.

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1 Introduction

Atherosclerosis and its clinical manifestations are the leading causes of morbidity and mortality in the Western World. For decades, atherosclerosis has been considered only as a disease associated with dyslipidemia.[1]

More recently, both preclinical and clinical research has provided important evidence that inflammation and immune response are integral components of atherogenesis. Therefore, atherosclerosis is now considered a chronic immune-inflammatory disease characterized by the presence of immune cells during all stages of the progression of atherosclerotic plaque.[2]

During the early phase of the disease, an endothelial injury initiates the entire process. According to the "oxidation hypothesis," endothelial dysfunction causes the retention of low-density lipoproteins (LDL) in the intima where they undergo oxidative modifications.[1] These modified lipids induce the expression of adhesion molecules, chemokines, proinflammatory cytokines, and other mediators of inflammation. Then, leucocytes, penetrated into subendothelial space, actively participate to perpetuate local inflammatory response.

The monocytes-macrophages express scavenger receptors for modified lipoproteins, permitting them to ingest lipid and become foam cells. In addition to monocyte chemoattractant protein-1 (MCP-1), macrophage colony-stimulating factor (M-CSF) contributes to the differentiation of the blood monocyte into the macrophage foam cell.[1]

T cells likewise encounter signals that cause them to elaborate inflammatory cytokines such as interferon and tumor necrosis factor that in turn can stimulate macrophages as well as vascular endothelial cells and smooth muscle cells (SMCs).[2]

As this inflammatory process continues, the activated leukocytes and arterial cells can release fibrogenic mediators, including a variety of peptide growth factors that can promote replication of SMCs and contribute to elaboration by these cells of a dense extracellular matrix, characteristic of the more advanced atherosclerosis lesion.[1]

2 High density lipoproteins (HDL)

HDL possess a number of physiological activities. Mature HDL present a hydrophobic core composed of cholesteryl esters and triglycerides with proteins embedded in a lipid monolayer composed mainly of phospholipids and free cholesterol. HDL contain several apolipoproteins including apolipoprotein A-I (apoA-I) and apoA-II, the two main

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proteins, and a large number of less abundant proteins including apoCs, apoE, apoD, apoJ and some enzymes such as lecithin-cholesterol acyltransferase, serum paraoxonase (PON1) and platelet-activating factor acetylhydrolase (PAF-AH).[3] The most relevant function of HDL is to promote the efflux of excess cholesterol from peripheral tissues to the liver for excretion,[4,5] a pathway known as reverse cholesterol transport (RCT). The efflux of cholesterol is important for maintaining cellular cholesterol homeostasis. This process is most likely compromised in the atherosclerotic lesion also because the development of atherosclerosis is usually associated with low HDL-cholesterol. Multiple mechanisms for efflux of cell cholesterol exist. Efflux of free cholesterol via aqueous diffusion occurs with all cell types but is inefficient. Efflux of cholesterol is accelerated when scavenger receptor class-B type I (SR-BI) is present in the cell plasma membrane. Both diffusion-mediated and SR-BI-mediated efflux occur to phospholipid-containing acceptors (i.e., HDL and lapidated apolipoproteins). In both cases, the flux of cholesterol is bidirectional, with the direction of net flux dependant on the cholesterol gradient. The adenosine triphosphate binding cassette transporter AI (ABCA1) and GI (ABCG1) mediate efflux of both cellular cholesterol and phospholipid. In contrast to SR-BI-mediated flux, efflux via ABCA1 and ABCG1 are unidirectional, occurring to lipid-poor apolipoproteins.[6] Of note, these transporters are clustered together with many other functional proteins [including B and T cell receptors (BCR and TCR), sphingosine-1-phosphate receptors (S1PR)] in cellular membrane micro-domains called lipid rafts.[7] Lipid rafts are regions of membranes with a distinct, characteristic structural composition and that appear to act as platforms to co-localize proteins involved in intracellular signaling pathways. The organization of membranes into such micro-domains recognizes that, far from being randomly arranged, lipids may actually be highly organized within different parts of the membrane, and that this organization influences the way membrane proteins are distributed. Rafts are particularly rich in sphingolipids and cholesterol, and the side chains of the phospholipids present are usually highly enriched in saturated fatty acids compared with the surrounding non-raft regions of the membrane. Enrichment of phospholipids with saturated fatty acids allows for the close packing of lipids within rafts. As a result of the presence of cholesterol and saturated fatty acids, lipid rafts are more ordered and less fluid than the surrounding membrane. Cytoplasmic proteins that are covalently modified by saturated fatty acids (palmitoyl or myristoyl moieties) and cell surface proteins that are attached via a glycosyl phosphatidylinositol anchor are highly concentrated within lipid rafts. Many proteins involved in signal transduction, such as Src family kinases, G proteins, growth factor receptors, mitogen-activated protein kinases (MAPK), and protein kinase C, are predominantly found in lipid rafts, which appear to act as signaling platforms by bringing together (i.e., co-localizing) various signaling components, thus facilitating their interaction.[8]

