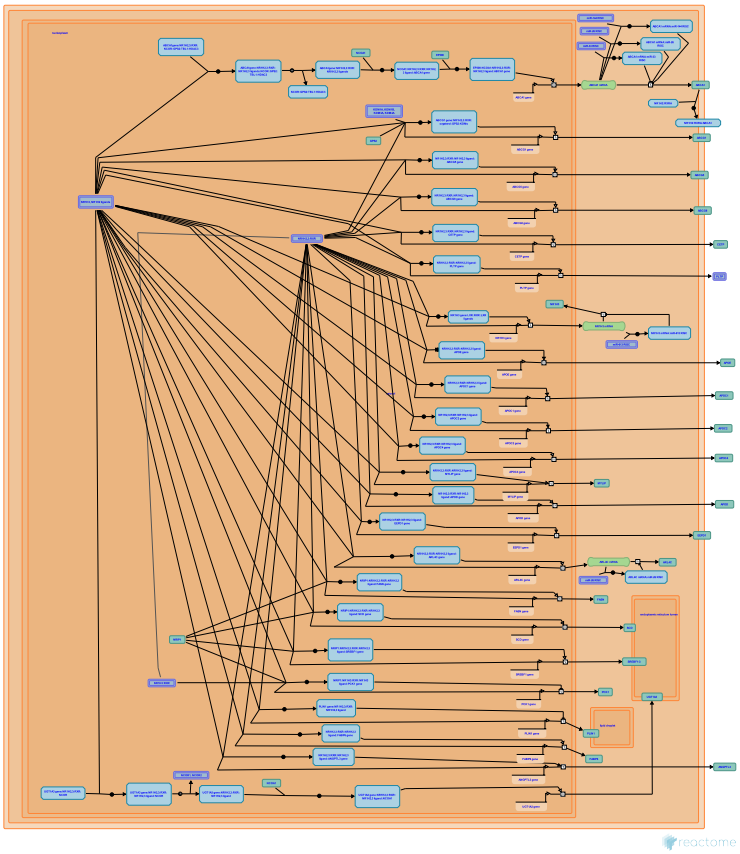
NR1H2 and NR1H3-mediated signaling



Cummins, CL., D'Eustachio, P., Repa, JJ., Shamovsky, V.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

03/05/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

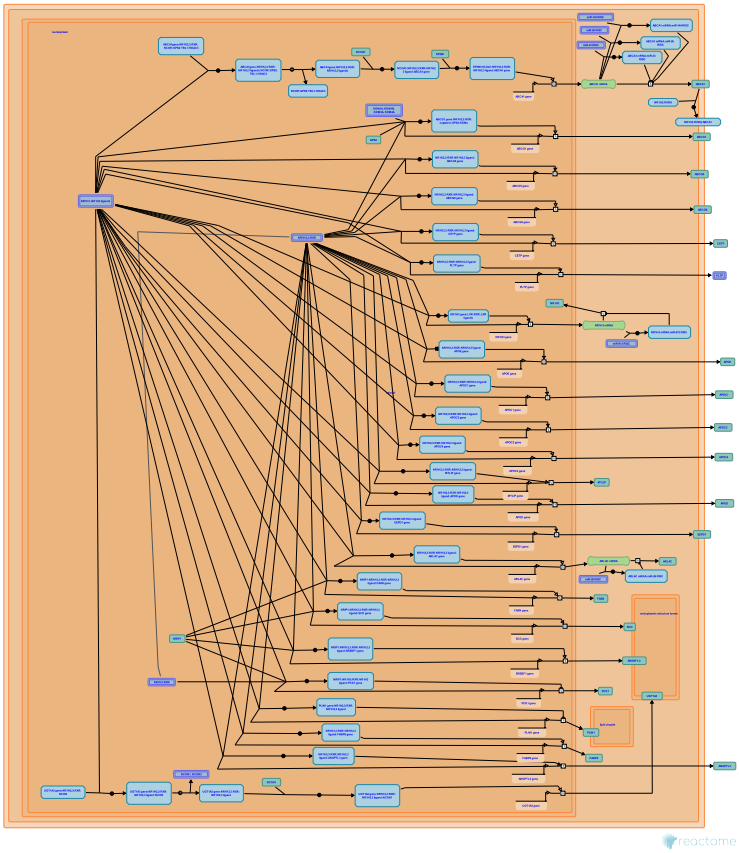
Reactome database release: 88

This document contains 7 pathways (see Table of Contents)

