The effect of LCAT mutations and CTα in the biogenesis of HDL

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Objectives: To investigate the effect of overexpression of CTP:phosphocholine cytidylyltransferase (CTα) and Lecithin cholesterol acyltransferase (LCAT) as well as LCAT mutants on the biogenesis of HDL in different mouse models.

Methods and results: Adenovirus-mediated gene transfer of human apoAI along with CTα in apoAI-/−-mice increased 1.5-fold plasma cholesterol and phospholipid levels, mainly due to an increase in the HDL fraction, increased the large size HDL subpopulations and formed spherical HDL particles.

Gene transfer of WT LCAT in LCAT-/− mice increased approximately 2.5-fold total plasma cholesterol levels mainly due to increase in HDL cholesterol. In contrast gene transfer of human LCAT carrying the natural mutations LCAT[T123I] and LCAT[P250S] did not affect significantly plasma cholesterol levels. Fractionation of plasma by density gradient ultracentrifugation showed that WT LCAT increased the plasma apoE and apoAIV levels and shifted the distribution of apoAI to lower densities. The LCAT[T123I] and LCAT[P250S] mutants restored partially the presence of apoAI in the HDL2/HDL3 fraction and in the case of the LCAT[T123I] mutant increased apoE in the VLD/IDL/LDL fractions. The LCAT[T123I] caused a biphasic and LCAT[P250S] a monophasic distribution of the HDL cholesterol. Deficiency in LCAT is associated with formation of two pre-β HDL subpopulations and a small size α-HDL particle. Gene transfer of the LCAT[T123I] and LCAT[P250S] mutants in LCAT-/−-mice generated pre-β and α-HDL subpopulations with similar size whereas treatment with WT LCAT generated α-HDL subpopulations.

Conclusion: Overexpression of CTα and LCAT promotes the biogenesis of HDL and the mutations in LCAT affect differently the biogenesis of HDL.