Disruption of TR4 orphan nuclear receptor reduces the expression of liver apolipoprotein E/C-I/C-II gene cluster

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摘要

Abstract

Apolipoprotein E (apoE) is synthesized in many tissues, and the liver is the primary site from which apoE redistributes cholesterol and other lipids to peripheral tissues. Here we demonstrate that the TR4 orphan nuclear receptor (TR4) can induce apoE expression in HepG2 cells. This TR4-mediated regulation of apoE gene expression was further confirmed in vivo using TR4 knockout mice. Both serum apoE protein and liver apoE mRNA levels were significantly reduced in TR4 knockout mice. Gel shift and luciferase reporter gene assays further demonstrated that TR4 can induce apoE gene expression via a TR4 response element located in the hepatic control region that is 15 kb downstream of the apoE gene. Furthermore our in vivo data from TR4 knockout mice prove that TR4 can also regulate apolipoprotein C-I and C-II gene expression via the TR4 response element within the hepatic control region. Together our data show that loss of TR4 down-regulates expression of the apoE/C-I/C-II gene cluster in liver cells, demonstrating important roles of TR4 in the modulation of lipoprotein metabolism.