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Dysfunctional high-density lipoprotein

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Abstract

Purpose of review—To address the progress of the investigation on dysfunctional high-density lipoprotein (HDL).

Recent findings—HDL is generally considered to be an independent protective factor against cardiovascular disease. However, emerging evidence indicates that HDL can be modified under certain circumstances and lose its protective effect or even become atherogenic. The underlying mechanisms responsible for generating the dysfunctional HDL and the chemical and structural changes of HDL remain largely unknown. Recent studies focus on the role of myeloperoxidase in generating oxidants as participants in rendering HDL dysfunctional *in vivo*. Myeloperoxidase modifies HDL in humans by oxidation of specific amino acid residues in apolipoprotein A-I, which impairs cholesterol efflux through ATP-binding cassette transporter A1 and contributes to atherogenesis.

Summary—HDL may not always be atheroprotective and can be atherogenic paradoxically under certain conditions. The mechanisms responsible for generating the dysfunctional HDL remain largely unknown. Recent data suggest that myeloperoxidase-associated modification of HDL may be one of the mechanisms. Further studies are needed to investigate the in-vivo mechanisms of HDL modification and identify therapeutic approaches aiming at controlling HDL modification.

Keywords

apolipoprotein A-I; cardiovascular disease; high-density lipoprotein; lipoprotein; myeloperoxidase

Introduction

It is well established that high-density lipoprotein cholesterol (HDL-C) concentration in the blood is independently and inversely associated with an increased risk of cardiovascular disease (CVD) [1•,2]. However, it is apparent that many patients with ‘normal’ or even ‘elevated’ plasma HDL experience clinical events [3]. Furthermore, the recent clinical trial ILLUMINATE, which targets to increase plasma HDL levels with a new selective cholesteryl ester transfer protein (CETP) inhibitor, Torcetrapib, was prematurely terminated because of an increase in all-cause mortality despite an increase in HDL-C levels. These disappointing results suggest that HDL may not always be atheroprotective [4••,5•], and in some conditions, it paradoxically enhances the process of atherosclerosis.

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Structure of 'normal' high-density lipoprotein

HDLs are a heterogeneous class of lipoproteins. They vary in diameter, density, and composition [6]. Generally speaking, HDLs are organized complexes of lipids (cholesterol, cholesteryl esters, triglycerides, and a variety of phospholipids) and proteins (apolipoproteins and enzymes). The surface of these particles is composed of the charged head groups of phospholipids (phosphatidylcholine, phosphatidylserine, cardiolipin, and phosphatidylethanolamine) and amino acids of proteins that project into the aqueous phase. The particle core is a reservoir of hydrophobic lipid (triglycerides and cholesteryl ester) sequestered from the aqueous phase. Analytic ultracentrifugation subdivides HDL into HDL_2 (large, buoyant, and lipid enriched; density = 1.063–1.125 g/ml) and HDL_3 (small and dense; density = 1.125–1.210 g/ml) with diameters ranging from 70 to 120Å.

Apolipoprotein A-I (apoA-I) comprises roughly 70% of the HDL mass and apoA-II another 15–20%. The remainders are made up of amphipathic proteins including the apoCs, apoE, apoD, apoM, apoA-II, paraoxonase (PON), serum amyloid A (SAA), and many other proteins. Early study [7] reported that serum amyloid P (SAP) binds to HDL in a calcium-dependent manner, indicating that some of the HDL components may not be present in isolated HDL due to use of EDTA in isolation processes. Recently, Vaisar *et al*. [8••] and Reilly and Tall [9•] used shortgun proteomics to investigate the composition of HDL isolated from participants and identified multiple complement-regulatory proteins, as well as a diverse array of distinct serpins with serine-type endopeptidase inhibitor activity and many acute phase response proteins. These lower abundance proteins are not present on all HDL particles and may actually be sequestered on compositionally distinct particles within the density class. These amphipathic proteins form stable micellar complexes with phospholipids, cholesterol, triglycerides, and cholesteryl esters.

