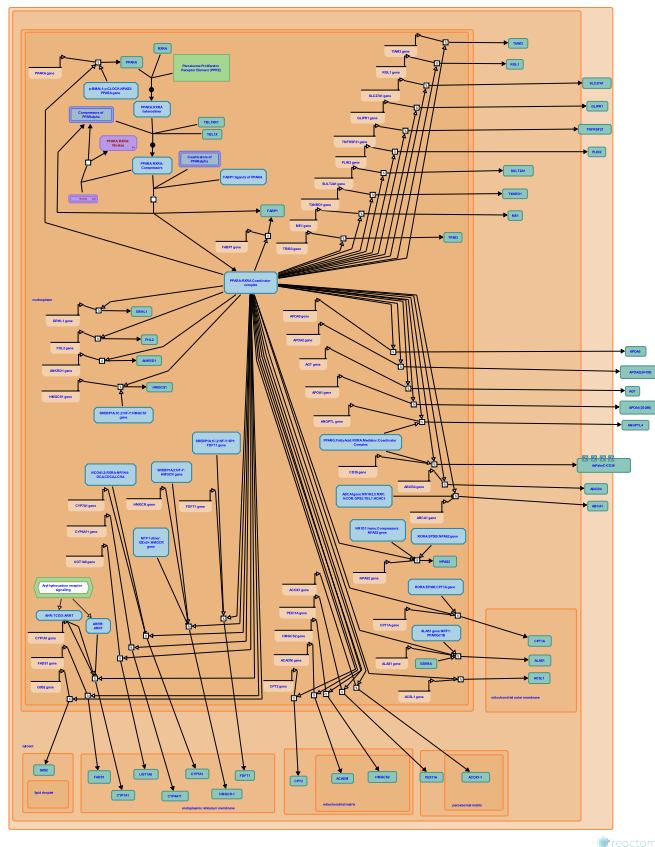


Regulation of lipid metabolism by PPAR α



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

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.

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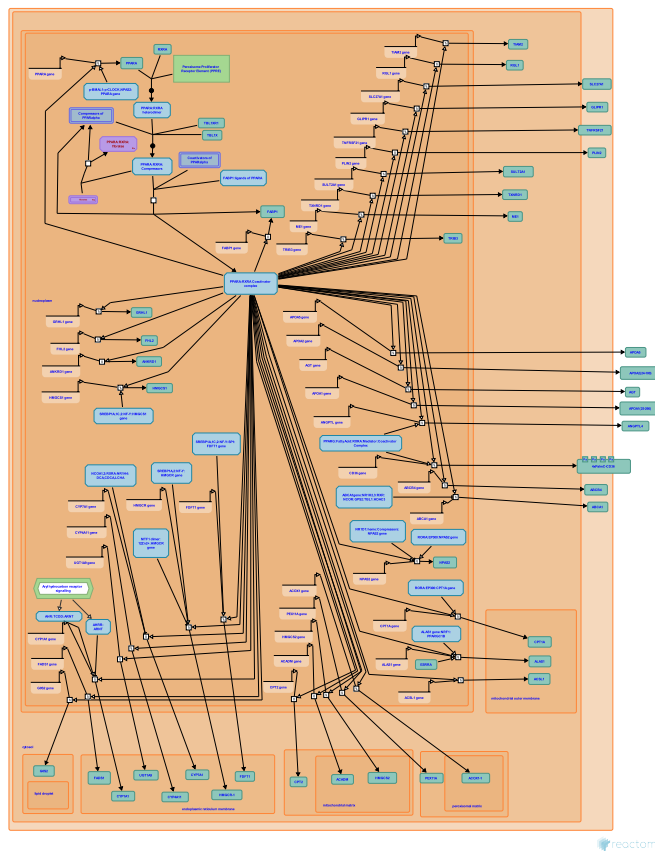
Reactome database release: 88

This document contains 2 pathways and 4 reactions ([see Table of Contents](#))

Regulation of lipid metabolism by PPARalpha ↗

Stable identifier: R-HSA-400206

Compartments: nucleoplasm, cytosol



Peroxisome proliferator-activated receptor alpha (PPAR-alpha) is the major regulator of fatty acid oxidation in the liver. PPARalpha is also the target of fibrate drugs used to treat abnormal plasma lipid levels.