NR1H2 and NR1H3-mediated signaling ↗

Stable identifier: R-HSA-9024446

Compartments: nucleoplasm



The liver X receptors LXRα (NR1H3) and LXRβ (NR1H2) are members of the nuclear receptor superfamily and function as ligand-activated transcription factors. The natural ligands of NR1H2 and NR1H3 are oxysterols (e.g., 24(S),25-epoxycholesterol, 24(S)-hydroxycholesterol (OH), 25-OH, and 27-OH) that are produced endogenously by enzymatic reactions, by reactive oxygen species (ROS)-dependent oxidation of cholesterol and by the alimentary processes (reviewed in:Jakobsson T et al. 2012; Huang C 2014; Komati R et al. 2017). It has been shown that these oxysterols bind directly to the ligand-binding domain of LXRs with Kd values ranging from 0.1 to 0.4 microM. 24(S), 25-epoxycholesterol was found to be the most potent endogenous agonist (Janowski BA et al. 1999). NR1H3 (LXRα) and NR1H2 (LXRβ) showed similar affinities for these compounds (Janowski BA et al. 1999). In physiological conditions, oxysterols are formed in amounts proportional to cholesterol content in the cell and therefore the LXRs operate as cholesterol sensors to alter gene expression and protect the cells from cholesterol overload via: (1) inhibiting intestinal cholesterol absorption; (2) stimulating cholesterol efflux from cells to high-density lipoproteins through the ATP-binding cassette transporters ABCA1 and ABCG1: (3) activating the conversion of cholesterol to bile acids in the liver; and (4) activating biliary cholesterol and bile acid excretion (reviewed in: Wójcicka G et al. 2007; Baranowski M 2008; Laurencikiene J & Rydén M 2012; Edwards PA et al. 2002; Zelcer N & Tontonoz P 2006; Zhao C & Dahlman-Wright K 2010). In addition, LXR agonists enhance de novo fatty acid synthesis by stimulating the expression of a lipogenic transcription factor, sterol regulatory element-binding protein-1c (SREBP-1c), leading to the elevation of plasma triglycerides and hepatic steatosis (Wójcicka G et al. 2007; Baranowski M 2008; Laurencikiene J & Rydén M 2012). In addition to their function in lipid metabolism, NR1H2,3 have also been found to modulate immune and inflammatory responses in macrophages (Zelcer N & Tontonoz P 2006). The NR1H2 and NR1H3 molecules can be viewed as having four functional domains: (1) an amino-terminal ligand-independent activation function domain (AF-1), which may stimulate transcription in the absence of ligand; (2) a DNA-binding domain (DBD) containing two zinc fingers; (3) a hydrophobic ligand-binding domain (LBD) required for ligand binding and receptor dimerization; and, (4) a carboxy-terminal ligand-dependent transactivation sequence (also referred to as the activation function-2 (AF-2) domain) that stimulates transcription in response to ligand binding (Robinson-Rechavi M et al. 2003; Jakobsson T et al. 2012; Färnegardh M et al. 2003; Lin CY & Gustafsson JA 2015). Although both NR1H3 and NR1H2 are activated by the same ligands and are structurally similar, their tissue expression profiles are very different. NR1H3 is selectively expressed in specific tissues and cell types, such as the liver, intestine, adrenal gland, adipose tissue and macrophages, whereas NR1H2 is ubiquitously expressed (Nishimura M et al. 2004; Bookout AL et al. 2006). Upon activation NR1H2 or NR1H3 heterodimerizes with retinoid X receptors (RXR) and binds to LXR-response elements (LXREs) consisting of a

direct repeat of the core sequence 5'-AGGTCA-3' separated by 4 nucleotides (DR4) in the DNA of target genes (Wiebel FF & Gustafsson JA 1997). An inverted repeat of the same consensus sequence with no spacer region(IR-0) and an inverted repeat of the same consensus sequence separated by a 1 bp spacer (IR-1) have also been shown to mediate LXR transactivation (Mak PA et al. 2002, Landrier JF et al. 2003). NR1H3 and NR1H2 have been shown to regulate gene expression via LXREs in the promoter regions of their target genes such as UDP glucuronosyltransferase 1 family, polypeptide A3 (UGT1A3) (Verreault M et al. 2006), fatty acid synthase (FAS) (Joseph SB et al. 2002a), carbohydrate response element binding protein (ChREBP, also known as MLX-interacting protein-like or MLXIPL) (Cha JY & Repa JJ 2007) and phospholipid transfer protein (PLTP) (Mak PA et al. 2002). LXREs have also been reported to be present in introns of target genes such as the ATP-binding cassette transporter G1 (ABCG1) (Sabol SL et al. 2005). NR1H3 has been shown to activate gene expression via the FXR-responsive element found in the proximal promoter of the human ileal bile acid-binding protein (FABP6) (Landrier JF et al. 2003). The NR1H2,3:RXR heterodimers are permissive, in that they can be activated by ligands for either NR1H2,3 (LXR) or RXR (Willy PJ et al. 1995).

