REVIEW ARTICLE

High-density Lipoprotein and Inflammation and Its Significance to Atherosclerosis

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ABSTRACT

Great advances are being made in the understanding of the structural and functional diversity of high-density lipoprotein at the mechanistic level. High-density lipoprotein possesses numerous physiological activities, the most studied of which is the ability to promote excess cholesterol efflux from peripheral tissues to the liver for excretion via a mechanism believed to confer protection against atherosclerosis. Accumulating evidence has demonstrated that atherosclerosis is a chronic inflammatory response. Recent studies have suggested that high-density lipoprotein possesses anti-inflammatory properties and regulates both innate and adaptive immune responses. However, further complicating this very complex system is the finding that inflammation, via alteration of the proteomic and lipidomic composition of high-density lipoprotein species, can modulate at least some of their functional activities. Modified high-density lipoprotein exhibits a reduced ability to mediate cholesterol efflux from peripheral tissues and to inhibit cytokine-induced adhesion molecule expression and even promotes the occurrence of inflammation. This review focuses on the underlying mechanism of the interaction between high-density lipoprotein and inflammation to clarify the pathologic process of atherosclerosis.

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INTRODUCTION

Since the seminal publication by Miller and Miller,[1] high-density lipoprotein (HDL) has been associated with the risk of cardiovascular disease (CVD). Therefore, much work has focused on understanding the metabolism and function of HDL. In 2003, ETC-216 (rapoA-IMilano, a synthetic variant of HDL) was tested in a small proof-of-concept clinical trial in which sequential intravascular ultrasound examinations were performed before and after 5 weekly infusions of ETC-216 or placebo. That study showed rapid coronary plaque regression following administration of apoA-IMilano.[2] CER-001, an engineered pre-β HDL mimic, consists of recombinant human apolipoprotein A-I (apoA-I) and 2 different phospholipid carriers. In a preclinical study, CER-001-enhanced reverse lipid transport reduced vascular inflammation and promoted regression of atherosclerosis in hypercholesterolemic low-density lipoprotein (LDL) receptor–deficient mice.[3] Furthermore, CER-001 stimulated cholesterol mobilization and reduced arterial wall thickness and inflammation in patients with the orphan disease familial hypoalphalipoproteinemia.[4] These findings support for the concept that HDL plays an important role in reducing atherosclerosis and inflammation. Therefore, HDL has become one of the most commonly measured biomarkers of atherosclerosis and has been regarded as a major therapeutic target in the setting of CVD.

Nowadays, atherosclerosis is seen as an inflammatory disease characterized by inflammatory and immune responses that contribute to disease initiation and progression and to plaque destabilization. Recent results have suggested that HDL may play additional roles in the regulation of inflammation, including the inhibition of monocyte activation and the modulation of the immune system. However, chronic inflammation induces significant changes to HDL, resulting in the reduction of the plasma HDL levels, HDL-mediated reverse cholesterol transport (RCT) and the inhibition of enzymes. These enzymes consist of lecithin cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP), phospholipid transfer protein, hepatic lipase, apoA-I and paraoxonase-1 (PON-1).[5] HDL activity related to inflammation is also affected, as demonstrated by increased serum amyloid A (SAA) content in patients with atherosclerosis. Furthermore, HDL is depleted in cholesterol esters but is enriched in free cholesterol, triglycerides and free fatty acids.[6] These alterations to HDL structure and function result in the conversion of HDL to a proinflammatory molecule. Several large randomized controlled trials in which plasma HDL-C levels were elevated failed to identify benefits with respect to CVD events or the progression of atherosclerosis.[7,8] This unexpected finding raises the question of whether HDL is an innocent bystander or acts as a mediator of atherogenesis and CVD. This review summarizes the cross talk between HDL and inflammation in the setting of atherosclerosis.

HDL STRUCTURE AND BIOLOGY

HDL, the smallest and densest of the plasma lipoproteins, has a density ranging from 1.063-1.21 g/mL. HDL exists as various subclasses of particles in plasma, differing in shape, size and protein and lipid composition. HDL is a macromolecular complex of proteins and lipids, including apoA-I, apoA-II, apoCs, apoE, apo-D, apoJ and enzymes such as LCAT, PON-1 and platelet-activating factor acetylhydrolase.[9] The primary apolipoproteins in HDL are apoA-I and apo-AII, which represent up to 70% and 20% of the total HDL protein, respectively. Furthermore, based on 2-dimensional gel electrophoresis results, HDL particles can be subdivided into large cholesterol-rich spherical HDL particles, intermediate spherical HDL particles and small discoidal HDL particles.[10]

The atheroprotective role of HDL in the cardiovascular system has been attributed to its pleiotropic effects, including anti-inflammatory,[11] antithrombotic,[12] antioxidative,[13] antiapoptotic[14] and vasodilatory effects. Among many components included in HDL, apoA-I possesses many HDL effects ranging from scavenging of RCT, LPS and LTA to inhibition of different proinflammatory, pro-oxidant and prothrombotic pathways. HDL and apoA-I appear to defend against many biological and chemical hazards.

