

## Novel Aspects of HDL Biochemistry and Pharmacology

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High density lipoprotein (HDL) has been for years an intriguing lipoprotein which attracted the attention of biomedical community, mainly because of its important role in atheroprotection. Even though HDL-cholesterol is usually referred to as the “good cholesterol”, certainly it is far more than just a “cholesterol”. HDL is a macromolecular assembly of proteins and lipids formed in the circulation as a result of a concerted action of apolipoproteins, lipid transporters and plasma enzymes. Studies in cell cultures as well as in experimental mice showed that biogenesis of classical ApoA1-containing HDL particles (ApoA1-HDL) involves lipid transporters ATP-binding cassette A1 (Abca1) and G1 (Abcg1) and plasma enzyme Lecithin:Cholesterol Acyl Transferase (Lcat).

Previously, we showed in mice that other apolipoproteins such as apolipoprotein E (APOE) and apolipoprotein CIII (APOC3) are also capable of promoting the *de novo* biogenesis of HDL in the absence of a functional APOA1. In addition to the studies in mice, we recently observed the existence of APOE-HDL and APOC3-HDL particles in the circulation of morbidly obese human subjects; analysis of HDL particle composition showed that rapid weight loss was associated with a significant switch from primarily APOE-HDL and APOC3-HDL to primarily APOA1-HDL displaying increased antioxidant capacity. In another clinical paradigm we observed that young asymptomatic subjects ( $\leq 35$  years of age) who suffered an acute non-fatal myocardial infarction possessed elevated levels of plasma APOE-HDL and APOC3-HDL that correlated with reduced antioxidant potential. These clinical observations supported the hypothesis that variations in HDL apolipoprotein composition may set basis for its functional heterogeneity. Indeed, our more recent data support the contention that APOA1-HDLs are functionally distinct from APOE-HDL particles and that HDL proteome determines its lipidome.

The apparent differences in the HDL apolipoprotein content, lipidome and functionality between APOE3-HDL and APOA1-HDL that we identified through our preclinical and clinical studies reinforce the idea that not all HDL particles are equally active and that apolipoprotein composition is a key factor for defining HDL lipid content and particle functionality. Therefore, creation of effective pharmaceuticals that aim at improving HDL functionality requires deep understanding of the impact of apolipoprotein composition of HDL on its properties associated with protection from atherosclerosis and possibly from other metabolic disorders.

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