Literature references

Jakobsson, T., Gustafsson, JA., Steffensen, KR., Treuter, E. (2012). Liver X receptor biology and pharmacology: new pathways, challenges and opportunities. *Trends Pharmacol. Sci., 33,* 394-404. ↗

Horoszewicz, K., Wójcicka, G., Bełtowski, J., Jamroz-Wiśniewska, A. (2007). Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism. *Postepy Hig Med Dosw (Online), 61,* 736-59. ↗

Editions

2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

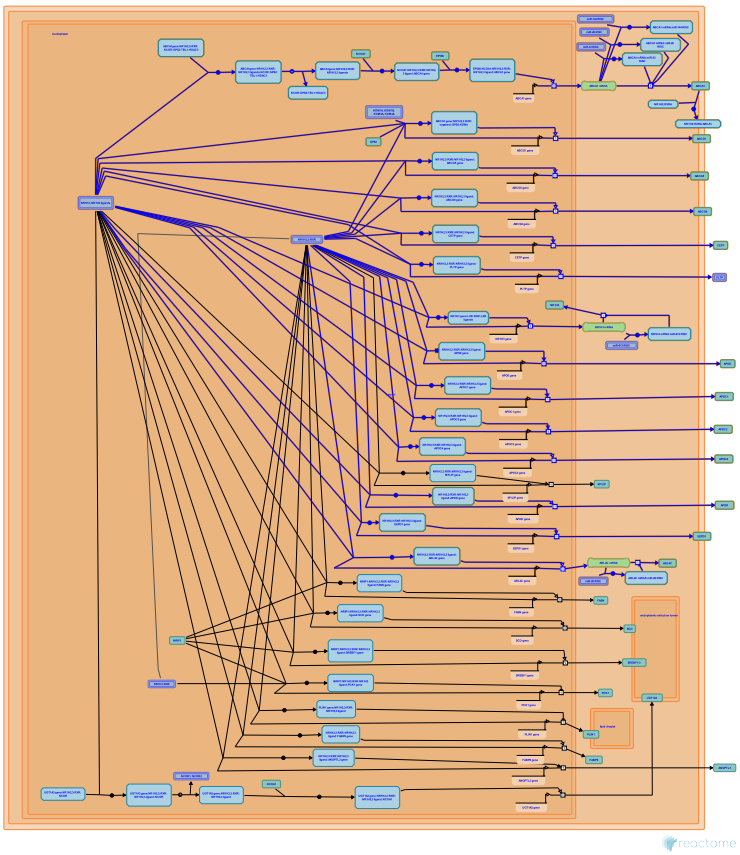
NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux

↗

Location: NR1H2 and NR1H3-mediated signaling

Stable identifier: R-HSA-9029569

Compartments: nucleoplasm



The liver X receptors (LXRs), LXRα (NR1H3) and LXRβ (NR1H2), are nuclear receptors that are activated by endogenous oxysterols, oxidized derivatives of cholesterol (Janowski BA et al. 1996). When cellular oxysterols accumulate as a result of increasing concentrations of cholesterol, NR1H2,3 induce the transcription of genes that protect cells from cholesterol overload (Zhao C & Dahlman-Wright K 2010; Ma Z et al. 2017). In peripheral cells such as macrophages, NR1H2 and NR1H3 increase cholesterol efflux by inducing expression of ATP-binding cassette subfamily A type 1 (ABCA1), ABCG1, and apolipoprotein APOE (Jakobsson T et al. 2009; Laffitte BA et al. 2001; Mak PA et al. 2002). In the intestine, LXR agonists decrease cholesterol absorption through induction of ABCA1, ABCG5, and ABCG8 (Repa JJ et al. 2000; Back SS et al. 2013). Cholesterol removal from non-hepatic peripheral cells, such as lipid-laden macrophages, and its delivery back to the liver for catabolism and excretion are processes collectively known as reverse cholesterol transport (RCT) (Francis GA 2010; Rosenson RS et al. 2012). This Reactome module describes the activation of several direct NR1H2,3 target genes that are closely associated with the RCT pathway, including genes encoding membrane lipid transporters, such ABCA1, ABCG1, ABCG5, ABCG8 and a cluster of apolipoprotein genes APOE, APOC1, APOC2 and APOC4 (Jakobsson T et al. 2009; Back SS et al. 2013; Mak PA et al. 2002).

