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Functions of cholesterol ester transfer protein and relationship to coronary artery disease risk

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Abstract: The protective role of HDL in atherosclerotic cardiovascular disease reflects in part its ability to promote cholesterol efflux via ATP binding cassette transporters ABCA1 and ABCG1 in macrophage foam cells. This initiates a process of reverse cholesterol transport from the arterial wall to the liver. Inhibition of cholesteryl ester transfer protein (CETP) raises HDL and probably stimulates cholesterol efflux and anti-inflammatory effects in macrophage foam cells but does not increase the overall process of reverse cholesterol transport. Single nucleotide polymorphisms in the CETP gene are associated with lower CETP, higher HDL and probably with reduced CAD. Initial clinical trials with the CETP inhibitor torcetrapib were associated with an adverse outcome that mainly seemed to arise from offtarget toxicity.

The story of high-density lipoprotein (HDL) and its role in athero-protection begins in the artery wall, where cholesterol-loaded macrophages have developed defense mechanisms to help them unload excess cholesterol. These defense mechanisms involve macrophage membrane proteins that use ATP-binding cassette transporters, or ABCs, to promote cholesterol efflux onto HDL and its apolipoproteins.[1] It is now clear that there are at least two major players in this regard. One is ABCA1, the molecule that is mutated in Tangier disease, and the other one is ABCG1. ABCA1 promotes efflux of cholesterol and phospholipids onto lipid-poor Apo-A1, the major protein constituent of HDL (Fig. 1), whereas ABCG1 promotes cholesterol efflux onto HDL particles that have already been formed. ABCA1 and ABCG1 can act sequentially to promote cholesterol efflux, with ABCA1 serving to make HDL (this occurs mainly in the liver where ABCA1 adds free cholesterol and phospholipids to apoA-1 synthesized in the liver), and then ABCG1 acting to promote cholesterol efflux onto HDL particles.

Interestingly, both ABCA1 and ABCG1 are controlled transcriptionally by a specialized transcription factor called LXR (liver-X-receptor) that acts in a complex with RXR (retinoid-X-receptor) so that when cells accumulate cholesterol, some of that cholesterol is transformed into specific oxidized forms of cholesterol (oxysterols) that activate LXR and then up-regulate ABCA1 and ABCG1. Very recently, it has been discovered by Moore and Fernandez-Hernando[2] that there is another level of control of ABCA1 and ABCG1 involving a suppressor microRNA (a small kind of RNA that targets mRNAs for degradation) called miR-33 that acts to cause degradation of ABCA1 or ABCG1 protein and mRNA. miR-33 is embedded in the sterol regulatory element binding protein 2 (*SREBP2*) gene, the master transcriptional regulator of cholesterol biosynthetic genes, so when cells are deprived of cholesterol they up-regulate their SREBP2 and in so doing they activate this micro RNA, which turns off ABCA1 and ABCG1, limiting cholesterol efflux and helping to conserve cellular cholesterol.

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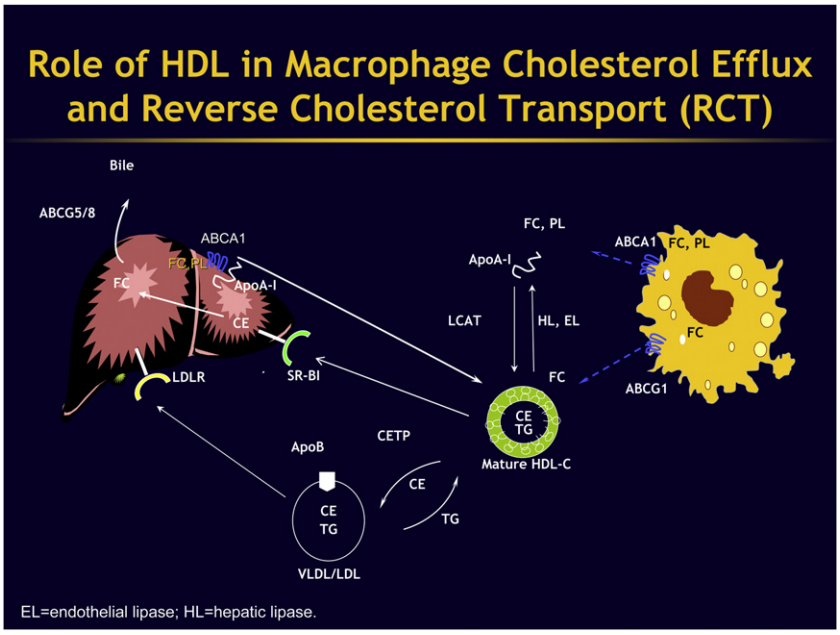