HDLs are metabolically active molecules and constantly remodel and interconvert among their various forms by the activity of a number of enzymes [10]. As a result of qualitative and quantitative differences in lipid, protein, and enzyme content, HDL particles are multishaped molecules with varying density, fluidity, charge, and antigenicity. For example, in addition to phosphatidylcholine, the surface of HDL contains other phospholipids such as sphingomyelin, phosphatidylserine, phosphatidylinositol, and phosphatidylethanolamine [11,12]. There is also considerable variation in the length and unsaturation of HDL phosphatidylcholine acyl chains, as well as the effects on the inhibition of vascular cell adhesion molecule 1 (VCAM-1) [13]. As another example, apoA-I, the predominant protein of HDL, either in its lipid-free form or as a component of different HDL species, can bind to fibroblasts and macrophages and promote extracellular lipid translocation within blood vessel walls. As demonstrated by both the AFCAPS/TexCAPS Trial [14] and the European Concerted Action on Thrombosis and Disabilities (ECAT)-Angina Pectoris Study [15], as serum levels of apoA-I progressively increase, the risk for coronary events decreases. Thus, the modification of apoA-I may readily impair the atheroprotective function of HDL. So, both protein and phospholipid content can affect the functionality of HDL.

Biological functions of 'normal' high-density lipoprotein

The cardiovascular protective effects of HDL have been mainly attributed to its role in reverse cholesterol transport. However, a number of pleiotropic atheroprotective effects of HDL are emerging, including antioxidative, anti-inflammatory, antiapoptotic, antithrombotic properties, and so on.

High-density lipoprotein and reverse cholesterol transport

The atheroprotective effect of HDL is often explained by the ability of HDL to remove cholesterol from the periphery for delivery to the liver and excretion into the bile, a process named reverse cholesterol transport [16]. As shown in Fig. 1, lipid-free apoA-I is produced in the intestine or liver or shed from the surface of triglyceride-rich lipoproteins during lipolysis. These particles initiate efflux of phospholipids and cholesterol from cell membranes [17]. This process is facilitated by the ATP-binding cassette transporter A1 (ABCA1) that moves cellular lipids across the bilayer in a process requiring hydrolysis of ATP [18]. As ABCA1 does not bind cholesterol [19], it is believed to induce translocation of phospholipids to lipid-poor apoA-I, thus triggering cholesterol efflux to the apoA-I-phospholipids complex. Of note, patients with Tangier disease present a severe deficiency in plasma HDL because of the dysfunctional ABCA1 [20]. Cholesterol in nascent discoidal HDL is then esterified by the action of lecithin-cholesterol acyltransferase (LCAT). Cholesteryl esters readily move to the core of HDL particles, producing a steady gradient of free cholesterol and enabling HDL to further accept cholesterol from various donors. The reciprocal exchange of cholesteryl ester for triglycerides mediated by CETP moves the bulk of the cholesteryl esters to apoB-containing lipoproteins, which are eventually cleared by the liver. At the same time, HDL becomes enriched with triglycerides, which are substrates for CETP and hepatic lipase. The concerted action of CETP-mediated cholesteryl ester transfer and hepatic lipase-mediated hydrolysis of triglycerides and phospholipids leads to smaller HDL particles that are the preferred binding partners for scavenger receptor B type I (SR-BI), the major HDL receptor in hepatic cells. SR-BI mediates the selective uptake of cholesteryl esters from HDL, resulting in the removal of cholesterol from circulation. Lipid-free apolipoproteins or lipid-poor preβ-HDL is also formed during the remodeling by phospholipids transfer protein (PLTP), CETP, and hepatic lipase. The cells comprising vessel walls are unable to catabolize cholesterol [21]. Consequently, if reverse cholesterol transport is impaired, more cholesterol accumulates within the sub-endothelial space, leading to progressive atherosclerotic plaque development [17].

Atheroprotective effects beyond reverse cholesterol transport

In addition to its role in reverse cholesterol transport, HDL shows many other protective properties towards atherosclerosis. HDL inhibits the chemotaxis of monocytes [22,23], prevents endothelial dysfunction and apoptosis [24], prohibits low-density lipoprotein (LDL) oxidation [25,26], and stimulates the proliferation of endothelial cells and smooth muscle cells [27,28]. These anti-inflammatory, antioxidative, antiaggregatory, anticoagulant, and pro-fibrinolytic activities are exerted by different components of HDL, namely apolipoproteins, enzymes, and even specific phospholipids. This complexity further emphasizes that changes in the functionality of HDL rather than changes in plasma HDL-C levels determine the antiatherogenicity of therapeutic alterations of HDL metabolism.

