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STATE-OF-THE-ART PAPER

Targeting Cholesteryl Ester Transfer Protein for the Prevention and Management of Cardiovascular Disease

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Epidemiologic studies have shown that the concentration of high-density lipoprotein cholesterol (HDL-C) is a strong, independent, inverse predictor of coronary heart disease risk. This identifies HDL-C as a potential therapeutic target. Compared with low-density lipoprotein cholesterol (LDL-C)-lowering agents, however, currently available HDL-raising drugs are relatively ineffective. Consequently, recent years have seen considerable efforts expended on identifying new drugs that can raise HDL-C. Cholesteryl ester transfer protein (CETP) plays an important role in cholesterol metabolism, being responsible for the transfer of cholesteryl esters from HDL to very low-density lipoproteins and LDLs. The observation that Japanese populations with CETP deficiency exhibited high levels of HDL-C has led to the concept that drugs targeting CETP activity may elevate HDL-C levels and potentially decrease cardiovascular risk. Support of this proposition has been obtained in rabbits where inhibition of CETP activity is markedly antiatherogenic. Two CETP inhibitors—torcetrapib and JTT-705—are currently in the preliminary stages of clinical development. Initial studies with these drugs in humans show that they substantially increase HDL-C levels and modestly decrease LDL-C levels. Larger, long-term, randomized, clinical end point trials are required to determine whether the beneficial effects of CETP inhibitors on lipoprotein metabolism can translate into reductions in cardiovascular events. (J Am Coll Cardiol 2006;47:492–9)

Epidemiologic studies have identified high-density lipoprotein cholesterol (HDL-C) as a strong, independent, inverse predictor of coronary heart disease (CHD) risk (1,2). In the Framingham Heart study, HDL-C was a more potent risk factor for CHD than low-density lipoprotein cholesterol (LDL-C), total cholesterol, or plasma triglycerides (1). An analysis of four large studies has indicated that each 1 mg/dl increase in HDL-C is associated with a 2% to 3% decrease in the risk of CHD (3). Despite this, evidence from large-scale, randomized clinical trials that elevating HDL-C reduces risk is sparse (4). The most compelling results, to date, are from the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial (VA-HIT) and the Helsinki Heart study (HHS). In VA-HIT, CHD patients randomized to the fibrate gemfibrozil experienced a 6% increase in HDL-C, a 31% decrease in plasma triglycerides, and no change in LDL-C. Major coronary events were reduced by 22% compared with placebo. The change in HDL-C was significantly associated with reductions in coronary events, whereas the change in triglycerides was not (5). This was also apparent in a primary prevention setting in the HHS in which an 8% increase in HDL-C translated into a 24% reduction in events, independent of changes in LDL-C and triglycerides (6). Niacin, another HDL-raising agent, has been shown in one long-term trial to achieve a significant reduction in major coronary events, and, in a 15-year follow-up 9 years after the trial completed, there was a significant reduction in total mortality in the group initially assigned to niacin (7). Statins also have HDL-raising properties in addition to their ability to lower LDL-C, with the statin-induced increase in HDL-C in the Scandinavian Simvastatin Survival Study (4S) trial contributing significantly to event reduction (8).

These results have stimulated the search for new more effective HDL-raising therapies (9). Here, we review a novel approach to increasing HDL-C—inhibition of the cholesteryl ester transfer protein (CETP), a plasma protein that regulates the distribution of cholesterol between HDLs and LDLs (10).

CHOLESTEROL METABOLISM

Atherosclerosis develops and the risk for cardiovascular disease (CVD) events increases when modified LDL particles are taken up by macrophages in the artery wall to form foam cells in a process that leads ultimately to the development of plaque. In contrast to LDLs, HDLs are antiatherogenic, partly because of their role in reverse cholesterol transport but also due to a spectrum of documented antioxidative, anti-inflammatory, antithrombotic, and antiapoptotic properties (11–13). The primary pathways involved in cholesterol metabolism and the role that CETP plays in transferring triglycerides and cholesteryl esters (CEs) between lipoproteins are illustrated in Figure 1.

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Abbreviations and Acronyms

ABCA1	= ATP-binding cassette A1
apo	= apolipoprotein
CE	= cholesteryl ester
CETP	= cholesteryl ester transfer protein
CHD	= coronary heart disease
CVD	= cardiovascular disease
FH	= familial hypercholesterolemia
HDL	= high-density lipoprotein
HDL-C	= high-density lipoprotein cholesterol
HHS	= Helsinki Heart study
LDL	= low-density lipoprotein
LDL-C	= low-density lipoprotein cholesterol
SR-B1	= scavenger receptor-B1
VA-HIT	= Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial
VLDL	= very low-density lipoprotein

LDLs. Low-density lipoproteins contain a core of mainly CEs and a small amount of triglycerides surrounded by surface of phospholipids, free cholesterol, and apolipoprotein (apo) B (14). Cholesterol is secreted from the liver into plasma in very low-density lipoproteins (VLDLs), which in turn are converted to LDLs. Low-density lipoproteins deliver cholesterol to tissues after binding to the LDL receptor.

