ApoAII Controversy Still in Rabbit?

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apoAII is a key component of HDL for cholesterol efflux, and its antiatherogenic action has been long established. Meanwhile, roles of apoAII, the second major HDL component, in the lipoprotein metabolism have not been fully understood. Effect of apoAII on atherosclerosis has not been determined because there were conflicting clinical and epidemiological studies. Interpretation of data from transgenic and knockout mice of genes involved in lipoprotein metabolism has been often complicated as clinical implications because of species difference. ApoAII has been a good example for this problem. Mouse apoAII and human apoAII have different molecular properties: human apoAII dimerizes whereas mouse apoAII is a monomer and could cause different phenotypes in transgenic mice. Mouse is essentially deficient in cholesterol ester transfer protein (CETP), a key enzyme for HDL modification in which apoAII may be involved.

In contrast, rabbit has lipoprotein metabolism similar to that of human in the light of CETP and apoB editing enzyme activities and is better as an animal model for studies of human lipoprotein metabolism. Few laboratories can handle the problems in mouse studies by use of transgenic rabbit technology. Koike and Fan’s group in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* created and investigated human apoAII transgenic rabbits. The transgenic rabbits exhibited elevated plasma levels of triglycerides, total cholesterol, and phospholipids mainly due to accumulation of TG-rich lipoproteins accompanied by reduced HDL-cholesterol. These results clearly demonstrate that human apoAII has crucial roles in metabolism of both TG-rich lipoproteins and HDL. It should be noted that normal rabbits genetically lack endogenous apoAII, and thus the transgene expression at a roughly normal human plasma level caused robust changes in lipoprotein metabolism and helped understanding of its roles that have been controversial in previous human and mice studies. Meanwhile, it should be estimated how lack of hepatic lipase in the rabbit influenced the phenotypes of this new model because apoAII is an inhibitor for hepatic lipase.

Although the observational messages from these animals are clear, there are a lot of mechanistic questions left that should be addressed. The apoAII transgenic rabbits showed a significant reduction in activity of lipoprotein lipase, the key enzyme for catabolism of triglycerides, partially explaining for the increase in the plasma triglyceride level. However, the precise molecular mechanism for accumulation of TG-rich lipoproteins is still a complex and intriguing question. The human apoAII from transgene was mainly localized on HDL particles. It is unlikely that residual apoAII on VLDL directly and efficiently affects LPL activity. How did apoAII on HDL suppress LPL and retard TG-rich lipoproteins? Further investigation is required to elucidate effects of apoAII on lipid transfer interaction of between VLDL and HDL.

As for changes in HDL metabolism, transgenic apoAII is likely to kick-out apoAI from HDL and accelerate its catabolism resulting in considerable reduction in HDL cholesterol. It has been proposed that apoAII regulates HDL remodeling as well as interaction with VLDL/IDL, and the current model supports this hypothesis. Interactions of apoAII and other lipoprotein modifying enzymes such as PLTP and EL that may be important for HDL size and catabolism also need to be evaluated in more details.

The next subject for these animals is to determine whether they are more susceptible to hyperlipidemia and atherosclerosis on a high-cholesterol diet. Odds are pretty fair for acceleration of both, but contribution of apoAII-containing HDL to atherosclerosis should be estimated. It would be nice...
to test the atheroma formation in both apoAII transgenic rabbits on high-cholesterol diet and apoAII transgenic/LDL-receptor deficient WHHL double mutant rabbits on a normal diet. Investigation of human apoAII transgenic rabbits on a high-energy diet in the light of insulin resistance and glucose metabolism is another interesting issue.

Finally, the authors claim that dyslipidemia of human apoAII transgenic rabbits resemble familial combined hyperlipidemia (FCHL). Elevated apoAII level is biochemically and genetically associated with FCHL. Recently the upstream transcription factor 1 (USF1) gene was identified as a new underlying gene for FCHL in addition to LPL gene and apolipoprotein A1/C3/A4/A5 gene cluster. Interestingly, apoAII as well as apoAV were reported to be regulated by USF1. This model confirms that apoAII is involved in phenotypes of FCHL as another clinical implication in this article.

Disclosures

None.

References


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