Recent researches [29] focused on the multiple anti-inflammatory effects of HDL. The oxidized phospholipids within LDL stimulate arterial wall production of monocyte chemoattractant protein (MCP) 1, which increases recruitment of mononuclear cells and the expression of cellular adhesion molecules that promote leukocyte interaction with endothelial cells and entry into atheroma [30]. By limiting LDL oxidation, HDL thus plays a key anti-inflammatory role in slowing atherogenesis. However, in the setting of acute phase response and systemic inflammation, the anti-inflammatory character of HDL can markedly diminish, even to the point where it becomes proinflammatory [31,32].

Inhibition of LDL oxidation by HDL is usually attributed to the high content of antioxidants in this lipoprotein, antioxidative properties of apoA-I, and the association with HDL of

several enzymes, such as PON, platelet activating factor acetylhydrolase (PAF-AH), and glutathione peroxidase (GPX), which prevent LDL oxidation and/or contribute to the degradation of bioactive products that are formed during oxidation. The ability of HDL to act as an antioxidant, at the same time, renders HDL itself more susceptible to oxidation. The delicate relation between the modification and the impairment of HDL function probably plays a role in determining the antiatherogenic potential of HDL.

A number of studies [33–36] demonstrated that HDL binding to SR-BI stimulates endothelial nitric oxide synthase (eNOS) activity and enhances endothelium-dependent and nitric oxide-dependent relaxation in the aorta. Moreover, HDL prevents ox-LDL-induced eNOS inactivation by preserving the cholesterol concentration in caveolae, thereby maintaining the subcellular location of eNOS [37]. HDL can also suppress SR-BI-induced apoptosis [38]. In these ways, HDL may be critical in atheroprotective properties.

Dysfunctional high-density lipoprotein as an atherogenic particle

Although epidemiological studies have consistently demonstrated an inverse association between plasma HDL, as well as apoA-I concentration, and the risk of myocardial infarction, a subset of patients with high plasma HDL concentrations have enhanced rather than reduced atherosclerosis [39]. It has been proposed that modification of HDL may lead to changes in its antiatherogenic properties or even result in an actual promotion of atherogenic events [29,40•]. Meanwhile, when an independent safety monitoring committee in ILLUMINATE revealed an unfavorable imbalance in mortality and revascularizations in the Torcetrapib treatment study in early December 2006 [41•], the scientific community was shocked. Despite the significant increase in HDL level with the treatment of CETP inhibitor, the HDL particles may lose their normal constructions and protective effects. It has been speculated that CETP inhibition by Torcetrapib produced dysfunctional HDLs, leading to impaired reverse cholesterol transport.

It is of interest that HDL recovered from different participants often exhibits marked heterogeneity in its in-vitro functional properties. Several methods of identifying these processes have been described, including the monocyte chemotaxis assay (MCA) and a cell-free assay (CFA) [42,43•], which measures HDL's ability to alter LDL-induced chemotaxis in a human artery wall coculture and alter oxidized phospholipid-induced fluorescence in a cell-free system, respectively. Using these methods, Ansell *et al.* [29] examined the characteristics of HDL sampled from patients who developed coronary heart disease (CHD) despite very high HDL cholesterol levels (i.e., HDL ≥84 mg/dl). The difference in the anti-inflammatory potential of HDL was marked: those individuals who had CHD despite supernormal levels of HDL cholesterol had uniformly proinflammatory MCA and CFA results. They proposed that in setting of both vascular and nonvascular systemic inflammation, including CHD, diabetes, surgery, and influenza infection, the atheroprotective effects of HDL can markedly diminish, even to the point where it becomes proinflammatory. Several similar observations are reported. For example, Gowri *et al.* [44] reported the decreased protection against LDL oxidation by HDL from poorly controlled diabetic patients, due to the abnormal composition of HDL, and White *et al.* [45•] demonstrated that, in contrast to promoting eNOS activity, HDL from diabetic patients actually inhibits eNOS activity because of the abnormally high level of myristic acid in HDL. A number of studies [46–48] showed the functional changes of HDL during acute phase responses in humans, rabbits, and mice. All these studies indicate that the dysfunctional form of HDL is associated with alterations in lipid or protein content of circulating HDL.