HDLs. The major protein of HDLs is apo A1, which is synthesized in the liver and secreted into plasma in a lipid-poor form. Lipid-poor apo A1 rapidly acquires free cholesterol from tissues via the adenosine triphosphate (ATP)-binding cassette A1 (ABCA1) transporter to form discoidal HDL particles. Discoidal HDLs interact with lecithin:cholesterol acyltransferase, which converts a proportion of their free cholesterol into CEs that migrate into a hydrophobic core in a process that converts the disc into a mature, spherical HDL particle (Fig. 2). The fact that discoidal HDL particles are normally present at only very low concentration in plasma reflects the rapidity with which they are converted into spheres. The cholesterol in mature HDL particles interacts with the hepatic scavenger receptor class B type 1 (SR-B1) to deliver cholesterol (mainly as free cholesterol) to the liver (Fig. 1) (15). The process of transferring cholesterol from peripheral cells to the liver for removal from the body by biliary secretion is called reverse cholesterol transport. The role of HDLs in facilitating reverse cholesterol transport is one of the mechanisms by which HDLs protect against atherogenesis.

It has recently become clear that ABCA1 is not the only means by which peripheral cells can efflux cholesterol to HDLs. Other mechanisms include interaction of HDLs with SR-B1 (16) and passive diffusion (17). Another transporter, the ATP-binding cassette G1, is expressed in macrophages where it promotes the efflux of cholesterol from the cell to mature, spherical HDLs (Fig. 2) (18,19).

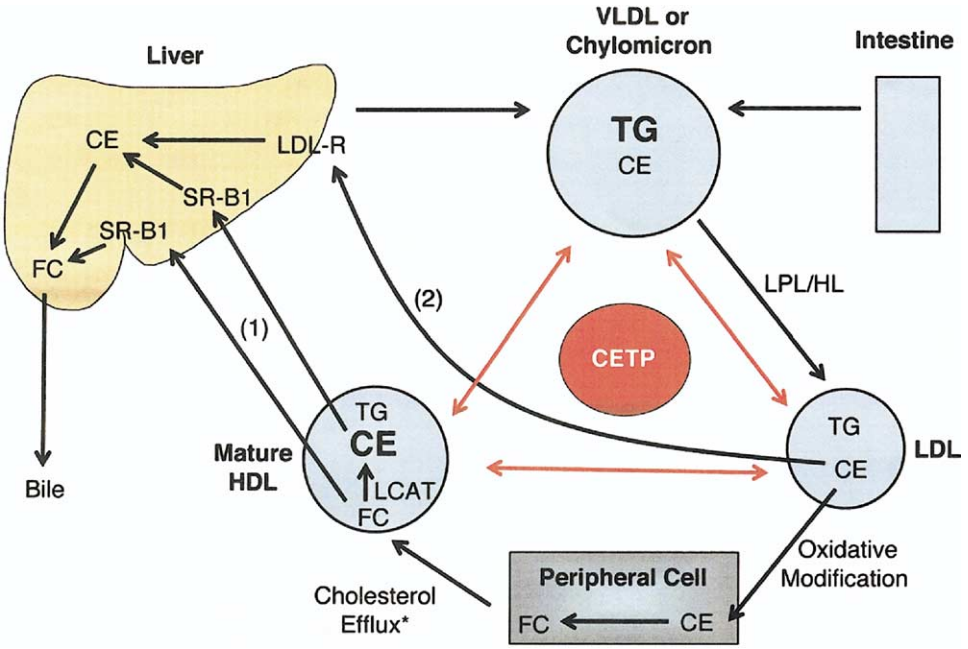

Figure 1. Role of cholesteryl ester transfer protein (CETP) in plasma lipid transport. Cholesteryl ester transfer protein promotes bidirectional transfers (shown by the **red arrows**) of cholesteryl esters (CE) and triglycerides (TG) between high-density lipoproteins (HDLs), very low-density lipoproteins (VLDLs), and low-density lipoproteins (LDLs). Most of the CEs in plasma originate in HDLs in a reaction catalyzed by lecithin:cholesterol acyltransferase (LCAT), while the majority of the TG enters plasma as a component of TG-rich lipoproteins secreted either from the liver as VLDLs or from the intestine as chylomicrons. Very low-density lipoproteins are subsequently converted into LDLs after hydrolysis of a proportion of their TG by lipoprotein lipase (LPL) and hepatic lipase (HL). The overall effect of the CETP-mediated CE exchanges between these lipoproteins is a net mass transfer of CE from the antiatherogenic HDLs to the potentially proatherogenic VLDLs and LDLs. The cholesterol in LDLs is taken up by all cells (both in liver and peripheral tissues) that express the LDL receptor. Modified (oxidized) LDLs are also taken up by macrophages in a scavenger receptor-mediated process that converts the macrophage into a foam cell. Cholesterol, both in its free or unesterified form (FC) and in its esterified form as CE, is returned to the liver by HDLs via the scavenger receptor-B1 (SR-B1) (pathway 1) and by LDLs via the LDL receptor (LDL-R) (pathway 2). See Figure 2 for mechanisms through which peripheral cells may efflux cholesterol to HDL particles.