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Plasma high density lipoproteins: Therapeutic targeting and links to atherogenic inflammation

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ABSTRACT

Plasma HDL levels have an inverse relationship to coronary artery disease (CAD) risk, which led to the idea that increasing HDL levels therapeutically would ameliorate atherosclerosis. Human genetic deficiency of CETP caused markedly elevated HDL and moderately reduced non-HDL cholesterol levels, suggesting that CETP inhibitors might produce cardiovascular benefit. The CETP inhibitor anacetrapib reproduced the phenotype of homozygous CETP deficiency and showed a highly significant benefit for CAD in the REVEAL trial. However, the magnitude of this effect was moderate, and the mechanism of benefit remains unclear. Insights into the mechanisms underlying macrophage cholesterol efflux and reverse cholesterol transport have come from monogenic human disorders and transgenic mouse studies. In particular, the importance of the ATP binding cassette transporters ABCA1 and ABCG1 in promoting cholesterol efflux from myeloid and other hematopoietic cells has been shown and linked to aberrant myelopoiesis and macrophage inflammation. Recent studies have shown that myeloid deficiency of ABCA1 and ABCG1 leads to macrophage and neutrophil inflammasome activation, which in turn promotes atherosclerotic plaque development and notably the formation of neutrophil extracellular traps (NETs) in plaques. In addition, clonal hematopoiesis has emerged as an important CAD risk factor, likely involving macrophage inflammation and inflammasome activation. Further elucidation of the mechanisms linking plaque accumulation of cholesterol and oxidized lipids to myeloid cell inflammation may lead to the development of new therapeutics specifically targeting atherogenic inflammation, with likely benefit for CAD.

1. HDL and atherosclerosis

In epidemiological studies, plasma HDL-cholesterol levels show a robust inverse relationship with coronary heart disease (CHD) independent of other risk factors [1]. Infusions of HDL or increased expression of the main HDL protein, apoA-1, consistently reduce atherosclerosis in animal models [2–5]. In most studies, the ability of HDL to promote cholesterol efflux from macrophage foam cells is inversely correlated with human coronary atheroma burden and with incident CHD [6–11]. In contrast, Mendelian Randomization studies have failed to find a relationship between SNPs that increase HDL cholesterol levels and coronary heart disease [12]. Nonetheless, preclinical studies and studies of human HDL functionality suggest that some approaches to increasing HDL levels or beneficial functions might be a way to reduce the substantial burden of CHD that remains in subjects optimally treated by LDL lowering [13].

The idea that HDL might mediate protection from atherosclerosis by stimulating an overall process of reverse cholesterol transport was originally proposed by Glomset [14]. Over the subsequent four decades, the factors controlling HDL metabolism and the molecular underpinnings of the reverse cholesterol transport pathway have been elucidated with contributions by many laboratories [2,3,15–18]. The most important insights have been gained by the elucidation of human genetic deficiency states affecting HDL and by transgenic mouse studies. Fig. 1 illustrates the overall process of reverse cholesterol transport. This is initiated in the arterial wall by the ATP binding cassette transporters ABCA1 and ABCG1, which are induced in arterial wall macrophage foam cells by LXR activation and promote the efflux of cholesterol onto lipid poor ApoA-1 and HDL particles. Cholesterol in HDL may be esterified by lecithin:cholesterol acyltransferase (LCAT) and directly taken up in the liver by a process of selective free and esterified cholesterol removal mediated by scavenger receptor B1 (SR-BI). In humans,

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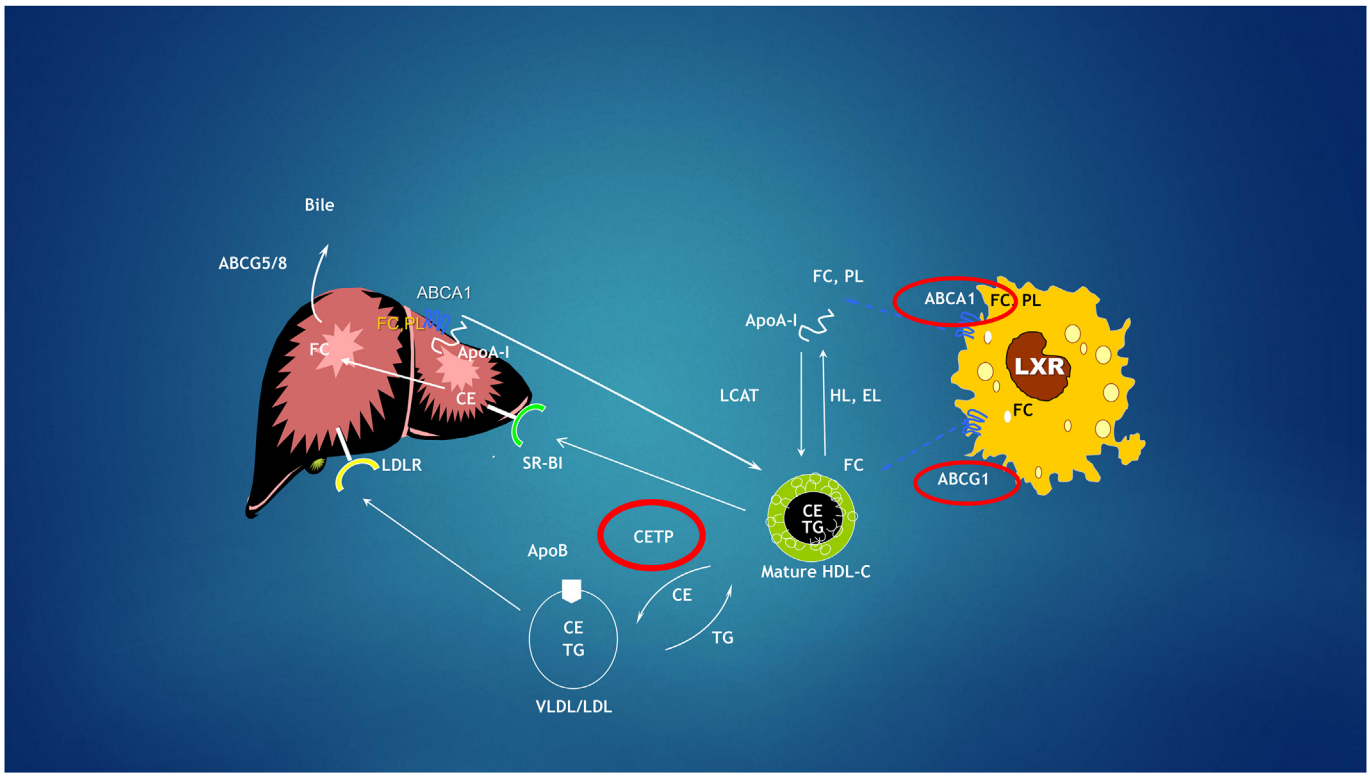

