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Expression of Human ApoA II in Transgenic Rabbits Leads to Dyslipidemia: a New Model for Combined Hyperlipidemia

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High levels of plasma high-density lipoproteins (HDL) are associated with a low incidence of cardiovascular disease[1]. HDL contains two major apolipoproteins (apo): apoA I and apoA II. It is generally accepted that apoA I plays a central role in reverse cholesterol transport and protects against atherosclerosis[2,3]; however, apoA II functions have not been clearly characterized[4-6].

Clinical and epidemiological studies have yielded conflicting results regarding the relationship between plasma apoA II levels and coronary heart disease: apoA II is either pro-atherogenic[7] or atheroprotective[8]. The -265C polymorphism in the apoA II promoter region was shown to be associated with decreased plasma apoA II concentration and enhance postprandial metabolism of large VLDL[9]. Nevertheless, apoA II has long been considered to be of physiologically minor importance in lipoprotein metabolism since apoA II deficiency is not associated with a high susceptibility to coronary heart disease[10].

ApoA II transgenic (Tg) mice along with knock-out (KO) mice have revealed multiple functions of apoA II[4,5]. Both human and mouse apoA II in Tg mice are involved in VLDL metabolism, but mouse apoA II is also associated with obesity and insulin resistance[11-13]. In addition, mouse apoA II is pro-atherogenic in chow-fed Tg mice, whereas human apoA II is either atheroprotective or pro-atherogenic in Tg mice dependent upon an atherogenic diet[14-16,17]. Although the cause of these discrepancies in different mice expressing different transgenes is unclear, it seems that there is a species difference in apoA II functions between human and mouse, and that the precise physiological functions of apoA II in vivo remain to be elucidated. Studies using Tg mice are often complicated by additional factors such as the effect of human homodimer apoA II vs murine monomer apoA II, transgenic apoA II (either human or murine) vs endogenous murine apoA II, and the absence of cholesteryl ester transfer protein (CETP), a critical modulator of lipoprotein metabolism[18], in the plasma of mice. To overcome these problems, we investigated the functions of human apoA II in lipid and lipoprotein metabolism using rabbits. Like humans but unlike mice, rabbits have abundant plasma CETP and exhibit hepatic apoB100 and intestinal apoB48 synthesis, and their lipoprotein profiles are LDL-rich[19]. Interestingly, wild-type rabbits are genetically deficient in an apoA II analogous gene[20]; therefore, they can be considered as an "apoA II-KO" model. To gain insight into the in vivo functional roles of human apoA II, we generated and characterized Tg rabbits expressing human apoA II and examined the effect of human apoA II on lipid and lipoprotein metabolism[21]. Plasma levels of human apoA II in Tg rabbits were ~ 30 mg/dL, similar to the plasma levels in healthy humans. The expression of human apoA II in Tg rabbits resulted in increased levels of plasma triglycerides, total cholesterol and phospholipids accompanied by a marked reduction in HDL-cholesterol levels compared with non-Tg littermates. Analysis of lipoprotein fractions showed that hyperlipidemia exhibited by Tg rabbits was caused by elevated levels of very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins. Furthermore, postheparin lipoprotein lipase activity significantly decreased in Tg rabbits compared with non-Tg rabbits. These results indicate that apoA II plays an important role in both VLDL and HDL metabolism, possibly through the inhibition of lipoprotein lipase activity. ApoA II Tg rabbits may become a new model for the study of human familial combined hyperlipidemia.

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