Several animal models associated with dysfunctional HDL were established. Berard *et al.* [49] developed a transgenic mouse model overexpressing human LCAT, the major enzyme promoting the esterification of free cholesterol to cholesteryl ester and packaging cholesterol into the core of HDL. The transgenic mice have elevated HDL and increased diet-induced atherosclerosis, and the observation shows the abnormal HDLs in both composition and function, and corresponding ineffective transport of HDL-C to the liver and impaired reverse cholesterol transport. Using SR-BI-null mice, numerous studies [33,36,50•] demonstrate that despite a marked increase in HDL concentration, the mice developed enhanced atherosclerosis. These genetically manipulated mouse models provide in-vivo evidence for dysfunctional HDL as a potential mechanism leading to increased atherosclerosis in the presence of high plasma HDL levels.

Evidence for the presence of modified HDL in atherosclerotic tissues has also been reported recently. Artola *et al.* [51] showed the presence of cross-linked apolipoproteins in the absence of elevated lipid peroxidation products in HDL isolated from hypercholesterolemic chickens. Furthermore, by using histochemical analysis and immunoblot [52,53], these modified lipoproteins were detected in atheromatous plaques of the abdominal aorta [54] and in the sera from patients with chronic renal failure [55]. More recently, two independent groups have shown that chlorotyrosine (a specific product of HOCl) modified HDL (ClTyr-HDL) is present in human atherosclerotic tissue and human plasma [56,57]. The same groups have also shown that plasma ClTyr-HDL levels are increased in patients with CVD, suggesting that circulating levels of modified HDL represent a unique marker for clinically significant atherosclerotic disease. Also, nitrotyrosine-modified HDL (NO_2Tyr-HDL) levels are increased in patients with CVD [57]. These observations suggest that dysfunctional HDL can be generated *in vivo* and promote atherosclerosis.

High-density lipoprotein modification

Accumulating data suggest that HDL can easily be modified and lose its antiatherogenic activities through multiple mechanisms. Based on the nature of modification, we classify the modification into three types (Fig. 2): spontaneous oxidative modification [58–60], due to the presence of free metal ions and free radicals in the atherosclerotic plaques, similar to the oxidation of LDL; enzyme-induced modification, including myeloperoxidase (MPO), chymase-tryptase, matrix metalloproteinases (MMPs), PMN-associated enzyme, endothelial lipase, and so on [61–66]. These enzymes can degrade or oxidize apolipoproteins without significant changes in lipid moiety, or alternatively induce apolipoprotein cross-linking and lipid oxidation; metabolic modification, such as glycation [45•,67,68] that occurs under hyperglycaemic conditions, and acute phase reactants-induced modification during inflammation and so on [7,69,70].

Myeloperoxidase-induced dysfunctional high-density lipoprotein

Recently, MPO has been focused on to explain the mechanisms of generating dysfunctional HDL *in vivo*. MPO is an important member of self-defense systemthat catalyzes the generation of highly reactive oxidants, including hypochlorous acid (HOCl) and peroxynitrite. These powerful oxidants are used to kill microbial pathogens [71]. However, they can also oxidize other molecules due to their high reactivity. Important insights into the mechanisms that oxidize HDL in human artery wall have come from the mass spectrometric (MS) detection of oxidized amino acids that result from specific reaction pathways. Zheng *et al.* [57] reported the dramatic selective enrichment in NO_2Tyr and ClTyr contents within apoA-I recovered from serum and human atherosclerotic lesions, and analysis of serum from sequential participants demonstrates that the NO_2Tyr and ClTyr contents of apoA-I are markedly higher in individuals with CVD. These findings support a direct role for nitric

oxide-derived oxidants and MPO-catalyzed halogenation as oxidation pathways relevant to apoA-I oxidation *in vivo*, because NO_2Tyr and ClTyr serve as selective molecular markers of posttranslational protein modification by these respective pathways [72,73].MPO is the only known enzyme in mammals capable of generating chlorinating oxidants. Thus, Zheng *et al.* [57] demonstrated that apoA-I serves as a selective target of oxidation both within the systemic circulation and in human atherosclerotic plaque. Further independent confirmation of the role of apoA-I as a target for MPO-catalyzed oxidation has been reported by Bergt *et al.* [56] recently.