Literature references

Zhou, J., Wang, D., Fan, C., Hu, W., Liu, D., Yang, Y. et al. (2017). Liver X Receptors and their Agonists: Targeting for Cholesterol Homeostasis and Cardiovascular Diseases. *Curr Issues Mol Biol, 22*, 41-64. ↗

Dahlman-Wright, K., Zhao, C. (2010). Liver X receptor in cholesterol metabolism. *J. Endocrinol., 204*, 233-40. ↗

Edwards, PA., Mangelsdorf, DJ., Curtiss, LK., Mak, PA., Desrumaux, C., Tontonoz, P. et al. (2002). Regulated expression of the apolipoprotein E/C-I/C-IV/C-II gene cluster in murine and human macrophages. A critical role for nuclear liver X receptors alpha and beta. *J. Biol. Chem., 277*, 31900-8. ↗

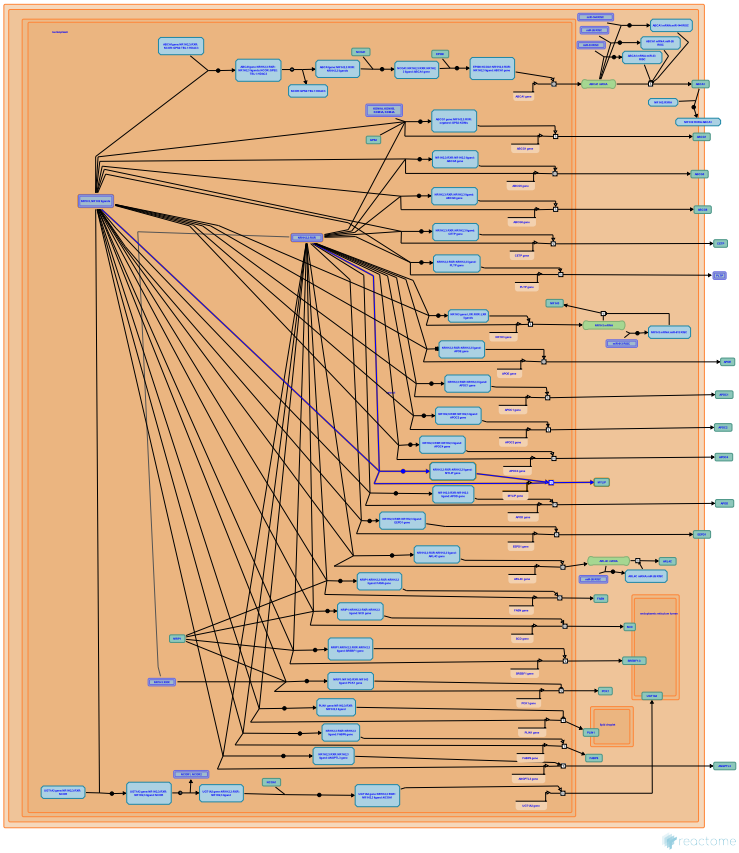
Editions

2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

NR1H2 & NR1H3 regulate gene expression to limit cholesterol uptake ↗

Location: NR1H2 and NR1H3-mediated signaling

Stable identifier: R-HSA-9031525



Liver X receptors NR1H3 (LXR alpha) and NR1H2 (LXR beta) are sterol-responsive transcription factors that become activated upon the engagement with their cognate oxysterol ligands. Ligand-activated NR1H2 & NR1H3 induce a genetic program aimed at reducing the cellular sterol load by limiting cholesterol uptake, attenuating cholesterol biosynthesis and promoting cholesterol efflux. This Reactome module describes the NR1H2 & NR1H3-regulated expression of MYLIP (IDOL) gene, an E3 ubiquitin ligase, that triggers ubiquitination of the low-density lipoprotein receptor (LDLR) on its cytoplasmic domain, targeting it for degradation and thereby limiting cholesterol uptake (Zelcer N et al. 2009; Zhang L et al. 2012).

