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Commentary

HDL-cholesterol: Is it really good? Differences between apoA-I and HDL

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ABSTRACT

Since the very first report showing the regression of established atherosclerotic lesions by means of high-density lipoprotein cholesterol (HDL-C) plasma fraction, much information has been generated about the protective role of HDL-C in atherosclerosis. Nonetheless, this positive point of view about HDL has been nearly surpassed since modern informations concerning torcetrapib have appeared. Disappointment was palpable when its pivotal morbidity-and-mortality clinical trial, ILLUMINATE, was abruptly stopped due to excess mortality amongst the group randomized to receive torcetrapib. In this work we will try to put things in perspective.

Lowering low-density lipoprotein cholesterol (LDL-C) levels with statins is a proven strategy for reducing the cardiovascular disease (CVD) risk. Despite the impressive benefits of statins, there remain a significant proportion of treated patients in which cardiovascular events are not prevented. Low HDL-C levels are an important independent risk factor for CVD. There is a need to develop suitable therapies to reduce this residual risk through HDL-C related mechanisms. Therefore, we will first review HDL-C pathways and we will subsequently state the new pharmacological approaches to HDL-C metabolism.

1. Vessel wall lipid deposition in atherosclerosis

Cholesterol accumulation plays a central role in atherogenesis. Low-density LDL-C penetrates the vessel wall following endothelial dysfunction (the early phenomenon in atherosclerosis). It binds to the proteoglycans of the subendothelial space, where it undergoes an oxidative process. Oxidized cholesterol is highly toxic, and as part of a mechanism of defense, it is phagocytosed by the vessel wall macrophages. The presence of the oxidized lipids triggers a series of proinflammatory reactions via different mediators, perpetuating the activation and recruitment of monocytes-macrophages and inflammatory cells. Macrophages, by engulfing the lipid material, become foam cells. Failure of macrophages to remove cholesterol from the vessel wall promotes its apoptotic death, releasing cholesterol to the vessel wall and, more importantly, inflammatory substances like tissue factor and metalloproteases (enzymes able to digest the matrix scaffold), making atherosclerotic lesions more prone to rupture (the so-called vulnerable plaque). Secondary changes may occur in the underlying media and adventitia, particu-

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larly in advanced disease stages. Lesions progress to fibroatheroma by developing a cap of smooth muscle cells and collagen.

Therefore, the excess of vessel wall unesterified cholesterol is the pivotal phenomenon in atherosclerosis. Glomset coined the term ''reverse cholesterol transport'' (RCT) in 1968 [4] to describe the process by which peripheral cholesterol is returned to the liver for excretion in the bile and ultimately the feces. RCT is believed to be one of the main explanations in HDL-C atheroprotective effect.

2. Metabolism of HDL-C

HDL is a class of heterogeneous lipoproteins containing approximately equal amounts of lipid and protein. HDL particles are characterized by high density (>1.063 g/mL) and small size (5–17 nm). When separated by agarose gel electrophoresis, HDLs exhibit either α, pre-β, or γ migration. α-Migrating HDLs are mature, spherical particles that account for the major proportion of HDLs in plasma; a minor subpopulation of α-HDLs consists of large, spherical particles containing apoE and phospholipids (PL). Pre-β HDLs represent either discoidal particle consisting of apolipoprotein A-I (apoA-I) complexed with PL and free cholesterol (FC) or monomolecular, lipid-poor apoA-I.

Most of apoA-I, the predominant HDL protein, migrates in agarose gels with α-electrophoretic mobility and is designated α-LpA-I. This fraction accounts for almost all of the cholesterol quantified in the clinical laboratory as HDL-C. α-HDL can be further fractionated by density using ultracentrifugation into two major subfractions, HDL2 ($1.063 < d < 1.125$ g/mL) and HDL3 ($1.125 < d < 1.21$ g/mL. Approximately 5–15% of apoA-I in human plasma is associated with particles with pre-β-electrophoretic mobility [5].

These different properties of different types of molecules all named ''HDL-cholesterol'' highlights the fact that not all HDL-particles are equal, and their function (and therefore their role in atherosclerosis) is different from each other.

Fig. 1 shows a schematic view of the HDL metabolism and fate.

3. Synthesis of HDL-C

apoA-I is present on the majority of HDL particles and constitutes about 70% of the apolipoprotein content of HDL particles; thus, plasma apoA-I concentrations correlate closely with plasma HDL-C. apoA-II is the second most abundant apolipoprotein of HDL, but its physiologic role has not yet been fully defined; anyway, both apolipoproteins are required for normal HDL biosynthesis. HDL also contains a variety of other proteins, including apoA-IV, apoC-I, apoC-II, apoC-III, apoD, apoE, apoJ, apoL-I, apoM, serum amyloid A proteins, ceruloplasmin, transferrin, and enzymes such as LCAT, PON1, and PAF-AH/Lp-PLA2 [6].

As expected, gene deletion of apoA-I results in extremely low levels of HDL-C in mice [7]. Atherosclerosis-prone mice lacking apoA-I develop significantly increased atherosclerosis [8]. Hepatic overexpression of apoA-I significantly raises HDL-C levels and inhibits the progression of and even regresses atherosclerosis in mice [9,10]. Thus, upregulation of endogenous apoA-I expression is widely considered one of the most promising approaches in HDL-related therapies. However, in vivo studies of HDL metabolism in human populations have shown that clearance of apoA-I, rather than its production

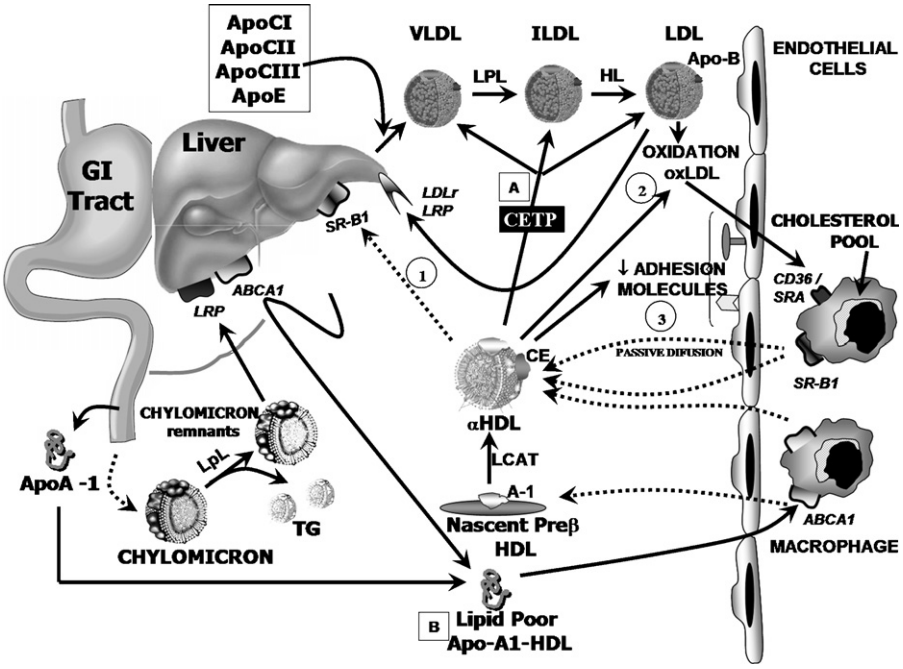

Fig. 1 – Schematic view of cholesterol metabolism and reverse cholesterol transport. See text for further details. Taken from Choi et al. [3].