Expression of SREBF1 (SREBP1) regulated by NR1H2 or NR1H3

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


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The sterol regulatory element-binding protein 1 (SREBP1) is encoded by the SREBF1 gene. SREBF1 is transcribed to yield mRNA and the mRNA is translated to yield protein. The SREBF1 gene can produce two proteins, SREBP1α and SREBP1c, by use of different promoters (Hua X et al. 1995) and unique first exons (Shimomura I et al. 1997). In humans and mice, the SREBP1c is the predominant SREBF1 isoform in the liver that regulates fatty acid (FA) metabolism (Shimomura I et al. 1997; Sato R 2010; Horton JD et al. 2002). The oxysterol receptors liver X receptor alpha (LXRα, NR1H3) and LXRβ (NR1H2) were reported to mediate hepatic lipogenesis in rodents and humans by direct binding and upregulation of SREBF1 (SREBP1c) which controls the transcription of genes involved in FA biosynthesis (Schultz JR et al. 2000; Repa JJ et al. 2000; Yoshikawa T et al. 2001). NR1H2 & NR1H3 were shown to activate the mouse SREBF1 (SREBP1c) promoter (Yoshikawa T et al. 2001). In cell transfection studies using human embryonic kidney 293 (HEK293) cells, expression of either NR1H2 or NR1H3 activated the SREBF1 promoter-luciferase reporter gene in a dose-dependent manner (Yoshikawa T et al. 2001). Deletion and mutation studies, as well as gel mobility shift assays, identified two LXR response elements (LXRE) in the SREBF1c promoter region that regulate expression of SREBP1c by both LXR and RXR agonists (Repa JJ et al. 2000; Yoshikawa T et al. 2001). In mice receiving oral cholesterol, T0901317 (LXR agonist) or LG268 (RXR agonist), SREBP1c mRNA levels were elevated in nearly all tissues tested (Repa JJ et al. 2000). In human hepatoma HepG2 cells, SREBP1 mRNA and precursor protein levels were induced by treatment with 22(R)-hydroxysterol and 9-cis-retinoic acid, confirming that endogenous LXR:RXR activation can induce endogenous SREBP1 expression (Yoshikawa T et al. 2001). The activation of SREBF1 by NR1H2 or NR1H3 is associated with an increase in nuclear SREBP1c protein, resulting in the activation of many genes involved in lipogenesis, such as fatty acid synthase (FASN) gene, acetyl-CoA carboxylase (ACC), and stearoyl-CoA desaturase 1 (SCD1) (Yoshikawa T et al. 2001; Chen G et al. 2004). However, NR1H2, NR1H3 may activate lipogenic gene transcription directly by binding LXRE found in the promoter regions of several genes, such as FASN (or FAS), ACCα and SCD1 (Yoshikawa T et al. 2001; Joseph SB et al. 2002; Chu K et al. 2006; Talukdar S & Hillgartner FB 2006). Mice carrying a targeted disruption in the NR1H3 (LXRa) gene were deficient in expression of FAS, SCD1, and SREBP1 (Peet DJ et al. 1998). These data demonstrate that...
LXR:RXR can modify the expression of genes for lipogenic enzymes directly or by regulating SREBP1c expression. Liang and colleagues genetically deleted only the SREBP-1c isoform from mice and provided these animals with the LXR agonist T0901317. These knockout mice continued to exhibit enhanced hepatic lipogenesis, albeit only about 40% that observed in ligand-treated wildtype mice, suggesting that SREBP1c is responsible for over half of LXR-associated lipogenic capacity (Liang G et al. 2002).

**Literature references**