Literature references

Zelcer, N., Hong, C., Tontonoz, P., Boyadjian, R. (2009). LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. *Science, 325*, 100-4. ↗

Zhang, L., Reue, K., Fong, LG., Tontonoz, P., Young, SG. (2012). Feedback regulation of cholesterol uptake by the LXR-IDOL-LDLR axis. *Arterioscler. Thromb. Vasc. Biol., 32*, 2541-6. ↗

Editions

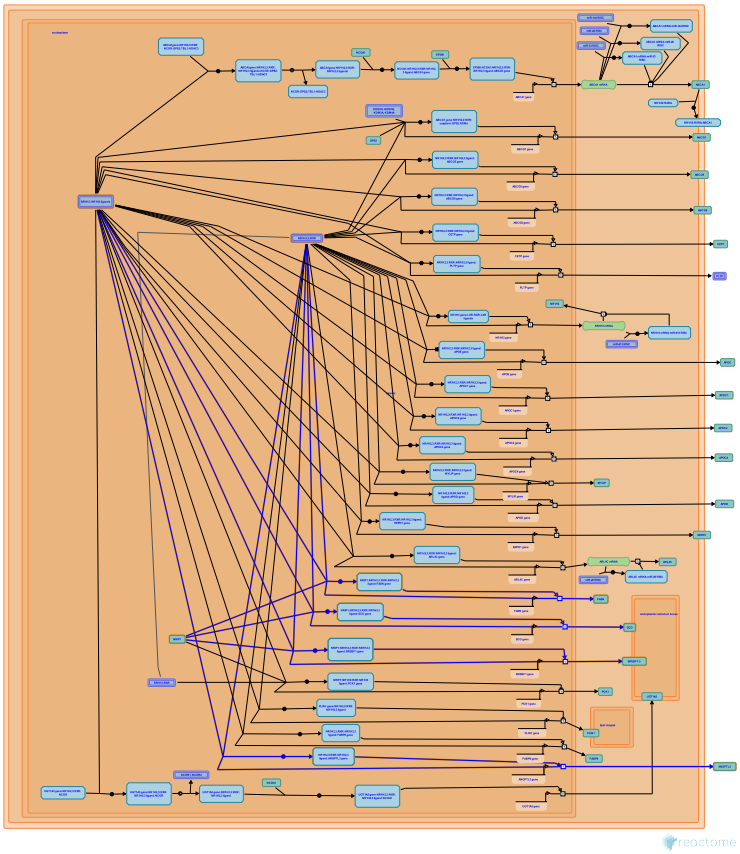
2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

NR1H2 & NR1H3 regulate gene expression linked to lipogenesis ↗

Location: NR1H2 and NR1H3-mediated signaling

Stable identifier: R-HSA-9029558

Compartments: nucleoplasm



The liver X receptor α (LXRα or NR1H3) and LXRβ (NR1H2) are nuclear receptors that are activated by endogenous oxidized derivatives of cholesterol known as oxysterols (Janowski BA et al. 1999; Jakobsson T et al. 2012). NR1H2 and NR1H3 act as whole-body cholesterol sensors and their activation results in a net elimination of cholesterol from the body and amelioration of the plasma lipoprotein profile by mobilizing cholesterol from the periphery (Venkateswaran A et al. 2000; Repa JJ et al. 2000a; Ishibashi M et al. 2013). NR1H3 (LXRα) and NR1H2 (LXRβ) also contribute to lowering of whole-body cholesterol levels by shifting acetyl-CoA units from cholesterol de novo biosynthesis to fatty acid synthesis. NR1H2 or 3-induced hepatic lipogenesis in rodents and humans is mediated by direct upregulation of sterol regulatory element-binding protein 1 (SREBF1), the main regulator of hepatic lipogenesis that controls the transcription of genes involved in fatty acid biosynthesis (Schultz JR et al. 2000). NR1H2 & NR1H3 may activate lipogenic gene transcription directly by biding LXR responsive element (LXRE) found in the promoter regions of several genes, such as fatty acid synthase (FAS or FASN) and stearoyl-CoA desaturase 1 (SCD1) (Repa JJ et al. 2000b; Yoshikawa T et al. 2001; Joseph SB et al. 2002; Chu K et al. 2006). Mice carrying a targeted disruption in the NR1H3 (LXRα) gene were deficient in expression of FAS, SCD1, ACC, and SREBF1 (Peet DJ et al. 1998). Mice ablated of both NR1H3 and NR1H2 showed defective hepatic lipid metabolism decreasing lipogenesis by 80% and were resistant to obesity (Repa JJ et al. 2000; Kalaany NY et al. 2005; Beaven SW et al. 2013). Further, the administration of the synthetic NR1H2 or NR1H3 ligands to mice triggered induction of the lipogenic pathway and raised plasma triglyceride levels (Schultz JR et al. 2000). These studies demonstrate the role of NR1H3 (LXRα) and NR1H2 (LXRβ) in the control of lipogenesis.

