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Review

Understanding high-density lipoprotein function in disease: Recent advances in proteomics unravel the complexity of its composition and biology

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ABSTRACT

Although the epidemiology of high-density lipoprotein (HDL) cholesterol and cardiovascular risk has been consistent, pharmacologic interventions to increase HDL-cholesterol by delaying HDL catabolism did not translate into reduction in cardiovascular risk. HDL particles are small, protein-rich when compared to other plasma lipoprotein classes. Latest progresses in proteomics technology have dramatically increased our understanding of proteins carried by HDL. In addition to proteins with well-established functions in lipid transport, iron transport proteins, members of the complement pathway, and proteins involved in immune function and acute phase response were repeatedly identified on HDL particles. With the unraveling of the complexity of the HDL proteome, different laboratories have started to monitor its changes in various disease states. In addition, dynamic aspects of HDL subgroups are being discovered. These recent studies clearly illustrate the promise of HDL proteomics for deriving new biomarkers for disease diagnosis and to measure the effectiveness of current and future treatment regimens. This review summarizes recent advances in proteomics and lipidomics helping to understand HDL function in health and disease.

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1. Introduction

Lipids are distributed in the human body by a complex lipid transport system consisting of five main classes of lipoproteins which, in order of molecular size, largest to smallest, are chylomicrons, very low-density lipoproteins, intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDL) [1]. Plasma levels of LDL-cholesterol are causally involved in the development of atherosclerosis and cardiovascular disease. LDL transfers cholesterol to peripheral tissue and lowering LDL-cholesterol by statins in people with pre-existing cardiovascular disease is effective in decreasing mortality [2,3].

HDL is the smallest of the lipoprotein particles containing the highest proportion of apolipoproteins to lipids. The major HDL associated apolipoproteins A-I (apoA-I) and apoA-II are secreted into plasma by the liver and the intestine, where they are lipidated to form lipid poor, discoidal, nascent HDL [4]. Nascent HDL takes up cholesterol from cell membranes and other lipoproteins. Lecithin-cholesterol acyltransferase (LCAT) converts free cholesterol into cholesteryl-ester thereby remodeling the particle to a spherical shape. Epidemiological studies have clearly shown that levels of HDL-cholesterol are inversely associated with the risk of coronary artery disease (CAD) and its thrombotic complications [5]. Consequently, it was assumed that HDL-cholesterol raising therapies could potentially further reduce cardiovascular mortality. Unexpectedly, pharmacologic interventions to increase HDL-cholesterol by delaying HDL catabolism did not translate into reduction in cardiovascular risk. The inability of HDL-cholesterol raising therapies and new insights into the complexity of HDL composition and function have prompted researchers to redefine the understanding of how HDL might exert its cardioprotective functions [6,7]. Recent studies clearly showed that inflammation is a critical parameter in modifying the proteome and lipidome of HDL [8–10]. HDL is most widely recognized for its ability to transport cholesterol from the periphery to the liver for excretion during the process of reverse cholesterol transport (RCT). Numerous studies have shown that HDL and several of its apolipoproteins can promote lipid efflux from macrophages and other cells via several mechanisms [11–13] and deliver cholesteryl-esters to the liver in the process of selective uptake [13]. Studies in animals have consistently shown that HDL is protective on several processes involved in atherosclerosis, at least in part by mediating the removal of cholesterol from lipid-laden macrophages. In mice, genetic lowering of plasma HDL decreases the appearance of macrophage-derived cholesterol in the feces [14] and transgenic expression of apoA-I increases HDL and suppresses atherosclerosis in the apoE deficient mouse [15–17]. In humans, regressive changes in human atherosclerotic plaques were reported in relatively small studies when reconstituted HDL or apoA-I was provided exogenously [18–21]. However, the mechanisms by which HDL may impact cardiovascular health and disease are complex and remain to be fully understood.

2. Novel insights into potential protective activities of HDL

2.1. HDL mediated cholesterol removal from the vessel wall

Removal of cholesterol from peripheral tissues to the bloodstream via RCT is a process of major biological importance and is believed to be a main reason how HDL might prevent cardiovascular disease. Active export of excess cholesterol to lipid-poor apoA-I and lipid-enriched mature HDL is mediated by the ATP-binding cassette transporters ABCA1 and ABCG1/G4 [22] (Fig. 1). In situations of excess cellular cholesterol, the nuclear liver X receptors induce the transcription of ABCA1 and ABCG1 and thus cholesterol efflux. In addition, tethering of HDL to SR-BI and aqueous diffusion facilitates cholesterol efflux [23].

Of particular interest is the recent observation that the lymphatic vessel route is critical for efficient RCT from multiple tissues, including the aortic wall [24] (Fig. 1). This challenges the current view that lymphatic endothelium is a passive exchange barrier for cholesterol transport. Removal of cholesterol by lymphatic vessels is dependent on the uptake and transcytosis of HDL by SR-BI expressed on lymphatic endothelium [24,25]. These results suggest that supporting lymphatic transport function may facilitate cholesterol clearance in therapies aimed at reversing atherosclerosis.

The cholesterol taken up by HDL is esterified by LCAT and transported to the liver directly and indirectly via two major pathways (Fig. 1). In humans, CETP transfers HDL-cholesteryl esters to apoB-containing lipoproteins, which then are removed by the LDL receptor pathway or the liver-independent transintestinal excretion of cholesterol [26]. RCT thus also involves both formation and catabolism of LDL. Significant proportions of HDL-cholesterol are removed by selective uptake through SR-BI into the liver and steroidogenic organs [27].

2.2. Recent evidence links cholesterol efflux capability with anti-inflammatory activities of HDL

Although it is clear that macrophage foam cell formation and macrophage inflammation are both central processes in atherogenesis, the detailed mechanisms linking these processes remain incompletely understood. HDL has been shown to have anti-inflammatory and anti-oxidative properties itself [28]. For example, the major proteins of HDL, apoA-I and apoA-II, as well as other proteins such as LCAT, paraoxonase and lipoprotein associated phospholipase A_2 that cotransport with HDL in plasma, are known to have antioxidant properties [29,30]. As a consequence, HDL has the capacity to inhibit the oxidative modification of LDL thereby reducing the atherogenic properties of these lipoproteins. HDL also possesses anti-inflammatory properties itself, by inhibiting adhesion molecules expression in endothelial cells and thereby reducing the recruitment of blood monocytes into the artery wall (Fig. 1) [28,31]. An interesting cellular mode of action