MPO as a likely mechanism for oxidative modification of apoA-I *in vivo* is apparently facilitated by MPO binding to apoA-I, as revealed by cross-immunoprecipitation studies in plasma, recovery of MPO within HDL-like particles isolated from human atheroma, and identification of a probable contact site between the apoA-I moiety of HDL and MPO. A specific binding site for MPO on HDL within the helix 8 domain of apoA-I has been identified through biophysical studies employing hydrogen deuterium exchange coupled with tandem mass spectrometry [74]. Site-specific liquid chromatography–mass spectrometry quantitative analyses demonstrated that the favored modification sites following exposure to MPO-generated oxidants are Tyr-166 and Tyr-192. Parallel functional studies demonstrated that site-specific modifications of apoA-I by MPO are associated with impaired lipid binding and ABCA1-dependent cholesterol efflux activity, providing a molecular mechanism that likely contributes to the clinical link between MPO levels and CVD risk. The corresponding functional alterations in apoA-I cholesterol efflux activity, combined with clinical observations linking chemical signatures of apoA-I nitration and chlorination with increased risk for cardiovascular disease, strongly support the concept that MPO-mediated oxidation of HDL generates a dysfunctional lipoprotein capable of contributing to the atherosclerotic process (Fig. 3). Independent groups have now demonstrated that systemic levels of apoA-I modified by nitration or chlorination are correlated with CVD prevalence [56,57,75], suggesting the potential of these modified forms of lipoprotein to serve as markers of cardiovascular risk prediction.

Nevertheless, the in-vivo mechanisms involved in HDL modification are largely unknown. A better knowledge of these pathways may provide possible therapeutic target aiming at reducing HDL modification.

Conclusion

Recent studies suggest that under some conditions, HDL can readily be modified to lose its atheroprotective properties and become dysfunctional or even atherogenic. Therefore, we should not only evaluate HDL level but also measure HDL function while we predict the risk of CVD. Future studies are clearly warranted to investigate the in-vivo mechanisms of HDL modification in relation to CVD and to identify nutritional and therapeutic approaches aiming at controlling HDL modification.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 196).

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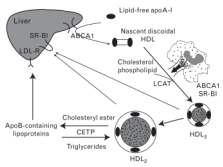

Figure 1. High-density lipoprotein metabolism and reverse cholesterol transport

Lipid-free apoA-I is produced in the intestine or liver or shed from the surface of triglyceride-rich lipoproteins during lipolysis. This particle initiates efflux of phospholipids and cholesterol from cell membranes that is facilitated by ABCA1. As the apoA-I adsorbs more lipids, it is converted into a hockey puck-like structure, nascent discoidal high-density lipoprotein (HDL). Cholesterol and phospholipid are esterified by the action of lecithin-cholesterol acyltransferase (LCAT) and then packed into the core of HDL. In macrophages, ABCA1 mediates cholesterol efflux to apoA-I. As more and more cholesteryl esters are incorporated into the particle, it becomes rounder and progressively larger (HDL_3–HDL_2). The reciprocal exchange of cholesteryl ester for triglycerides mediated by CETP moves the bulk of the cholesteryl esters to apoB-containing lipoproteins, which are eventually cleared by the liver through low-density lipoprotein (LDL) receptor (LDL-R). Peripheral cholesteryl esters can also be delivered to the liver through the binding of HDL to scavenger receptor B type I (SR-BI) and can also be secreted to bile.

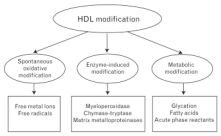

Figure 2. High-density lipoprotein modification

High-density lipoprotein (HDL) modification can be classified into three types based on the nature of modification: spontaneous oxidative modification; enzyme-induced modification; and metabolic modification.

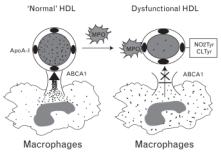

Figure 3. Myeloperoxidase-induced dysfunctional high-density lipoprotein

Myeloperoxidase (MPO) site specifically binds to apoA-I and produces reactive oxidative species that are responsible for the nitration and chlorination of tyrosine residues within apoA-I. Consequently, the modified high-density lipoprotein (HDL) impairs the ABCA1-dependent cholesterol efflux activity in macrophages.