Literature references

Mansourian, R., Macé, K., Avanti, O., Leone-Vautravers, P., Zbinden, I., Giusti, V. et al. (2006). Liver X receptor preferentially activates de novo lipogenesis in human preadipocytes. *Biochimie, 88*, 309-18. ↗

Herzog, B., Parker, MG., Hallberg, M., Woods, A., White, R., Seth, A. (2007). The nuclear receptor cofactor, receptor-interacting protein 140, is required for the regulation of hepatic lipid and glucose metabolism by liver X receptor. *Mol. Endocrinol., 21*, 2687-97. ↗

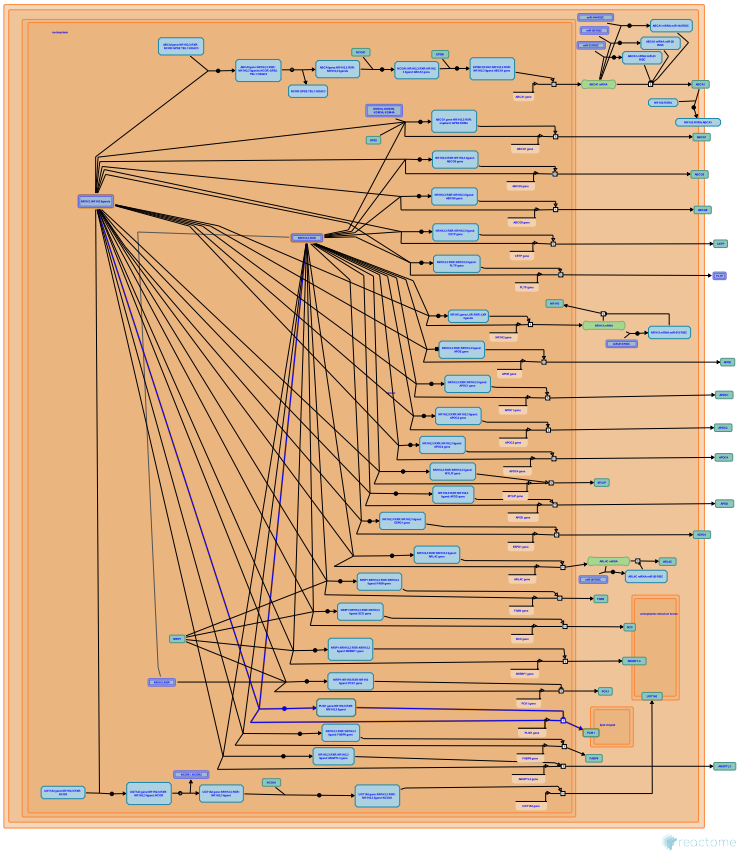
Editions

2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

NR1H2 & NR1H3 regulate gene expression linked to triglyceride lipolysis in adipose ↗

Location: NR1H2 and NR1H3-mediated signaling

Stable identifier: R-HSA-9031528



Adipose tissue triglycerides (TGs) represent the major energy store of the body. During adipocyte lipolysis triglycerides (TGs) are hydrolyzed into free fatty acids (FFAs) and glycerol by the action of adipose triglyceride lipase (ATGL, encoded by PNPLA2), then hormone-sensitive lipase (HSL), which is activated by glucagon and adrenaline (epinephrine) and inhibited by insulin. Both isoforms of liver X receptor, LXRα (NR1H3) and LXRβ (NR1H2), are expressed in mature mouse and human adipocytes (Juvet LK et al. 2003). Expression of NR1H3 is up-regulated during adipocyte differentiation (Juvet LK et al. 2003; Darimont C et al. 2006). Ligand activation of LXRs (NR1H2 or NR1H3) can induce adipocyte lipolysis and FFA oxidation (Stenson BM et al. 2011; Ross SE et al. 2002). For instance, in mouse 3T3L1 adipocytes and human primary adipocytes, LXR activation led to an increase in basal, but not hormone-stimulated, lipolysis as measured by glycerol release (Ross SE et al. 2002; Stenson BM et al. 2011). Another study showed that administration of synthetic ligands of NR1H2/ NR1H3, T0901317 or GW3965, to mice resulted in smaller adipocytes and increased serum free fatty acid and glycerol concentrations, suggesting increased adipocyte lipolysis (Commerford SR et al. 2007). Further, microarray analysis of human adipocytes following NR1H3 or NR1H2 activation revealed altered gene expression of several lipolysis-regulating proteins such as perilipin1 (PLIN1), which was also confirmed by quantitative real-time PCR (Stenson BM et al. 2011). Selective knockdown of either NR1H2 or NR1H3 showed that NR1H3 (LXRα) was the major isoform mediating the lipolysis-related effects of LXR agonists (Stenson BM et al. 2011). In addition, the absence of NR1H3 (LXRα) in mouse adipose tissue resulted in elevated adiposity through a decrease of both lipolytic and oxidative capacities in white adipose tissue (Dib L et al. 2014).