The integrity of the lipid raft structure is a fundamental requirement for the correct functionality of all the present proteins. Thus, it can be understood why lipid rafts are the key structure responsible for the remarkable ability of HDL to regulate a number of physiological processes, including innate and adaptive immune responses.

In addition, apolipoproteins, lipids and enzymes carried by HDL can also modulate endothelial functions and have antioxidant activities that inhibit the oxidative modification of LDL, thereby reducing the atherogenic potential of these lipoproteins.[9] Of note, HDL is the predominant lipoprotein class in several species (from fish to ape) including those resistant to the development of atherosclerosis or cardiovascular diseases. Furthermore, the main constituent of HDL, apoA-I, is highly conserved throughout evolution,[10] as is the ability of HDL to modulate cholesterol bioavailability at the cellular level.[11] Cholesterol modulation in cells has also been associated with the ability of HDL to modulate hematopoietic stem cell maturation.[7,11–13] Other players of the immune response are modulated by HDL. HDL induce the expression of pentraxin 3 (PTX3)[14] which is involved in controlling leukocyte recruitment.[15] HDL induce PTX3 mRNA expression and protein release, whereas no effect was observed on CRP and SAP expression. This effect is mainly dependent on the activation of the lysosphingolipid receptor-PI3K/Akt axis and is mimicked by sphingosine-1-phosphate and other S1P mimetics.[14] *In vivo*, an increased expression of PTX3 mRNA was detected in the aorta of transgenic mice overexpressing human apoA-I, compared to apoA-I knock-out mice and plasma levels of PTX3 are significantly increased in C57BL/6 mice injected with HDL.[14] Of note, PTX3 deficiency is associated with cardiovascular disorders including atherosclerosis.[16,17] We have demonstrated that PTX3 deficient animals with the apolipoprotein $E^{-/-}$ background, develop larger and more inflamed atherosclerotic lesions compared to control animals.[17]

The aim of this brief review is to discuss the emerging role of HDL in modulating the activity of immune cells and immune-inflammatory mediators during atherogenesis.

3 Endotoxemia and acute phase response

In the acute phase response, HDL-cholesterol and apoA-I levels are reduced in humans.[18,19] The quick change in

HDL and apoA-I during acute response is commonly perceived as an adaptation of this system to inflammation. While the inflammatory response represents a host defense to invading pathogens, uncontrolled systemic inflammation can lead to serious complications, such as disseminated intravascular coagulation, tissue damage, and endotoxic shock.[20] For instance, lipopolysaccharides (LPS) are the primary cause of Gram-negative-induced sepsis. LPS, through its interaction with the LPS-binding protein (LBP)-CD14-TLR4 (Toll like receptor 4) complex, activates macrophages, causing a massive release of inflammatory cytokines.[21] LBP binds preferentially to HDL.[22] Of note, intravenous infusion of reconstituted HDL protects mice from the toxic effect of LPS,[23] an effect less evident in rabbits.[24] Furthermore, protection from LPS toxicity was achieved in transgenic mice with a two fold elevation of HDL;[23] this animal model shows more LPS bound to HDL, lower plasma cytokine levels and improved survival rates compared to control mice.

Also in humans, low HDL levels are associated with increased sensitivity toward inflammatory stimuli as reflected by enhanced inflammatory and coagulation responses on endotoxin challenge.[25] Transgenic animals lacking apoA-I, exhibit an increased lipopolysaccharide-driven mortality.[22,26] Because of the significant protection against LPS-induced damage, reconstituted HDL and apoA-I mimetics represent an interesting approach to improve the control of endotoxemia.[23,27] Milestones studies pointed out that the capacity of HDL to bind LPS is 10- to 1000-fold above the LPS concentrations reported in studies of septic patients.[28,29] It is therefore unlikely that the maximal increase in HDL levels achieved (2 to 3-fold) could result in rescue from LPS endotoxemia and lethality only through LPS sequestration and hepatic clearance. This has been widely investigated in the last two decades showing a series of additional HDL effects on the cells and the events involved in the immune-inflammatory response.

