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Differential Stability of High-density Lipoprotein Subclasses: Effects of Particle Size and Protein Composition

Xuan Gao, Shujun Yuan, Shobini Jayaraman and Olga Gursky*

Department of Physiology and Biophysics, Boston University School of Medicine, Boston, MA 02118, USA

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High-density lipoproteins (HDLs) are complexes of proteins (mainly apoA-I and apoA-II) and lipids that remove cholesterol and prevent atherosclerosis. Understanding the distinct properties of the heterogeneous HDL population may aid the development of new diagnostic tools and therapies for atherosclerosis. Mature human HDLs form two major subclasses differing in particle diameter and metabolic properties, HDL_2 (large) and HDL_3 (small). These subclasses are comprised of HDL(A-I) containing only apoA-I, and HDL(A-I/A-II) containing apoA-I and apoA-II. ApoA-I is strongly cardioprotective, but the function of the smaller, more hydrophobic apoA-II is unclear. ApoA-II is thought to counteract the cardioprotective action of apoA-I by stabilizing HDL particles and inhibiting their remodeling. To test this notion, we performed the first kinetic stability study of human HDL subclasses. The results revealed that the stability of plasma spherical HDL decreases with increasing particle diameter; which may facilitate preferential cholesterol ester uptake from large lipid-loaded HDL_2. Surprisingly, size-matched plasma HDL(A-I/A-II) showed comparable or slightly lower stability than HDL(A-I); this is consistent with the destabilization of model discoidal HDL observed upon increasing the A-II to A-I ratio. These results clarify the roles of the particle size and protein composition in HDL remodeling, and help reconcile conflicting reports regarding the role of apoA-II in this remodeling.

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Introduction

High-density lipoproteins (HDLs) are macromolecular complexes differing in shape (nascent discoidal or mature spherical), diameter (7–12 nm), density (1.21–1.063 g/mL), protein and lipid composition, and function.[1–3] Plasma levels of HDL, HDL cholesterol (mainly in the form of cholesterol esters (CE) sequestered in the particle core), and the major HDL protein, apolipoprotein A-I (apoA-I), are correlated inversely with the development of coronary artery disease, making HDL an attractive therapeutic target.[4,5] The cardioprotective action of HDL and apoA-I is attributed mainly to their central role in reverse cholesterol transport (RCT), which is the sole pathway of cholesterol removal, along with their antioxidant, anti-inflammatory and anti-apoptotic actions.[6,7] Efforts to design new diagnostic tools and therapies for atherosclerosis to complement statins, low-density lipoprotein-lowering drugs, have focused on increasing HDL quantity and, most recently, quality.[1–5] This requires an understanding of the distinct functional properties of the heterogeneous HDL population. Our goal is to provide the physicochemical basis for understanding aspects of

*Corresponding author. E-mail address: gursky@bu.edu.

Abbreviations used: HDL, high-density lipoprotein; rHDL, reconstituted high-density lipoprotein; HDL(A-I), HDL containing apolipoprotein A-I only; HDL(A-I/A-II), HDL containing both apopolipoprotein A-I and A-II; RCT, reverse cholesterol transport; CE, cholesterol ester; LCAT, lecithin:cholesterol acyltransferase, SR-BI, scavenger receptor class B type I; DMPC, dimyristoyl phosphatidylcholine; CD, circular dichroism; DSC, differential scanning calorimetry; EM, electron microscopy; T-jump, temperature-jump.

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functional remodeling of human HDL differing in particle size and protein composition.

HDL heterogeneity reflects multiple stages of HDL remodeling in RCT.[8] At an early stage, interaction of lipid-poor apoA-I with the plasma membrane, mediated by the ATP-binding cassette transporter A-1, leads to the formation of nascent discoidal HDL. These small particles are comprised of a cholesterol-containing phospholipid bilayer and two copies of apoA-I, whose amphipathic α-helices wrap around the disk perimeter, conferring particle stability and solubility.[9] Nascent HDLs form preferred substrates for lecithin:cholesterol acyltransferase (LCAT), which is activated by apoA-I and, to a lesser extent, by other exchangeable (water-soluble) apolipoproteins. Apolar CE produced by LCAT move to the particle interior, converting disks to small spheroid HDL_3 (d=7–9 nm, two copies of apoA-I per particle; Fig. 1). Upon further action of LCAT and other plasma factors, such as CE and phospholipid transfer proteins, small HDL_3 are converted to larger HDL_2 particles (d=10–12 nm, three or four copies of apoA-I per particle). Conversion of HDL_3 to HDL_2 involves lipoprotein fusion and dissociation of lipid-poor apoA-I that re-enters RCT.[8] After further remodeling, large HDL_2 upload their cargo of CE to the liver via the selective uptake of apolar lipids mediated by the scavenger receptor SR-BI.[11] At this final step, HDLs disintegrate and the dissociated apolipoproteins re-enter RCT or are catabolized.

