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Review

Structural stability and functional remodeling of high-density lipoproteins☆

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ABSTRACT

Lipoproteins are protein–lipid nanoparticles that transport lipids in circulation and are central in atherosclerosis and other disorders of lipid metabolism. Apolipoproteins form flexible structural scaffolds and important functional ligands on the particle surface and direct lipoprotein metabolism. Lipoproteins undergo multiple rounds of metabolic remodeling that is crucial to lipid transport. Important aspects of this remodeling, including apolipoprotein dissociation and particle fusion, are mimicked in thermal or chemical denaturation and are modulated by free energy barriers. Here we review the biophysical studies that revealed the kinetic mechanism of lipoprotein stabilization and unraveled its structural basis. The main focus is on high-density lipoprotein (HDL). An inverse correlation between stability and functions of various HDLs in cholesterol transport suggests the functional role of structural disorder. A mechanism for the conformational adaptation of the major HDL proteins, apoA-I and apoA-II, to the increasing lipid load is proposed. Together, these studies help understand why HDL forms discrete subclasses separated by kinetic barriers, which have distinct composition, conformation and functional properties. Understanding these properties may help improve HDL quality and develop novel therapies for cardiovascular disease.

1. Introduction

1.1. Lipoproteins are dynamic vehicles for lipid transport

Lipids in the body are transported via lipoproteins that are non-covalent dynamic assemblies of specific proteins, termed apolipoproteins (apos), and lipids. Lipoproteins vary in size (10^1–10^2 nm), density, composition, structure and function. Plasma lipoproteins are central to cardiovascular health and disease [1,2]; this disease remains the leading cause of death in the developed countries [3]. Lipoproteins are also central to other major disorders of lipid metabolism such as metabolic syndrome, obesity and diabetes II [1,2], whereas apoE, which is the main apolipoprotein in the brain [4], acts in an isoform-specific manner as a major genetic risk factor for Alzheimer's disease [5]. Moreover, apolipoproteins are prone to misfolding and can form fibrils that are found in most amyloid deposits in vivo [6–8]. Apolipoprotein misfolding can cause systemic amyloidoses and has been implicated in atherosclerosis [6–8]. Both normal functions of apolipoproteins and their pathologic misfolding are critically hinged on their remarkable structural flexibility that enables these amphipathic proteins to adapt their conformations to lipoproteins of various sizes and to the aqueous environment such as plasma [9–11].

Apolipoproteins comprise up to 50% of the total lipoprotein mass and form flexible structural scaffolds and essential functional ligands on the lipoprotein surface [11,12]. These proteins direct lipoprotein metabolism by activating lipophilic enzymes, interacting with lipid transfer proteins, and binding and activating lipoprotein receptors [11,12]. Each lipoprotein particle contains several apolipoproteins and hundreds of lipids. The particle surface is comprised of apolipoproteins embedded into a monolayer of polar lipids, mainly phospholipids and cholesterol. The polar moieties of the proteins and lipids face solvent and thereby confer lipoprotein solubility, while the apolar lipids (mainly cholesterol esters and triacylglycerides, or fat) are sequestered in the core (Fig. 1 below). This assembly helps solubilize lipids and transport them to and from peripheral cells in the aqueous environment of plasma, lymph and cerebrospinal fluid.

Lipoproteins form major classes differing in the particle size, density, biochemical composition and function: high-, low-,

Abbreviations: apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; CETP, cholesterol ester transfer protein; PLTP, phospholipid transfer protein; DMPC, dimyristoyl phosphatidylcholine; CD, circular dichroism; HX MS, hydrogen deuterium exchange mass spectrometry

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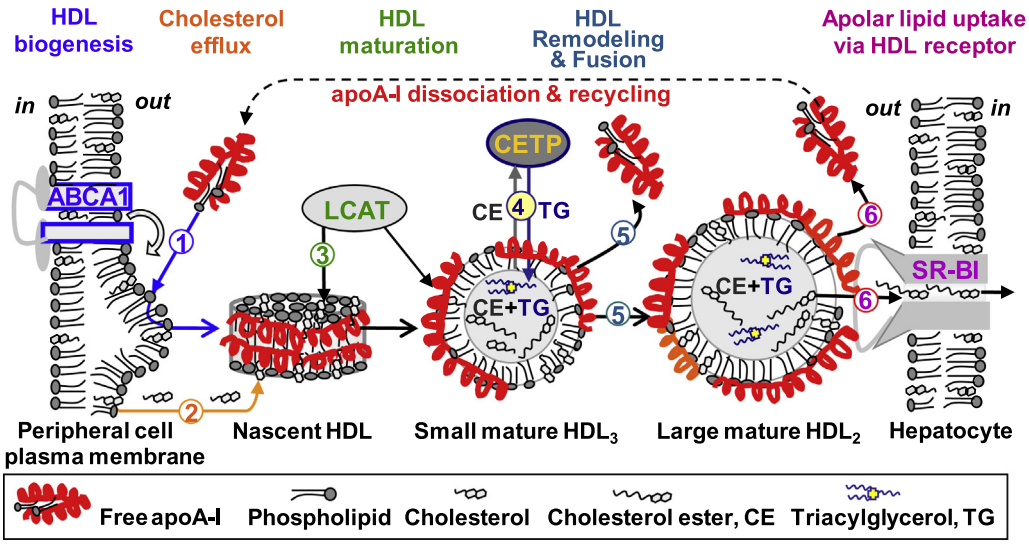

