Signaling by Nuclear Receptors

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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**


Reactome database release: 71

This document contains 4 pathways (see Table of Contents)
Nuclear receptors (NRs) are ligand-activated transcription factors that bind to small lipid based molecules to regulate gene expression and other cellular process. This family includes receptors for steroid hormones and derivatives (such as estrogen, progesterone, glucocorticoids, Vitamin D, oxysterols and bile acids, among others) as well as receptors for retinoic acids, thyroid hormones and fatty acids and their derivatives. These ligands are able to diffuse directly through cellular membranes as a result of their lipophilic nature (reviewed in Beato et al, 1996; Holzer et al, 2017).

The 48 human nuclear receptors share a conserved modular structure that consists of a sequence specific DNA-binding domain and a ligand-binding domain, in addition to various other protein-protein interaction domains. Upon interaction with ligand, NRs bind to the regulatory regions of target genes as homo- or heterodimers, or more rarely, as monomers. At the promoter, NRs interact with other activators and repressors to regulate gene expression (reviewed Beato et al, 1996; Simons et al, 2014; Hah and Kraus, 2010).

A number of nuclear receptors are cytoplasmic in the absence of ligand and exist as part of a heat shock protein complex that regulates their cellular location, protein stability, competency to bind steroid hormones and transcriptional activity (Echeverria and Picard, 2010). Ligand-binding to these receptors promotes dimerization and nuclear translocation. Other nuclear receptors are constitutively nuclear and their chromatin-modifying activities are regulated by ligand binding (reviewed in Beato et al, 1996).

In addition to the classic transcriptional response, NRs also have a role in rapid, non-nuclear signaling originating from receptors localized at the plasma membrane. Ligand-binding to these receptors initiates downstream phospholipase- and kinase-based signaling cascades (reviewed in Schwartz et al, 2016; Levin and Hammes, 2016).

Signaling by estrogen, liver X and retinoic acid receptors are currently described here.
Literature references


Editions

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Vitamin A (retinol) can be metabolised into active retinoid metabolites that function either as a chromophore in vision or in regulating gene expression transcriptionally and post-transcriptionally. Genes regulated by retinoids are essential for reproduction, embryonic development, growth, and multiple processes in the adult, including energy balance, neurogenesis, and the immune response. The retinoid used as a cofactor in the visual cycle is 11-cis-retinal (11cRAL). The non-visual cycle effects of retinol are mediated by retinoic acid (RA), generated by two-step conversion from retinol (Napoli 2012). All-trans-retinoic acid (atRA) is the major activated metabolite of retinol. An isomer, 9-cis-retinoic acid (9cRA) has biological activity, but has not been detected in vivo, except in the pancreas. An alternative route involves BCO1 cleavage of carotenoids into retinal, which is then reduced into retinol in the intestine (Harrison 2012). The two isomers of RA serve as ligands for retinoic acid receptors (RAR) that regulate gene expression. (Das et al. 2014). RA is catabolised to oxidised metabolites such as 4-hydroxy-, 18-hydroxy- or 4-oxo-RA by CYP family enzymes, these metabolites then becoming substrates for Phase II conjugation enzymes (Ross & Zolfaghari 2011).

**Literature references**


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Estrogens are a class of hormones that play a role in physiological processes such as development, reproduction, metabolism of liver, fat and bone, and neuronal and cardiovascular function (reviewed in Arnal et al, 2017; Haldosen et al, 2014). Estrogens bind estrogen receptors, members of the nuclear receptor superfamily. Ligand-bound estrogen receptors act as nuclear transcription factors to regulate expression of genes that control cellular proliferation and differentiation, among other processes, but also play a non-genomic role in rapid signaling from the plasma membrane (reviewed in Hah et al, 2014; Schwartz et al, 2016).

**Literature references**


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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 0.4μM. 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; Färnegårdh 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).

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