

Cholesteryl ester transfer protein: friend or foe?

C J Fielding, R J Havel

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Editorial

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High density lipoproteins (HDLs) represent a highly heterogeneous population of lipoprotein particles united by the presence of at least one molecule of apolipoprotein A-I (apo A-I). They include not only the familiar spherical HDL, with alpha electrophoretic mobility, which make up most of the population, but also several smaller, cholesterol-poor HDL containing only apo A-I, which have prebeta migration. Recent evidence suggests that apo A-I dissociating from mature, spherical HDL may serve as an efficient acceptor of cholesterol from peripheral cells (1), thereby initiating the process of "reverse" cholesterol transport. The small prebeta HDL in which the sole protein is apo A-I mature to spherical particles through the activity of lecithin:cholesterol acyltransferase. The HDL cholesteryl esters produced by lecithin:cholesterol acyltransferase are transferred away to cells or to other lipoproteins, and lipid-poor apo A-I is released, completing its metabolic cycle.

Cholesteryl ester transfer protein (CETP) was initially identified as a factor promoting the transfer of cholesteryl esters from HDL to VLDL and LDL in exchange for triglyceride (2). This triglyceride is hydrolyzed on HDL by hepatic lipase. Although CETP also is effective in transferring CE between HDL molecules, the CETP reaction has the obvious potential to increase circulating VLDL and LDL cholesterol levels. As a result, CETP has been often considered a "proatherogenic" factor. Transgenic mice expressing high levels of the simian CETP gene were reported to be more susceptible to an atherogenic, fat-rich diet than normal mice (3). CETP-deficient human subjects of Japanese origin did not show clinical signs of advanced atherosclerosis (2). These data were also interpreted to indicate that CETP is proatherogenic despite the low incidence of coronary heart disease generally found in the Japanese population.

Another recent study identified a second role for CETP (4). Like hepatic lipase (5), CETP can promote dissociation of apo A-I from mature HDL, to generate prebeta HDL particles that could accelerate the transfer of cellular cholesterol to HDL. This potentially antiatherogenic effect is consistent with reports of studies *in vitro* and in transgenic mice (for review see reference 1). The ability of plasma to promote transfer of cholesterol from peripheral cells to HDL was found to be dependent upon the HDL prebeta-migrating fraction. Mice transgenic for human apo A-I had increased levels of prebeta HDL and were protected against atherosclerosis. Mice transgenic for human hepatic lipase, which not only promotes dissociation of apo A-I from HDL but also the uptake of HDL-CE by the liver, had reduced aortic cholesterol (6). Hypertriglyceridemic mice expressing a CETP transgene were protected against atherosclerosis (7). Hepatic lipase knockout mice have high HDL cholesterol levels but low levels of prebeta HDL

(8). Their susceptibility to atherosclerosis would be of particular interest because mice normally lack CETP activity.

A fascinating window into this complex world is provided in the paper by Zhong et al. (9) in this issue of *The Journal*. The effect of partial genetic deficiency of CETP on the prevalence of coronary heart disease (CHD) was found to depend on the concentration of HDL cholesterol. At high and low HDL cholesterol concentrations, CETP deficiency was without effect, but at intermediate values (41–60 mg dl⁻¹) CETP deficiency was associated with an increased incidence of CHD. A recent study by Hirano et al. (10) also found that CETP deficiency was not necessarily antiatherogenic; some CETP-deficient patients were found to have CHD despite very high HDL cholesterol concentrations. These patients also had consistently low hepatic lipase activity, suggesting that deficiency of both mechanisms for generating lipid-poor apo A-I may substantially impede reverse cholesterol transport.

There are several important implications to these findings. They suggest that in the normal range of human HDL levels the antiatherogenic effect of CETP, which probably reflects its facilitation of cholesterol transport from peripheral tissues to plasma, may be more important that its potential to promote atherogenesis by increasing LDL cholesterol. As a result, partial CETP deficiency was associated with an increased incidence of CHD in Japanese men. When HDL levels are low, CETP is unlikely to remain rate-limiting for prebeta HDL production, particularly in the presence of normal levels of hepatic lipase, so the absence of effect of CETP deficiency in this case becomes explicable. When HDL levels are high, CETP will be active mainly in the transfer of cholesteryl esters to other HDL, not to VLDL and LDL. The absence of effect of partial CETP deficiency in this case can also now be explained from the biochemical properties of CETP (2).

The studies of Zhong et al. (9) and Hirano et al. (10) both illustrate the interplay between plasma lipoproteins (particularly HDL itself) and metabolic factors (CETP and hepatic lipase) in determining the significance of HDL cholesterol levels. It is now more than 20 yr since HDL cholesterol was first identified as a factor "protective" against CHD in human populations, independent of the level of LDL (11). This finding, now generally recognized, is still not fully explained, although most investigators accept a relationship between HDL concentration and its ability to promote the efflux of cholesterol from susceptible tissues. Most clinical investigations report only total HDL cholesterol, with no account of the activities of factors such as CETP and hepatic lipase that determine HDL size distribution. Determination of the levels of these factors, and the composition of HDL as well as its cholesterol content, will probably be needed to differentiate the hypo- and hyperalphalipoproteinemic syndromes, respectively, associated with susceptibility to and protection from CHD.

Christopher J. Fielding and Richard J. Havel
Cardiovascular Research Institute
University of California
School of Medicine
San Francisco, California

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