PPAR-alpha is a type II nuclear receptor (its subcellular location does not depend on ligand binding). PPAR-alpha forms heterodimers with Retinoid X receptor alpha (RXR-alpha), another type II nuclear receptor. PPAR-alpha is activated by binding fatty acid ligands, especially polyunsaturated fatty acids having 18-22 carbon groups and 2-6 double bonds.

The PPAR-alpha:RXR-alpha heterodimer binds peroxisome proliferator receptor elements (PPREs) in and around target genes. Binding of fatty acids and synthetic ligands causes a conformational change in PPAR-alpha such that it releases the corepressors and binds coactivators (CBP-SRC-HAT complex, ASC complex, and TRAP-Mediator complex) which initiate transcription of the target genes.

Target genes of PPAR-alpha participate in fatty acid transport, fatty acid oxidation, triglyceride clearance, lipoprotein production, and cholesterol homeostasis.

Literature references

Gouni-Berthold, I., Krone, W. (2005). Peroxisome proliferator-activated receptor alpha (PPARalpha) and atherosclerosis. *Curr Drug Targets Cardiovasc Haematol Disord*, 5, 513-23. ↗

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Kersten, S. (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. *PPAR Res*, 2008, 132960. ↗

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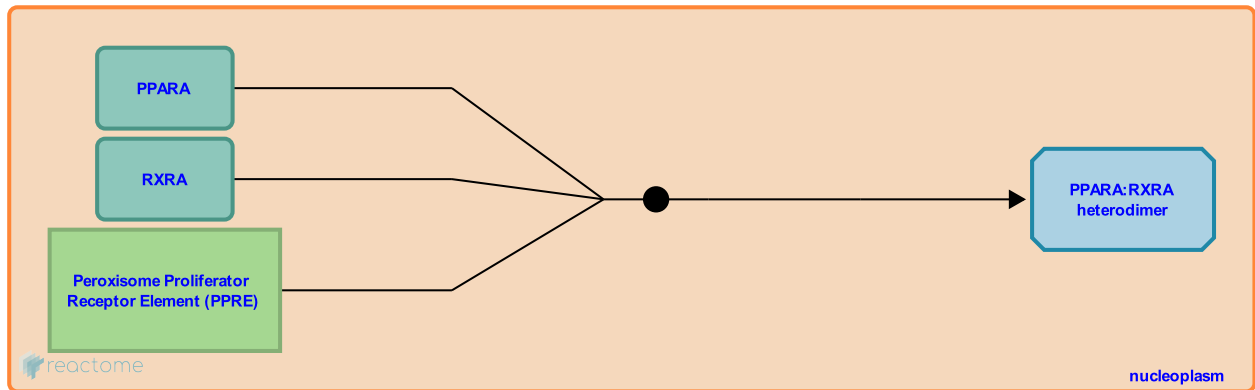
PPARA binds RXRA ↗

Location: [Regulation of lipid metabolism by PPARalpha](#)

Stable identifier: R-HSA-400204

Type: binding

Compartments: nucleoplasm



Peroxisome proliferator-activated receptor alpha (PPAR-alpha) is a type II nuclear receptor (its subcellular location is independent of ligand binding) related to PPAR-beta/delta and PPAR-gamma. PPAR-alpha is expressed highly in the liver where it functions to control lipid metabolism, especially fatty acid oxidation. PPAR-alpha forms heterodimers with Retinoid X receptor alpha (RXR-alpha). The heterodimers bind peroxisome proliferator receptor elements (PPREs) in and around genes regulated by PPAR-alpha.