In addition to apoA-I (243 amino acids), which comprises ~70% of the total HDL protein mass, nearly 20% of the protein in human HDL is comprised of apoA-II (an S–S-linked dimer of two 77 amino acid molecules). These two major HDL proteins are distributed in two HDL subclasses: HDL(A-I), which contain apoA-I only; and HDL(A-I/A-II), which contain both apoA-I and apoA-II in a molar ratio of approximately 2:1.[12] In contrast to apoA-I, whose cardioprotective action is well established, the function of apoA-II on HDL remains controversial.[13–15] Mouse model studies yielded conflicting results that, depending on the model, suggested pro- or anti-atherogenic properties of apoA-II.[16,17] Until recently, the consensus was that apoA-II is a poor cardioprotector and may even be pro-atherogenic;[13,14] however, recent epidemiologic studies report that apoA-II is cardioprotective.[15,17,18] Furthermore, apoA-II has been proposed to counteract the atheroprotective effects of apoA-I via several mechanisms, including inhibition of various steps of HDL remodeling in RCT;[14,19–22] however, not all reports claim that apoA-II inhibits HDL remodeling.[15] For example, some studies report that apoA-II prevents HDL remodeling and dissociation of lipid-poor apoA-I,[19,21] which is the primary acceptor of cell cholesterol,[22] while others report that apoA-II promotes such remodeling,[23] and may provide a reservoir of easily exchangeable apoA-I.[24] The latter is consistent with the well established ability of apoA-II to displace apoA-I from HDL.[25] This and other conflicting evidence suggests that apoA-II has a complex role in modulating metabolic remodeling of HDL, which may depend on the experimental system.[15]

We postulate that the effects of apoA-II on HDL remodeling and stability may be closely related. In fact, HDL remodeling *in vivo* by plasma factors and *in vitro* by thermal, chaotropic, detergent and other perturbations involves similar morphologic transitions, such as protein dissociation and lipoprotein fusion followed by the rupture and release of apolar core lipids. Consequently, HDL remodeling *in vivo* and *in vitro* may be modulated by similar kinetic barriers.[26–31] Therefore, analysis of the effects of apoA-II on HDL stability may help to better understand the role of this enigmatic protein in metabolic remodeling of HDL.

ApoA-II is widely believed to enhance HDL stability. Compared to apoA-I and other exchangeable apolipoproteins, apoA-II is thought to have

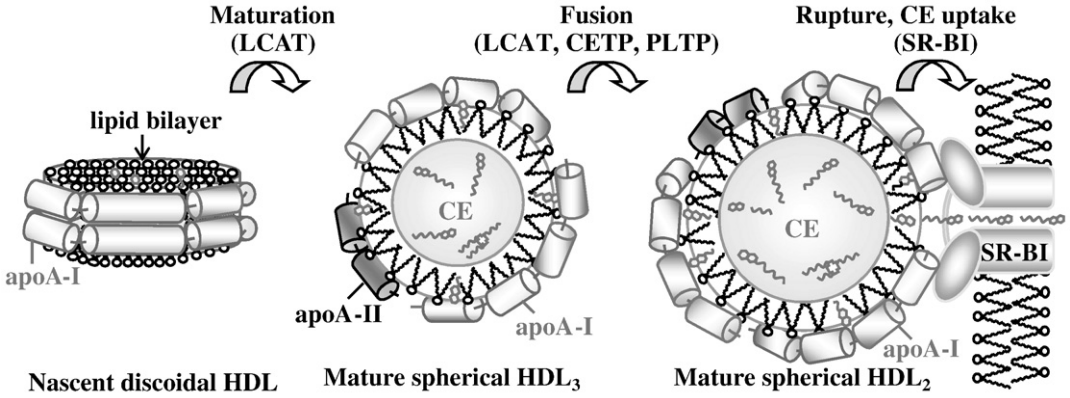

Fig. 1. A cartoon representation of the major subclasses of plasma HDL differing in shape and size and their interconversions. Nascent discoidal HDL, mature spherical HDL_3 (small, two copies of apoA-I per particle) and mature spherical HDL_2 (large, three to four copies of apoA-I per particle) are shown. ApoA-II comprises ~23% (w/w) of the total protein in HDL_3 (i.e. one copy of apoA-II per particle), but only ~10% in HDL_2; the CE content in HDL_2 is nearly double of that in HDL_3.[10] The LCAT reaction converts discoidal into small spherical HDL; further remodeling into large spherical HDL is mediated by LCAT and by cholesterol ester and phospholipid transfer proteins (CETP and PLTP).

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