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Adenoviral Vectors in the Treatment of HDL Deficiencies

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SUMMARY

Epidemiological studies and clinical intervention trials have established that levels of high density lipoproteins (HDL) in plasma are reversely associated with the incidence of coronary artery disease. We are using adenovirus-mediated gene transfer in appropriate mouse models in order to dissect the pathways of biogenesis and maturation of HDL *in vivo*. This technology involves the generation of recombinant adenoviruses carrying the gene of interest, amplification of the adenoviruses in appropriate mammalian cell lines, purification, titration and injection into the tail vein of mice. The resulting phenotype is monitored 1 to 5 days post-injection. Using this technology, we have functionally characterized natural human mutations in apolipoprotein A-I (apoA-I), the main protein component of HDL, such as apoA-I(R151C)$_{Paris}$, apoA-I(R160L)$_{Oslo}$, apoA-I(Leu141Arg)$_{Pisa}$ and apoA-I(Leu159Arg)$_{FIN}$ and have shown that these mutations disrupt HDL biogenesis and maturation. These defects in HDL caused by the natural apoA-I mutations can be corrected by administration of recombinant adenoviruses expressing lecithin cholesterol acetyl transferase (LCAT). Using this approach we have also studied the role of apoA-IV in the biogenesis of HDL. We have found that gene transfer of apoA-IV in apoA-I$^{-/-}$ x apoE$^{-/-}$ mice increased 1.5-fold plasma cholesterol levels and induced mild hypertriglyceridemia. The plasma cholesterol and apoA-IV were distributed mainly in the VLDL/IDL/LDL region and to a lesser extent in HDL. Electron microscopy analysis of the HDL fractions obtained by density gradient ultracentrifugation showed the presence of lipoprotein particles along with lipoprotein aggregates. Two-dimensional gel electrophoresis showed formation of distinct HDL subpopulations. Currently, we are also employing recombinant adenoviruses to investigate the effect of naturally occurring human LCAT mutations as well as the role of new genes, identified recently by genome-wide association studies, in the biogenesis and/or catabolism of HDL in mice.