THE ANTI-INFLAMMATORY MECHANISMS OF HDL

Inhibition of the Transendothelial Migration of Immunocompetent Cells and T Cell Contact–Mediated Monocyte Activation

ApoA-I inhibits the cytokine-induced expression of cell adhesion molecules, such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin, which are key mediators in the diapedesis of immunocompetent cells from the circulation to the arterial wall.[15] This physiological effect of apoA-I demonstrates that it could regulate the transendothelial activity of immunocompetent cells. Additionally, apoA-1 could inhibit both shear stress and phorbol-12 myristate 13-acetate (PMA) induced monocytic expression of CD11b, which is involved in the early stages of transendothelial migration. Research on this topic showed that inhibition of CD11b expression was accompanied by decreased transendothelial migration of monocytes toward chemotactic agents such as monocyte chemoattractant protein-1 (MCP-1). Furthermore, inhibition of CD11b expression in monocytes is increased with asymmetry and hydrophobicity but decreased with increasing numbers of positively charged residues, emphasizing the importance of the conformation of apoA-1 to its anti-inflammatory properties.[15,16]

Upon the transendothelial migration of inflammatory cells, interactions between macrophages and T cells represent another important step in the modulation of the chronic inflammatory response. Direct contact between activated T cells and monocytes or macrophages drives the production of several inflammatory cytokines such as IL-1β, IL-6, IL-8, MCP-1 and TNF-α, which are involved in atherogenesis and tissue destruction. However, apoA-1 inhibits contact-mediated monocyte stimulation and the subsequent production of IL-1β and TNF-α. A previous study determined that apoA-1 blocks T cell-monocyte interactions at the T cell level.[17] Additional studies using cell-cell interaction models demonstrated that HDL or apoA-1 inhibits T cell contact–activated expression of specific proinflammatory genes in monocytes.[18] These studies support the concept that apoA-I could inhibit inflammation by regulating the transendothelial migration of immunocompetent cells and T cell contact–mediated monocyte activation.

Inhibition of Lipid Oxidation

It is known that HDL can inhibit LDL oxidation. Several HDL-associated proteins, including PON-1 and -3, apoA-I, LCAT and CETP, are associated with this inhibitory effect. Among these proteins, PON-1 alone appears to be responsible for the attenuation of oxidative damage to macrophages,[19] stimulation of cholesterol efflux from macrophages[20] and attenuation of oxidative stress in atherosclerotic lesions.[21] Furthermore, PON-1 is believed to contribute to the anti-inflammatory activity of HDL by destroying biologically active lipids within mildly oxidized LDL particles,[22] which result in decreased inflammation within the arterial wall. Several studies have found that PON-1 decreases monocyte chemotaxis and adhesion to endothelial cells,[23] inhibiting monocyte-to-macrophage differentiation.[24] PON-1 significantly inhibited both the production and the secretion of the proinflammatory cytokines TNF-α and IL-6 in LPS-stimulated macrophages. The absence of PON-1 was associated with the overexpression of adhesion molecules.[25] These observations are suggestive of an anti-inflammatory role for PON-1.

Modulation of Inflammation by Activating Transcription Factor 3 (ATF3)

Most functions of HDL have been established. However, a new pathway of HDL activity that regulates inflammation has recently been reported. De Nardo et al[26] described a novel and cholesterol transport–independent mechanism by which HDL exerts its anti-inflammatory effects. HDL could stimulate ATF3, an ancient transcriptional modulator that provides negative feedback to toll-like receptor (TLR)–mediated innate immune signaling. ATF3 is a key transcriptional regulator of innate immune response genes that are induced by TLR and other innate immune ligands and inhibits TLR signaling by inactivating target genes via reduced histone acetylation. HDL increased ATF3 mRNA and protein expression in bone marrow–derived macrophages (BMDMs), and this effect was potentiated upon