Literature references

Rydén, M., Laurencikiene, J. (2012). Liver X receptors and fat cell metabolism. *Int J Obes (Lond), 36*, 1494-502. ↗

Arner, P., Langin, D., Blomqvist, L., Wang, V., Mairal, A., Laurencikiene, J. et al. (2011). Liver X receptor (LXR) regulates human adipocyte lipolysis. *J. Biol. Chem., 286*, 370-9. ↗

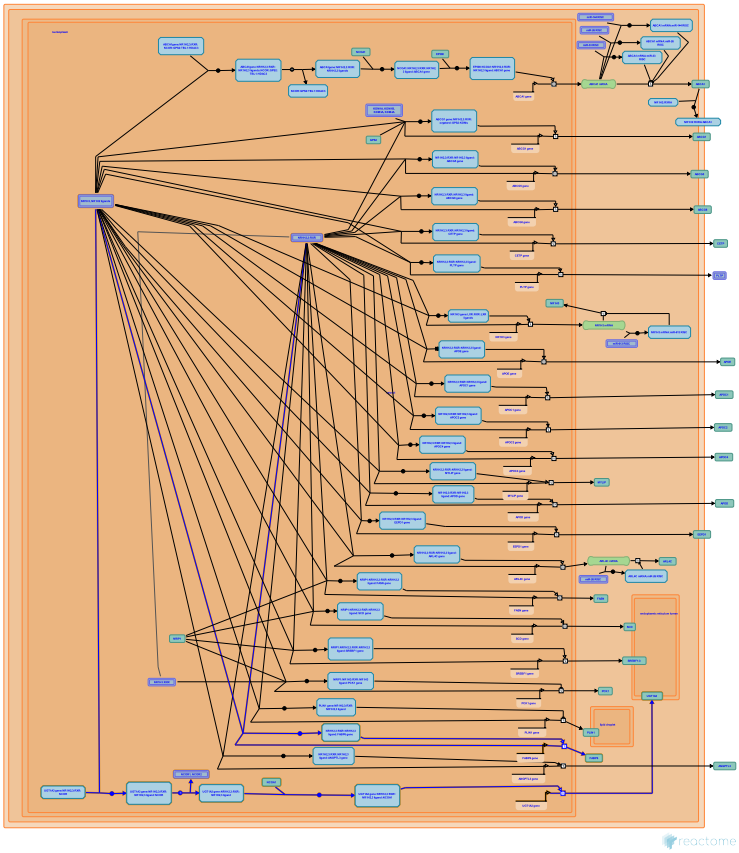
Editions

2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

NR1H2 & NR1H3 regulate gene expression to control bile acid homeostasis ↗

Location: NR1H2 and NR1H3-mediated signaling

Stable identifier: R-HSA-9623433



Liver X receptors NR1H3 (LXR alpha) and NR1H2 (LXR beta) are sterol-responsive transcription factors that become activated upon the engagement with their cognate oxysterol ligands. Besides inducing a genetic program aimed to reduce the cellular sterol load, ligand-activated NR1H2 & NR1H3 also modulate the expression and activity of genes controlling bile acid synthesis, transport and metabolism such as bile acid-glucuronidating enzyme UGT1A3 which converts hydrophobic bile acids into polar metabolites that can be excreted in the urine (Verreault M et al. 2006).

Literature references

Kaeding, J., Verreault, M., Trottier, J., Caron, P., Staels, B., Tukey, RH. et al. (2006). The liver X-receptor alpha controls hepatic expression of the human bile acid-glucuronidating UGT1A3 enzyme in human cells and transgenic mice. *Hepatology, 44*, 368-78. ↗

Demydchuk, J., Besnard, P., Grober, J., Landrier, JF. (2003). FXRE can function as an LXRE in the promoter of human ileal bile acid-binding protein (I-BABP) gene. *FEBS Lett., 553*, 299-303. ↗