Following an infection, circulating HDL, known as "acute-phase HDL" (sometimes regarded also as pro-inflammatory HDL), show altered chemical and physical characteristics. Mediators of inflammation, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, induce expression of serum amyloid A[30] and group IIA secretory phospholipase A_2 ($sPLA_2$-IIA),[31] which dramatically alter HDL apolipoprotein content and levels, respectively. Furthermore, during inflammation, the composition of HDL is modified by the binding of acute phase products, such as serum amyloid A (SAA) and ceruloplasmin.[32] The content of proteins associated with HDL is altered so that PON1 levels decrease, thus reducing the anti-oxidant properties of HDL,[33] while PAF-AH increases leading to an increase of pro-atherogenic lipids.[34,35] These structural changes in the HDL induce functional lipoprotein alterations that can account, at least in part, for the increased risk of atherosclerosis observed during the acute phase response. For instance, the antioxidant properties of HDL and its function as a cholesterol acceptor are significantly reduced in subjects undergoing an acute phase response.[36–38] During the acute phase, SAA rapidly associates with HDL becoming the main protein,[39,40] accounting for 17% to 87% of the total apoproteins in acute-phase HDL.

4 HDL and immune cells

One of the key events in the atherogenic process is the development of foam cells following monocytes-derived macrophage lipid engulfment.[41,42] Following cholesterol deposition, macrophages activate cholesterol removal mechanisms through the interaction of ABCA1 and ABCG1 and apoA-I or HDL.[43,44] This interaction negatively modulates macrophage expression of inflammatory mediators, such as MCP-1 and CD11b,[45] and inhibits the lymphocyte proliferative response.[46,47] Furthermore, macrophages lacking ABCA1 and/or ABCG1 exhibit an increased lipid raft formation.[48] The function of the lipid raft is correlated to its cholesterol content and the removal of cholesterol from these microdomains can interfere with signaling pathways in immune cells,[49] and with antigen-presenting function.[50] One main function of lipid rafts is the regulation of signaling through the T cell receptors.[51–53] As an example, the localization of major histocompatibility (MHC) class II molecules in lipid rafts[54–56] facilitate the function of antigen-presenting cells and is essential for T cell activation, as this process decreases the amount of antigen necessary for T cell activation.[57,58] For this reason, cholesterol depletion from lipid rafts can inhibit T cell activation. Both HDL and apoA-I remove cholesterol from lipid rafts via ABCG1, SR-BI and ABCA1, reducing the inflammatory response in macrophages and inhibiting the ability of antigen-presenting cells to stimulate T-lymphocytes.[48,59]

Dendritic cells (DCs) are immune cells whose main function is to process an antigen, present it on their surface and activate T-cells. DCs are present in atherosclerotic lesions[60] and co-localize with T-cells.[61] DCs produce mediators of the innate immune system and increase the expression of co-stimulatory molecules, including CD40, CD80 and CD86,[62,63] which are essential for T-cell responses. ApoA-I inhibits DCs differentiation from monocytes, inhibits the ability of DCs to secrete IL-12 when stimulated with anti-CD40 and

interferon γ (IFNγ), and increases the production of two inhibitors of DC differentiation, such as IL-10 and PGE2.[64]