Followed by: [PPARA:RXRA binds Corepressors of PPARA](#)

Literature references

- Gouni-Berthold, I., Krone, W. (2005). Peroxisome proliferator-activated receptor alpha (PPARalpha) and atherosclerosis. *Curr Drug Targets Cardiovasc Haematol Disord*, 5, 513-23. ↗
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- Qi, C., Reddy, JK., Zhu, Y. (2000). Peroxisome proliferator-activated receptors, coactivators, and downstream targets. *Cell Biochem Biophys*, 32, 187-204. ↗

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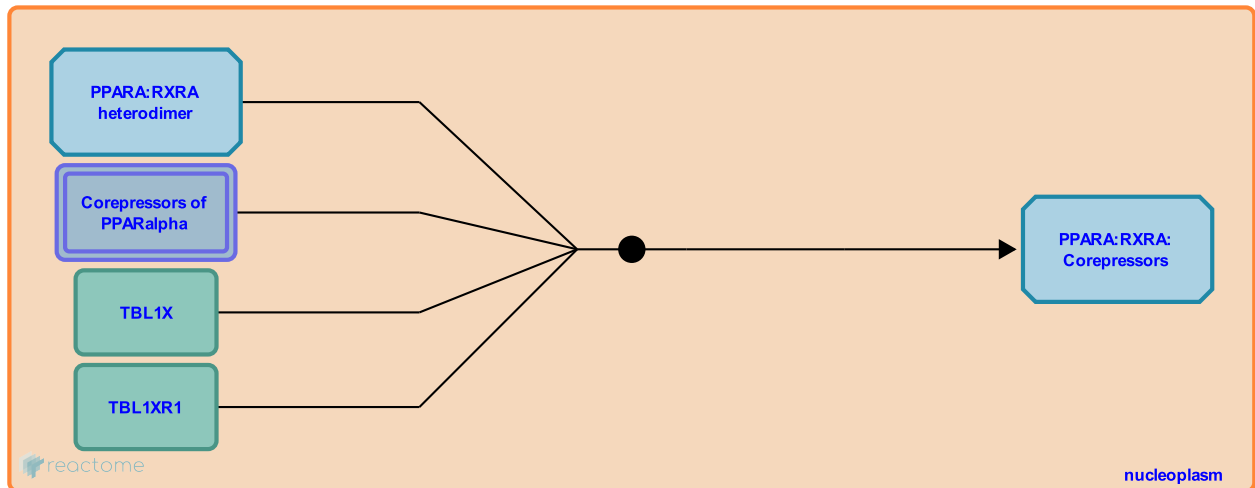
PPARA:RXRA binds Corepressors of PPARA ↗

Location: [Regulation of lipid metabolism by PPARalpha](#)

Stable identifier: R-HSA-400183

Type: binding

Compartments: nucleoplasm



In the absence of activating ligands of PPAR-alpha, the PPAR-alpha:RXR-alpha heterodimers recruit corepressors NCoR1, NCoR2(SMRT), and histone deacetylases (HDACs) to genes regulated by PPAR-alpha. The corepressors maintain chromatin at the gene in an inactive conformation and prevent expression of the gene.

Preceded by: [PPARA binds RXRA](#)

Followed by: [Fatty acid ligands activate PPARA](#)

Literature references

- Gouni-Berthold, I., Krone, W. (2005). Peroxisome proliferator-activated receptor alpha (PPARalpha) and atherosclerosis. *Curr Drug Targets Cardiovasc Haematol Disord*, 5, 513-23. ↗
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- Wahli, W., Desvergne, B. (1999). Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev*, 20, 649-88. ↗
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- Kersten, S. (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. *PPAR Res*, 2008, 132960. ↗

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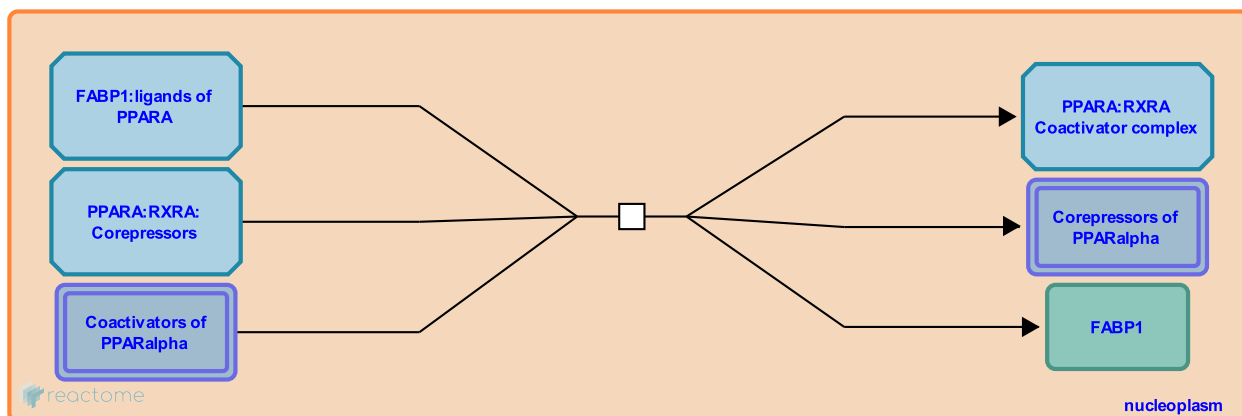
Fatty acid ligands activate PPARA ↗