Fig. 1. Reverse cholesterol transport in a nut shell. Cartoon illustrates selected steps in this complex process. ApoA-I interacts with the plasma membrane and ABCA1 transporter to generate nascent "discoidal" HDL (1). These HDL take up additional cholesterol from the membrane (2) which is esterified by LCAT. The hydrophobic cholesterol ester produced in this reaction moves from the HDL surface to its core, leading to HDL maturation and formation of small spherical particles termed HDL_3 (3). These small HDL are further remodeled by LCAT and other plasma factors, such as cholesterol ester transfer protein (CETP) (4). This remodeling can cause imbalance between the polar surface and the apolar core of the particle, leading to partial protein dissociation and lipoprotein fusion to form larger HDL_2 (5). Large lipid-loaded HDL_2 form preferential substrates for the scavenger receptor, SR-BI, that mediates uptake of apolar core lipids and HDL disintegration (6). The dissociated apoA-I is either recycled or gets degraded or misfolded. Figure modified from [61].

intermediate-, and very low-density lipoproteins (HDL, LDL, IDL, VLDL) and chylomicrons [11–14]. Since proteins, which are heavier than lipids, are located on the particle surface, the particle diameter increases with decreasing density, from high-density lipoprotein (HDL) (7–12 nm) and low-density lipoprotein (LDL) (20–24 nm) to very low-density lipoprotein (VLDL) (40–100 nm). Each lipoprotein class has specific functions in lipid transport. HDLs remove excess cholesterol from peripheral cells, such as arterial macrophages, and have other beneficial properties. Plasma levels of HDL cholesterol ("good cholesterol") and the major HDL protein, apoA-I (28kDa), have long been known to correlate inversely with the risk of cardiovascular disease [14–16]. In contrast, LDL, which is the major plasma carrier of cholesterol in the form of cholesterol ester, delivers it to the peripheral tissues. The plasma levels of LDL cholesterol ("bad cholesterol") and the major LDL protein, apoB (550kDa), are the main causative risk factors of atherosclerosis [1,2,13,16]. VLDL, which is the main plasma carrier of fat, is the metabolic precursor of LDL and a critical risk factor for metabolic syndrome and diabetes II [1,2,13,17]. Each lipoprotein class is further subdivided into subclasses with distinct particle size, biochemical composition, and functional properties [18–20]. Analysis of these properties is the major thrust in the ongoing efforts to improve lipoprotein functionality and develop novel diagnostic tools and therapies for cardiovascular disease to complement statins, fibrates and other lipid-lowering drugs [20–22].

Lipoprotein metabolism is an extremely complex process during which individual particles exchange their proteins and lipids and undergo extensive remodeling by lipophilic enzymes, lipid transfer proteins and lipoprotein receptors. One example of such remodeling is HDL maturation and growth in reverse cholesterol transport [23,24]. In this complex pathway, nascent HDLs, which can be envisioned as "discoidal" particles comprised of a cholesterol-containing phospholipid bilayer with proteins wrapped around the perimeter, are transformed into mature "spheroidal" HDLs that contain a core of apolar lipids, mainly cholesterol esters (Fig. 1). This transformation is driven by lecithin:cholesterol acyltransferase (LCAT) that converts polar molecules of cholesterol and phosphatidylcholine into apolar cholesterol ester and free fatty acid. This and many other remodeling reactions shift the balance between the polar surface of a lipoprotein and its apolar core. Below we describe how this balance can be restored upon spontaneous lipoprotein fusion, fission and protein dissociation.

Although over 90% of all apolipoproteins circulate on the lipoprotein surface in a stable highly α-helical conformation, a small sub-population is found in a transient lipid-poor or lipid-free form [24–27], termed "free" for brevity. This structurally labile metabolically active form can be generated de novo or upon dissociation from the lipoprotein surface. Free apos are rapidly recruited for binding to plasma membrane or to other lipoproteins (Fig. 1); alternatively, they are either degraded or misfolded and form amyloid [6–8]. Apolipoproteins undergo large conformational changes in these transitions, from the highly dynamic partially unfolded free state, to a more stable largely α-helical lipid-bound state, to intermolecular cross-β-sheet in amyloid.

Lipoprotein heterogeneity and ability to exchange their protein and lipid constituents raises several fundamental questions. First, what maintains the overall integrity of the lipoprotein assembly in the absence of unique specific packing of its proteins and lipids? Second, what structural stability is optimal for lipoprotein functions? A related question is: how do apolipoproteins adapt their conformation to the changing lipid load during lipid transport? What is the conformational ensemble of an apolipoprotein free in solution and on the surface of various lipoproteins? Finally, what makes apolipoproteins amyloidogenic? The answers are beginning to emerge as a result of decades of work by many research groups.

Here, we review our biophysical studies of lipoproteins, with the focus on HDLs which are the smallest particles whose structural and stability properties have been best characterized. First, we provide a brief overview of HDL metabolism. Next, we outline the thermodynamic stabilization of lipid-free apolipoproteins in solution, and contrast it with the kinetic stabilization of model and plasma HDL. This is followed by the description of the key determinants for HDL stability and their relevance to HDL functions at specific steps of cholesterol transport. Finally, we propose a structure-based mechanism for functional adaptation of HDL proteins to the increasing lipid load during reverse cholesterol

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