Atherosclerotic lesions also contain cells of the adaptive immune system, in particular T cell subsets known to modulate inflammatory process in atherogenesis. BCR and TCR are localized in lipid rafts. In resting cells, BCR and TCR are excluded from lipid rafts. Upon activation, these receptors associate with membrane micro-domains, resulting in a spatial organization of receptor signaling.[65] The association of BCR and TCR with lipid rafts is dependent on membrane cholesterol content and changes in lipid raft composition and structure induced by HDL or apoA-I can affect receptor activities.[66,67] Both B and T cells egression from lymph nodes is also affected by lysosphingolipids, in particular S1P, a component of HDL.[68–70] S1P carried by HDL positively correlates with HDL-cholesterol, apoA-I, and apoA-II levels. Furthermore, S1P is enriched in small dense subclass 3 of HDL (HDL_3).[71] Modulation of S1P1 receptors by a synthetic S1P analogue, FTY720, in LDL-R knockout mice resulted in a marked decrease of peripheral blood lymphocytes, thus preventing their recruitment into sites of inflammation.[72,73] Finally, FTY720 reduces the delivery of scavenged lipoprotein cholesterol to the endoplasmic reticulum and facilitates its release to physiological extracellular acceptors, resulting in decreased cholesterol toxicity in macrophages.[74] S1P1 is the main S1P receptor involved in the egress of T cells from lymphoid organs (Table 1).[58,59] In transgenic mice, S1P1 inhibited the differentiation of regulatory T cells (Tregs) while promoting the development of T helper type 1 (Th1) cells in a reciprocal manner.[70] We recently showed, in humans, an inverse relation between a HDL and $CD3^+$ $CD4^+CD25^{high}$ $CD127^{low}$ Treg cell levels, while no correlation was found between Tregs and LDL cholesterol, total cholesterol or triglyceride levels.[75] In animal models, other mechanisms by which HDL can modulate Treg have been proposed. ApoA-I administration reduces inflammation in LDL $receptor^{-/-}$, $apoA\text{-}I^{-/-}$ mice by decreasing the numbers of lymph node immune cells, by increasing Tregs and decreasing the percentage of effector memory T cells.[76] All these data suggest that some of the effects of HDL on atherosclerosis may result from the modulation of molecules and cells that act as sensors of the immune-inflammatory balance during atherogenesis.

Table 1. Immune cells and atherosclerosis: effects of HDL and its components.

	Macrophages/Dendritic cells	Lymphocytes
HDL	Inhibition of antigen-presenting cell function due to displacement of MHCII from lipid rafts Suppression of the LPS-induced type I IFN response. Reduction of inflammatory mediators expression	Prevention of hematopoietic stem and multi-potential progenitor cell proliferation Reduction of BCR and TCR activity Inhibition of lymphocytes proliferative response
ApoA-I	Inhibition of antigen-presenting cell function due to displacement of MHCII from lipid rafts Inhibition of dendritic cells differentiation from macrophages Reduction of DC ability to stimulate T-cells Cholesterol depletion from lipid rafts Reduction of co-stimulatory molecule expression in DCs Reduction of TLR4 and CD14 expression Macrophage arterial trafficking inhibition by apoA-I mimetic peptide D-4F	Reduction of BCR and TCR activity Reduction of lymph node immune cell number; increase of Treg; decrease of effector memory T cells percentage in $LDLr^{-/-}$, $apoA\text{-}I^{-/-}$ mice Inhibition of T-cell activation and proliferation in hypercholesterolemic mice Inhibition of leukocytosis Prevention of cholesterol-induced lymphocyte accumulation, activation and proliferation in peripheral lymph nodes of $LDLr^{-/-}$, $apoA\text{-}I^{-/-}$ mice
S1P/S1PRs	Inhibition of LPS-induced response and cholesterol toxicity by the S1P synthetic analogue FTY720	Reduction of peripheral blood lymphocyte; reduction of CD3+ T-cell content in atherosclerotic plaque Suppression of lymphocyte proliferation by FTY720 Inhibition of Treg differentiation Switch Treg to Th1 development

Apo: apolipoproteins; BCR: B cell receptors; HDL: high density lipoproteins; IFN: interferon; LDL: low-density lipoproteins; LPS: lipopolysaccharides; MHC: major histocompatibility complex; S1P: sphingosine-1-phosphate; TCR: T cell receptors; TLR: toll like receptor; Treg: regulatory T cells.

5 Conclusions

HDL acts as reservoir for a number of biologically active substances that may impact the immune system during atherogenesis. Of note, modifications in the lipid and lipoprotein profiles are highly correlated to lymphocyte T effector memory cells and the risk of cardiovascular events.[73] Therefore, the ability of HDL to promote cholesterol efflux results in the modulation of a series of responses in the immune cells involved in atherosclerosis, including monocyte-macrophages, B and T lymphocytes. Since the HDL composition varies to a large extent during inflammation, the understanding of how these interactions take place and how biologically active substances can be delivered to

relevant targets during atherogenesis is of great interest. Drugs targeting HDL levels and activity represent one of the emerging frontiers in lipidology and pharmacology. Whether these drugs impact the immune-inflammatory response in atherosclerosis will be extensively investigated in subsequent years.

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