Transgenic Mouse Model of Liver LDL Receptor Deficiency

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BACKGROUND

The low density lipoprotein (LDL) receptor (LDLR) is a cell surface-glycoprotein that mediates the binding and endocytosis of excess circulating LDL cholesterol to liver cells, where the cholesterol is further catabolized and eventually secreted in the feces by a biliary pathway. The importance of the LDLR in the regulation of plasma cholesterol levels is well established. Loss-of-function LDLR mutations in humans reduce hepatic LDL clearance, elevate plasma LDL levels, and accelerate atherosclerosis. The E3 ligase inducible degrader of the low-density lipoprotein receptor (IDOL) ubiquitinates and facilitates lysosomal degradation of LDLR. Previous studies have shown the molecular basis for IDOL target recognition and shown that the loss of IDOL expression in cells alters LDLR protein levels and cholersterol uptake. However, the tissue-specific effects of the IDOL pathway on plasma cholesterol levels and cardiovascular disease are unknown.

INNOVATION

Researchers in UCLA Department of Pathology and Laboratory Medicine have created a mouse model of LDL receptor deficiency for the study of atherosclerosis. IDOL targets both itself and LDLR for degradation through ubiquitination. Studies have demonstrated that the mutation of certain lysine residues in IDOL prohibits the protein's ability to undergo autoubiquitination but maintains its ability to degrade the LDLR. The model mice in the present invention express this degradation-resistant, dominant-active form of human IDOL (sIDOL) in C57B1/6J mice from the liver-specific albumin enhancer/promoter. The model can be used to study a wide range of effects of atherosclerosis.

STATE OF DEVELOPMENT

The model mice have been generated and have been used to study the consequence of chronic liver-specific expression of a dominant-active form of IDOL in mice (see related papers). Real-time PCR analysis confirmed that transgene expression was selective for liver, and that the mice strain indeed exhibits a marked reduction in hepatic LDLR protein expression, indicating increased IDOL activity.

RELATED MATERIALS

▶ Calkin AC, Lee SD, Kim J, Van Stijn CM, Wu XH, Lusis AJ, Hong C, Tangirala RI, Tontonoz P., Transgenic expression of dominant-active IDOL in liver causes diet-induced hypercholesterolemia and atherosclerosis in mice. Circ Res. 2014

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

▶ Targeting Sterol Transporters In Metabolic Disease

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OTHER INFORMATION

KEYWORDS

atherosclerosis, cholesterol, LDL, ubiquitin-protein ligase, transgenic mouse models

CATEGORIZED AS

▶ Research Tools
▶ Animal Models

RELATED CASES

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