Lipid Transfer Proteins and Receptors in HDL Metabolism

Alan R. Tall, Xian-cheng Jiang, Nan Wang, Takeshi Arai and David Silver.

College of Physicians and Surgeons of Columbia University, Department of Medicine, Division of Molecular Medicine, 622 West 168th Street Ph SE 101, New York, NY 10032, U.S.A.

SUMMARY

Plasma high density lipoprotein (HDL) levels are determined both by intravascular metabolism and by clearance pathways. Recent evidence indicates that plasma lipid transfer proteins play a major role in the intravascular metabolism of HDL, while HDL receptors in tissues are important in HDL catabolism. The role of the plasma lipid transfer proteins, cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP), have been elucidated by genetic deficiency states in humans or mice, or by overexpression experiments in mice. Human CETP deficiency results in increased HDL levels, but also increased coronary heart disease, suggesting an antiatherogenic function of CETP related to its role in reverse cholesterol transport. PLTP knock-out mice have absent plasma phospholipid transfer activity and markedly reduced HDL cholesterol and apoA-I levels, demonstrating the crucial role that the transfer of surface phospholipid of triglyceride-rich lipoproteins plays in the maintenance of HDL levels. Scavenger receptor BI has recently emerged as an authentic HDL receptor mediating the selective uptake of HDL CE in liver and steroidogenic tissue. Overexpression of SR-BI in transgenic mice results in low HDL levels, and also decreases VLDL and LDL cholesterol and apoB levels, and reduces atherosclerosis in response to a high cholesterol/bile salt diet. Knock-out of SR-BI results in increased HDL levels due to decreased selective uptake in the liver, but the catabolism of HDL proteins is unaltered. Recent studies in obese (ob/ob) mice show a catabolic defect of HDL protein in the liver and suggest a leptin-regulated liver catabolic process for apoA-I and apoA-II. Thus, while CETP, PLTP and SR-BI are important in the turnover of HDL lipids, it appears that distinct receptors are involved in the catabolism of HDL proteins.

Key words: cholesteryl ester transfer protein, phospholipid transfer protein, scavenger receptor BI, obesity, high density lipoproteins.

TEXT

The protective role of HDL in atherosclerosis is thought to reflect its role in reverse cholesterol transport. Increased expression of the major HDL apolipoprotein, apoA-I, result in decreased atherosclerosis, perhaps as a result of increased reverse cholesterol transport, but the regulation of apoA-I turnover and reverse cholesterol transport is poorly understood. The purpose of our studies is to investigate the regulation and role of lipid transfer proteins and receptors in HDL metabolism.
LIPID TRANSFER PROTEINS

The two major plasma lipid transfer proteins, cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP), belong to a gene family of lipopolysaccharide binding/lipid transfer proteins. The role of CETP in lipoprotein metabolism and atherogenesis has been demonstrated by human genetic deficiency states of CETP and transgenic mice overexpressing CETP. These studies suggest that while lowering HDL levels, CETP stimulates reverse cholesterol transport and has anti-atherogenic properties (1,2).

Recently, we have used targeted gene mutation to create mice deficient in PLTP (3). PLTP knockout (KO) mice have normal viability and development. Plasma from homozygous PLTP KO mice completely lacks the ability to stimulate transfer of a variety of phospholipids from vesicles into HDL, as is seen for wild type mouse plasma. Moreover, injection of VLDL containing radiolabeled PC ethers into wild type mice resulted in rapid transfer of PC radioactivity into HDL; this transfer was abolished in homozygous PLTP KO mice. Homozygous PLTP KO mice have markedly decreased HDL phospholipid, cholesterol and apoA-I. On a high fat, high cholesterol diet, these mice also have increased free cholesterol and phospholipid in IDL and LDL, suggesting accumulation of surface remnants. Negative stain electron microscopy shows vesicular lipoprotein in these fractions. Thus, PLTP is a unique activity stimulating transfer of all major plasma phospholipids into HDL and transfer of VLDL phospholipid into HDL. The studies also show for the first time the quantitative importance of the transfer of surface components of triglyceride-rich lipoproteins in the maintenance of HDL levels.

HDL RECEPTORS

Recent studies by Krieger et al (4) have shown that scavenger receptor BI (SR-BI) is an authentic HDL receptor mediating selective uptake of HDL cholesteryl esters. To further evaluate the role of SRB-I in lipoprotein metabolism, we have generated transgenic mice with liver-specific overexpression of murine SRB-I (5,6). SRB-I Tg mice have decreased HDL CE, apoA-I and apoA-II levels. Plasma triglycerides, LDL cholesterol and VLDL and LDL apoB were also decreased in SRB-I Tg mice. Turnover studies using non-degradable CE and protein labels showed markedly increased total and selective uptake of HDL-CE in the liver and increased HDL protein catabolism in the liver and kidney. The decrease in plasma apoB and VLDL plus LDL cholesterol was also confirmed on a high fat, high cholesterol diet, where plasma apoB levels were only 3-15% of control levels. Thus, steady state overexpression of hepatic SRB-I reduces HDL levels and increases reverse cholesterol transport. These studies also indicate the SRB-I plays an in vivo role in the metabolism of apoB lipoproteins. Similar results were obtained when the SR-BI transgene was crossed into an LDL receptor deficient background (Arai et al. 1999). Moreover, the SR-BI transgenic/LDL receptor deficient mice have reduced atherosclerosis, demonstrating a strong anti-atherogenic potential of SR-BI overexpression. The anti-atherogenic changes were better correlated with changes in non HDL cholesterol than HDL cholesterol.

Mice with decreased expression of SRB-I due to targeted gene mutation have increased HDL cholesterol and decreased selective uptake of HDL CE in the liver, but they do not show a catabolic defect in apoA-I, implying the existence of additional catabolic pathways (7). Two mouse models of obesity, ob/ob and db/db, were found to have increased HDL cholesterol (2-fold), apoA-I (1.3-fold) and apoA-II (4-fold) (8). However, apoA-I mRNA was markedly decreased (to 25% of wild type) and apoA-II mRNA was unchanged, suggesting that increased HDL reflects a defect in HDL catabolism. This was confirmed in HDL apoprotein turnover