Location: [Regulation of lipid metabolism by PPARalpha](#)

Stable identifier: R-HSA-400143

Type: transition

Compartments: nucleoplasm



PPAR-alpha is activated by binding polyunsaturated fatty acids especially those having 18-22 carbon groups and 2-6 double bonds. These ligands bind the C-terminal region of PPAR-alpha and include linoleic acid, linolenic acids, arachidonic acid, and eicosapentaenoic acid. The fibrate drugs are also agonists of PPAR-alpha.

Binding of a ligand causes a conformational change in PPAR-alpha so that it recruits coactivators. By analogy with the closely related receptor PPAR-gamma, PPAR-alpha probably binds TBL1 and TBLR1, which are responsible for recruiting the 19S proteasome to degrade corepressors during the exchange of corepressors for coactivators. The coactivators belong to the CBP-SRC-HAT complex (CBP/p300, SRC1, SRC2, SRC3, CARM1, SWI/SNF, BAF60C, PRIC320, and PRIC285), the ASC complex (PRIP/ASC2, PIMT), and the TRAP-DRIP-ARC-MEDIATOR complex (TRAP130, PBP/TRAP220). The coactivators contain LXXLL motifs (Nuclear Receptor Boxes) that interact with the AF-2 region in nuclear receptors such as PPAR-alpha. Additionally bilirubin binds to PPAR-alpha and acts as coactivator.

Preceded by: [PPARA:RXRA binds Corepressors of PPARA](#)

Literature references

Payne, HR., Storey, SM., Hostetler, HA., Schroeder, F., Kier, AB., McIntosh, AL. et al. (2009). L-FABP directly interacts with PPARalpha in cultured primary hepatocytes. *J Lipid Res*, 50, 1663-75. ↗

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Kersten, S. (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. *PPAR Res*, 2008, 132960. ↗

Qi, C., Reddy, JK., Zhu, Y. (2000). Peroxisome proliferator-activated receptors, coactivators, and downstream targets. *Cell Biochem Biophys*, 32, 187-204. ↗

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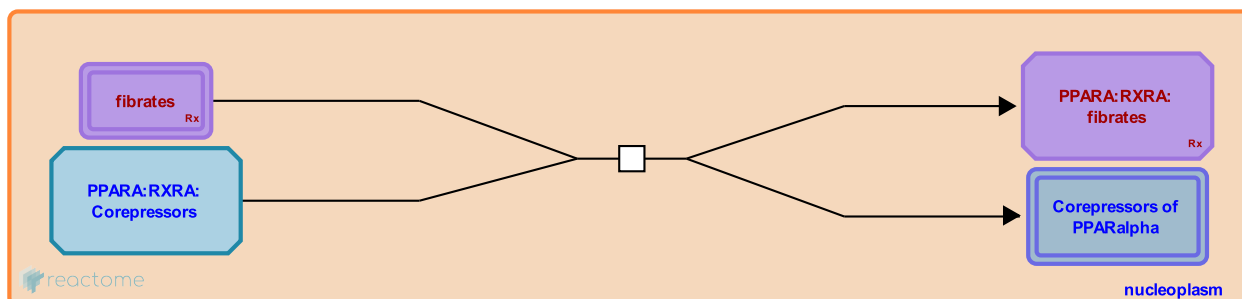
PPARA binds fibrates ↗

Location: Regulation of lipid metabolism by PPARalpha

Stable identifier: R-HSA-9734475

Type: transition

Compartments: nucleoplasm



The peroxisome proliferator-activated receptor alpha (PPARA) is a nuclear ligand-activated transcription factor that is a key regulator of fatty acid oxidation in the liver. Target genes of PPARA participate in fatty acid transport, fatty acid oxidation, triglyceride clearance, lipoprotein production, and cholesterol homeostasis. Its activation mediates lipid, glucose and amino acid homeostasis.