Figure 1 Role of HDL in macrophage cholesterol efflux and RCT.

Then, in the whole organism this cholesterol efflux pathway becomes integrated into a larger pathway mediating reverse cholesterol transport (RCT). The concept derives from original work by John Glomset, and the term "reverse cholesterol transport" was originally coined by Dan Steinberg. In the schematic of RCT the idea is that macrophage cholesterol efflux is followed by esterification of cholesterol to form cholesterol esters (CEs) by the lecithin:cholesterol acyltransferase enzyme in high-density lipoprotein (HDL). CEs are transferred in plasma by cholesterol ester transfer protein (CETP) from HDL to triglyceride-rich particles. The CETP pathway is especially important in humans. In rodents, HDL components may be directly removed from the plasma by the scavenger receptor B1 (SR-BI) pathway, which mediates a process of selective uptake of HDL CE in the liver, which may be followed by excretion of cholesterol into bile. One of the debates that is ongoing is whether the antiatherogenic activity of HDL requires up regulation of all of the steps involved in reverse cholesterol transport (i.e., cholesterol efflux from arterial wall foam cells, transport in the plasma, uptake in the liver and excretion into bile) or whether the antiatherogenic effect only requires increased cholesterol efflux from macrophage foam cells or other direct cellular activities of HDL such as anti-inflammatory effects.

Let me now discuss CETP and its inhibition in the overall context of RCT. When CETP is inhibited, the overall rate of RCT is not changed. However, the route of RCT has changed. It is occurring through HDL instead of through VLDL and LDL. When CETP is inhibited, cholesterol efflux may be increased from macrophages, but RCT overall is not increased. For that matter, niacin also increases HDL but probably does not increase fecal sterol output, so it also does not increase overall RCT. My personal view is that only the step at the interface between the artery wall and HDL needs to be up regulated to derive benefit.

Inhibiting CETP became a therapeutic strategy in 1989−1990 when we and our colleagues in Japan characterized a genetic deficiency state of CETP and patients who had homozygous deficiency were found to have remarkably elevated HDL levels of approximately 100 to 160 mg/dL.[3] Heterozygotes had an approximately 30% increase in HDL levels compared with unaffected family members. Thus, only 50% inhibition of CETP, equivalent to levels in heterozygotes, would be required to increase HDL by as much as niacin, so this attracted a lot of interest. In addition, in that initial description we noted that homozygotes also had a 40%lowering of low-density lipoprotein (LDL) cholesterol and apolipoprotein B (ApoB), whereas heterozygotes showed a nonsignificant decrease in their LDL. This high HDL, low LDL phenotype is also seen after treatment of humans with potent CETP inhibitors.[4] Such agents lower LDL appreciably, as well as increasing HDL, whereas less potent CETP inhibitors increase HDL without much effect on LDL.

It is important to recognize that different therapeutic approaches to raising HDL have really different effects on the kind of HDL that accumulates.[5] The most desirable agent for increasing HDL would be one that increased the synthesis of Apo-A1 in the liver, but so far this has proved tricky. Fibrate drugs do increase Apo-A1 and even more so Apo-A2 synthesis in the liver, and this is probably part of their HDL–increasing mechanism. However, as found in studies like ACCORD and FIELD, the degree of HDL elevation with agents like fenofibrate is quite modest. Infusing Apo-A1 appears to be beneficial in animal models and in humans. Recently, small molecules have been described