Phospholipid Transfer Protein and Atherosclerosis

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Genetic studies in humans and mice show that two related plasma lipid transfer proteins (cholesteryl ester transfer protein [CETP] and phospholipid transfer protein [PLTP]) have distinct roles in lipoprotein metabolism, despite their homology. In human homozygous CETP deficiency, HDL levels are massively elevated, and LDL levels are moderately decreased. While a human PLTP deficiency state has not been described, PLTP-/- mice have ≈50% reductions in HDL levels, indicating the essential role of PLTP in transferring phospholipids from triglyceride-carrying lipoproteins into HDL. When crossed with apoE-/-, or apoE transgenic mice, PLTP deficiency results in reductions in apoB lipoproteins, revealing a role of intracellular PLTP in the hepatic secretion of apoB lipoproteins.

Crosses of PLTP deficient mice into apoB transgenic, apoE-/-, or LDL R-/- backgrounds resulted in diminished atherosclerosis in all three of these standard mouse atherosclerosis models. In part this was related to the reduction of levels of apoB containing lipoproteins seen in apoB transgenic and apoE-/- mice. However, an anti-atherogenic effect of PLTP deficiency was also seen in LDL R-/- mice, despite a lack of reduction in apoB lipoprotein levels. A possible clue to understanding this unexpected observation was the finding that PLTP could facilitate the in vitro transfer of vitamin E from triglyceride rich lipoproteins (TRL) into HDL. An analysis of vitamin E revealed a build-up of levels in VLDL and LDL of PLTP deficient mice, associated with a reduction in susceptibility of apoB lipoproteins to Cu-mediated oxidation in vitro. Moreover, there was a reduction in antibodies to oxidized LDL in plasma. There was a 5-fold increase in VLDL vitamin E levels in apoE-/- mice, a level that was previously associated with atheroprotection in vitamin E feeding studies. Thus, in addition to reducing levels of apoB lipoproteins, PLTP deficiency resulted in an increase in their content of vitamin E and resistance to oxidation.

Somewhat surprisingly, overexpression of PTLP also is associated with an increase in atherosclerosis. This has been shown both in a transgenic model on a LDL R+/- background, and also now by Jiang et al by adenovirus overexpression in apoE-/- mice. The magnitude of the effect of PLTP overexpression on atherogenesis was large and does not seem to be readily explained by the reductions in HDL levels, because major reductions in HDL in apoA-I-deficient mice have either no or only moderate effects on atherosclerosis. The new study by Jiang et al offers a potential further mechanism to explain the increase in atherosclerosis, because they show that vitamin E levels in VLDL and LDL are reduced, and lag time for Cu-mediated oxidation is decreased in mice with PLTP overexpression. However, these changes were moderate in magnitude, and one suspects that there could be additional underlying mechanisms. Relevance to human pathophysiology in these overexpression models is somewhat uncertain: PLTP+/+ mice with ≈50% of normal activity have no lipoprotein phenotype, suggesting that small variations in PTLP activity around the normal level will not have much effect on lipoproteins. Increases in PLTP activity have been seen in humans with type I or type II diabetes and obesity, but the magnitude of change is only an increase from 15% to 50%. Notably, a comparable 1.3-fold increase in PLTP activity in the study of Jiang et al was not associated with a lipoprotein phenotype, and there was no effect on atherosclerosis.

Nonetheless, these findings add to the growing body of evidence suggesting that PLTP inhibition could be a therapeutic strategy for atherosclerosis. Unlike MTP inhibition, which is in some ways conceptually similar, PLTP deficiency does not result in fatty liver, presumably because secretion of apoB lipoproteins is inhibited at a later stage. Direct inhibition of PLTP by small molecules that bind to the putative N-terminal lipid binding pocket may be effective. Another approach could be to exploit the transcriptional regulation of PTLP expression. FXR activates PLTP expression, so FXR antagonists could reduce PLTP expression, in addition to reducing levels of TRL and possibly increasing HDL levels. Both PLTP and CETP are LXR targets, and presumably induction of both of these lipid transfer proteins would represent an adverse effect of LXR activators.

CETP inhibitors that recapitulate many of the features of the human deficiency state are now in advanced clinical trials, awaiting demonstration of efficacy on atherosclerosis. It is interesting to speculate on the phenotype that would result from combined inhibition of CETP and PLTP in humans. Since inhibition of CETP reduces apoB lipoproteins by increasing clearance, while PLTP affects synthesis, combined inhibition of PLTP and CETP could result in additive, substantial lowering of apoB-lipoproteins in humans. Moreover, there might be enrichment of the natural antioxidant, vitamin E. Although vitamin E supplementation trials in humans have been disappointing, a strategy that specifically increases vitamin E in apoB lipoproteins could be more effective. While PLTP inhibition would reduce HDL, this would be countered by the effects of CETP inhibition. In a future of combined drug therapies in the treatment of athero-
sclerosis, a combination inhibition of CETP and PLTP is not out of the question.

References
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