High-Density Lipoproteins
Effects on Vascular Function and Role in the Immune Response

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KEYWORDS

• HDL function • Immune response • Endothelial function • Atherosclerosis • Coronary disease

KEY POINTS

- Results of recent clinical trials and translational/genetic studies have led to a refined understanding of the role of high-density lipoproteins in coronary disease.
- Findings cumulatively suggest that plasma high-density lipoprotein cholesterol is likely not a causal cardiovascular risk factor and therefore is not an adequate therapeutic target in cardiovascular prevention.
- More recent data suggest that the functional properties of HDL and its effects on vascular cells are importantly altered in patients with high cardiovascular risk.
- Among pathologic conditions that promote high-density lipoprotein dysfunction, enhanced inflammation, for example, in chronic kidney disease, has been identified as a potential underlying mechanism.

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL HYPOTHESIS

The "high-density lipoprotein (HDL) cholesterol (HDL-C) hypothesis" was suggested largely by epidemiologic studies demonstrating an inverse relationship between HDL-C and the incidence of coronary heart disease.[1] Initial results of the Framingham Heart study also considered HDL-C as a potent predictor of death owing to coronary heart disease. These results were later supported by the Emerging Risk Factors Collaboration study, which was adjusted for other cardiovascular risk factors.[2] Importantly, however, in these studies the link between cardiovascular risk and HDL-C was only noticeable in patients with low HDL-C levels during 2.79 million person-years of follow-up, whereas in patients with higher HDL-C levels (>50 mg/dL), no significant relationship between HDL-C levels and coronary disease is found.

POTENTIAL ATHEROPROTECTIVE EFFECTS OF HIGH-DENSITY LIPOPROTEIN IN ENDOTHELIAL CELLS

As a key player of the so-called reverse cholesterol transport, HDL can transport excess cholesterol from peripheral cells either to the liver for excretion into the bile or to adrenals, testes, and ovaries for steroid hormone synthesis. In particular, cholesterol in macrophages from atherosclerotic lesions is thought to be taken up by HDL particles.[3] This so-called cholesterol efflux involves distinct transporters on macrophages, such as ATP-binding cassette subfamily G1 (ABCG1), ATP binding cassette transporter A1 (ABCA1), and scavenger receptor class B type 1.[4] Importantly, the cholesterol efflux capacity of HDL is not reflected by the absolute HDL-C plasma levels. This finding has been demonstrated by experimental studies using mice with genetic deletion of ABCG1 and

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Abbreviations

ABCA1	ATP binding cassette transporter A1
ABCG1	ATP-binding cassette subfamily G1
apo	Apolipoprotein
CAD	Coronary artery disease
CETP	Cholesterol ester transfer protein
eNOS	Endothelial nitric oxide synthase
HDL	High-density lipoprotein
HDL-C	HDL cholesterol
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MPO	Myeloperoxidase
NO	Nitric oxide
PCKßII	Protein kinase C ßII
PON1	Paraoxanase-1
S1P	Sphingosine-1-phosphate
SDMA	Symmetric dimethylarginine
TLR	Toll-like receptor

ABCA1 in macrophages leading to increased atherosclerosis without alteration of HDL-C plasma levels.[5]

However, beyond its cholesterol transportation functions, direct vascular protective and potentially antiatherogenic effects have been ascribed to HDL under physiologic conditions based on mechanistic studies.[6] In particular, HDL from healthy subjects is known to promote the release of nitric oxide from endothelial cells and endothelial nitric oxide synthase (eNOS).[7] Moreover, by downregulating the expression of leukocyte adhesion molecules, such as vascular cell adhesion molecule 1, HDL from healthy subjects is capable of inhibiting the adhesion of leukocytes.[8]

In addition, the antithrombotic effects of HDL from healthy subjects have been described, such as limiting tissue factor expression in endothelial cells.[9] Importantly, these potential vasoprotective effects of HDL have been observed by using HDL from healthy subjects. The underlying molecular mechanisms of potential protective vascular effects of HDL have been identified over the past years, among which the scavenger receptor class B type 1 receptor seems to be a major mediator of HDL effects on the endothelial cells, including stimulation of endothelial NO production.[10,11] Other mechanisms involving the transporter ABCG1 (releasing endothelial oxysterols) and sphingosine 1-phosphate (S1P) 3 receptors on endothelial cells have also been identified.[12,13]

POTENTIAL REGULATORY FUNCTIONS OF HIGH-DENSITY LIPOPROTEIN IN INFECTION CONTROL AND (AUTO-) IMMUNE DISORDERS

HDL has been suggested to exert innate defense functions, for example, on bacterial infection. These functions include suppression of proinflammatory effects of bacterial lipopolysaccharide and lipoteichoic acid, which are toxic components of bacterial cell membranes. These properties have been particularly noticeable in animal models of sepsis using either apolipoprotein (apo)A-I knockout mice with very low HDL-C, which resulted in an exaggerated inflammatory cytokine release,[14] or apoA-I transgenic mice with high HDL levels showing increased survival rate under septic conditions as compared with controls. This property of HDL is thought to be based on the interaction of lipopolysaccharide with lipopolysaccharide-binding protein with subsequent binding with the HDL receptor scavenger receptor class B type I promoting its clearance.[15]

Interestingly, also in humans, low HDL-C levels have been inversely correlated with the severity of sepsis and an amplified systemic inflammatory response.[16]

A role of HDL-C for autoimmune disorders has also been suggested based on studies on LDLR$^{-/-}$ and apoA-I$^{-/-}$ mice, which develop an autoimmune phenotype with enlarged peripheral lymph nodes and spleens, compared with LDLR2/2 mice, with a high expansion of all classes of lymph node immune cells, such as T and B cells, macrophages, and dendritic cells.[17] Moreover, mice deficient of scavenger receptor class B type I demonstrate excessive proliferation of T and B lymphocytes with increased proinflammatory cytokine production in lymphocytes and macrophages, circulating autoantibodies, deposition of immune complexes in glomeruli, and infiltration of leukocytes in the kidneys.[18] Cumulatively, these observations point to a protective role of HDL and HDL-related proteins and functional circuits against infectious and autoimmune diseases, although detailed mechanisms still need to be explored further.

REGULATORY PROPERTIES OF HIGH-DENSITY LIPOPROTEIN IN INNATE AND ADAPTIVE IMMUNITY: THE ROLE OF LIPID RAFTS

Accumulating evidence suggest a critical role of HDL and in particular its main structural and functional apoA-I in regulating immunologic functions of both innate and adaptive immune responses.[19] An underlying mechanism of HDL-regulated immune functions is the modulation of specific membrane microdomains enriched in cholesterol and sphingolipids called lipid rafts in which numerous receptors of immune cells are localized, such as Toll-like receptors (TLRs)[20] and T-cell receptors and B-cell receptors[21,22] (**Fig. 1**).

For example, HDL is capable to decrease lipid raft abundance on apoA-I/ABCA1–mediated cholesterol efflux of monocyte plasma membranes,[23] thereby