Fig. 1. The role of HDL in macrophage cholesterol efflux and reverse cholesterol transport.
Macrophage cholesterol efflux and reverse cholesterol transport are initiated in the arterial wall by the ATP binding cassette transporters ABCA1 and ABCG1, which are induced in arterial wall macrophage foam cells by LXR activation and promote the efflux of cholesterol onto lipid poor apoA-1 or HDL particles.
Cholesterol in HDL may be esterified by lecithin:cholesterol acyltransferase (LCAT) and directly taken up in the liver by a process of selective cholesteryl ester removal mediated by scavenger receptor B1 (SR-BI). This may be followed by the excretion of cholesterol into bile involving ABCG5/8. In humans, cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl esters (CE) in HDL with triglycerides in VLDL or chylomicrons leading to a net transfer of CE form HDL to the triglyceride-rich lipoproteins and LDL and subsequent removal in the liver via the LDL receptor and other pathways. ABCA1 also initiates the formation of HDL particles in the liver and small intestine (not shown) by binding ApoA-1 and promoting its lipidation. HL, hepatic lipase; EL, endothelial lipase.

cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl esters (CE) in HDL with triglycerides in VLDL or chylomicrons, leading to a net transfer of CE from HDL to the triglyceride-rich lipoproteins and LDL and subsequent removal in the liver via the LDL receptor and other pathways. Research in my laboratory initially focused on elucidating the role of CETP in lipoprotein metabolism. More recent studies have used mouse models to investigate the role of ABCA1 and ABCG1 in cholesterol efflux and atherosclerosis.

1.1. Human genetic CETP deficiency and the development of CETP inhibitors

In collaboration with colleagues in Japan, we first defined human genetic deficiency of CETP, which was characterized by markedly elevated levels of HDL cholesterol (HDL-C), as well as reduced levels of LDL cholesterol (LDL-C) and ApoB, a profile that is typically associated with reduced atherosclerosis [19]. This led to the development of CETP inhibitors. These were shown to raise HDL-C and ApoA-1 levels, and for the more potent CETP inhibitors, there was also a lowering of HDL cholesterol and ApoB levels. Based on epidemiological observations, it was expected that this dramatic increase in HDL would deliver a marked anti-atherogenic effect. However, this was not the case for CETP inhibitors that were initially developed. In fact, the first CETP inhibitor to enter human clinical trials, torcetrapib, caused an excess of deaths and cardiovascular disease [20]. This led many experts to conclude that the HDL itself was dysfunctional or harmful. However, significant off-target side effects, involving hyperaldosteronism and substantial hypertension, were attributed to torcetrapib [20]. The demonstration of an overall anti-atherogenic effect of CETP inhibition was suggested by the majority of animal studies showing a pro-atherogenic effect of CETP expression [21]. Moreover, multiple large human genetic studies showed that SNPs in the *CETP* gene, that are associated with increased HDL and reduced LDL cholesterol, are associated with reduced CHD [22–24]. This includes SNPs that likely reduce the function of the promoter region upstream of the *CETP* gene [24], and most importantly, CETP protein truncating mutations that abrogate the function of CETP [23]. This has permitted further human clinical studies to be performed to evaluate other members of this class of drugs. Subsequent studies trials with the relatively weak CETP inhibitor dalcetrapib [25] and with the potent inhibitor evacetrapib [26] were halted prematurely because of projected lack of efficacy.

Finally, in the largest study of a CETP inhibitor, and the first to go to completion, the potent CETP inhibitor anacetrapib was shown to significantly reduce major coronary events [27]. This study involved 30,449 patients with atherosclerotic cardiovascular disease who were randomized to receive anacetrapib 100 mg daily or placebo on top of effective statin therapy and followed for a median of 4.1 years. The study showed a highly significant reduction (rate ratio = 0.91, $p < 0.004$) in the composite primary endpoint of coronary death, myocardial infarction or coronary revascularization [27]. The modest degree of reduction in the primary endpoint likely reflected the fact that control patients, who were highly effectively treated with statins, had an LDL cholesterol of 61 mg/dl, making it a