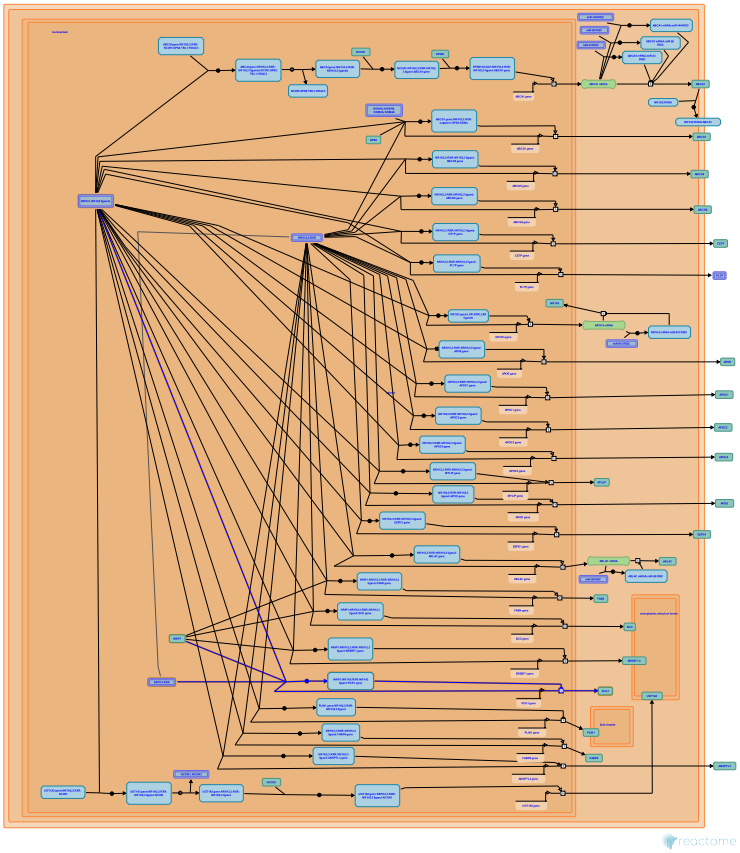
Editions

2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

NR1H2 & NR1H3 regulate gene expression linked to gluconeogenesis ↗

Location: NR1H2 and NR1H3-mediated signaling

Stable identifier: R-HSA-9632974



Activation of liver X receptor α (LXRα, NR1H3) alters the expression of genes in liver and adipose tissue that collectively may limit hepatic glucose output and improve peripheral glucose uptake (Laffitte BA et al. 2003). In the liver, activation of NR1H3 led to the suppression of the expression of genes involved in gluconeogenesis including glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PCK1 or PEPCK) (Laffitte BA et al. 2003; Dalen KT et al. 2003; Herzog B et al. 2007; Commerford et al. 2007). In adipose tissue, activation of NR1H3 led to the transcriptional induction of the insulin-sensitive glucose transporter, GLUT4 (Laffitte BA et al. 2003; Dalen KT et al. 2003). In contrast, basal expression of LXRβ (NR1H2) has been shown to be essential for the regulation of PCK1 by another nuclear receptor, the glucocorticoid receptor GR (NR3C1) (Patel et al. 2011; Patel et. al. 2017). The LXRs appear to have somewhat opposing roles in the regulation of PCK1 in the liver since NR1H3 (LXRα) activation represses PCK1 mRNA expression induced by glucocorticoids (Nader et al. 2012) and NR1H2 (LXRβ) antagonism reduces glucocorticoid-induced PCK1 mRNA expression (Patel et al. 2017).

Literature references

Li, J., Chao, LC., Castrillo, A., Hummasti, S., Mangelsdorf, DJ., Walczak, R. et al. (2003). Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue. *Proc. Natl. Acad. Sci. U.S.A., 100,* 5419-24. ↗

Editions

2018-01-19	Authored	Shamovsky, V.
2018-12-29	Reviewed	D'Eustachio, P.
2019-08-09	Reviewed	Repa, JJ., Cummins, CL.
2019-08-09	Edited	Shamovsky, V.

Table of Contents

Introduction 1

NR1H2 and NR1H3-mediated signaling 2

NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux 4

NR1H2 & NR1H3 regulate gene expression to limit cholesterol uptake 6

NR1H2 & NR1H3 regulate gene expression linked to lipogenesis 7

NR1H2 & NR1H3 regulate gene expression linked to triglyceride lipolysis in adipose 9

NR1H2 & NR1H3 regulate gene expression to control bile acid homeostasis 11

NR1H2 & NR1H3 regulate gene expression linked to gluconeogenesis 12

Table of Contents 13