Fibrate drugs are derivatives of fibric acid which act as PPARA agonists and are widely used to lower triglycerides, LDL-cholesterol, total-cholesterol and apolipoprotein C3 (Grundy & Vega 1987, Clavey et al. 1999) while increasing HDL-cholesterol concentrations in serum. They are used to treat hypercholesterolemia, dyslipidemia and hypertriglyceridemia (Katsiki et al. 2013, Laufs et al. 2020). Fibrate drugs include gemfibrozil (De Filippis et al. 2011), bezafibrate (Inoue et al. 2002), ciprofibrate (Quang et al. 2012), clofibrate (Henke et al. 1998) and fenofibrate (Caldwell 1989).

Literature references

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Editions

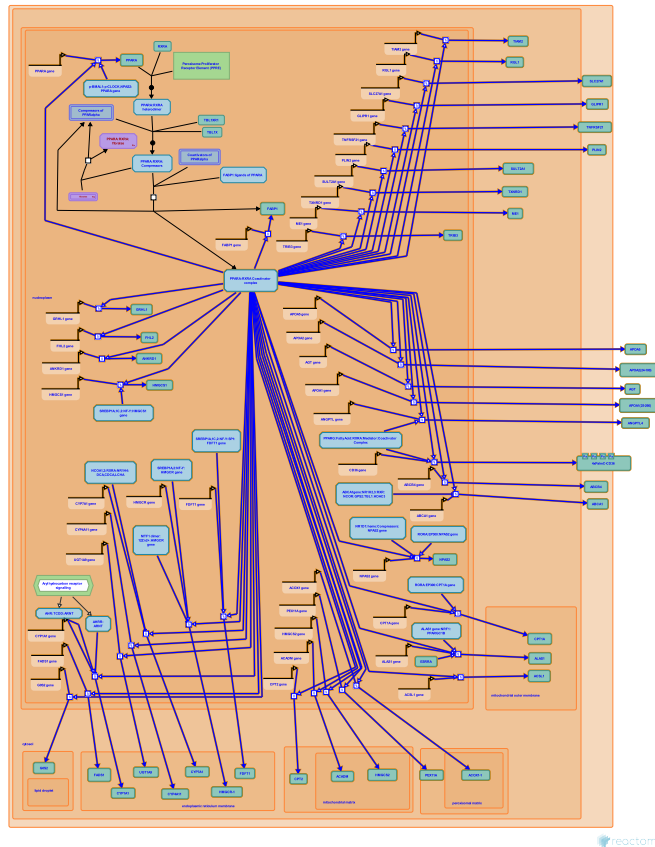
2021-06-17	Authored, Edited	Jassal, B.
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PPARA activates gene expression ↗

Location: Regulation of lipid metabolism by PPARalpha

Stable identifier: R-HSA-1989781

Compartments: peroxisomal matrix, endoplasmic reticulum membrane, plasma membrane, mitochondrial outer membrane, cytosol, mitochondrial matrix, extracellular region, lipid droplet, mitochondrial inner membrane, peroxisomal membrane, nucleoplasm



The set of genes regulated by PPAR-alpha is not fully known in humans, however many examples have been found in mice. Genes directly activated by PPAR-alpha contain peroxisome proliferator receptor elements (PPREs) in their promoters and include:

- 1) genes involved in fatty acid oxidation and ketogenesis (Acox1, Cyp4a, Acadm, Hmgcs2);
- 2) genes involved in fatty acid transport (Cd36, , Slc27a1, Fabp1, Cpt1a, Cpt2);
- 3) genes involved in producing fatty acids and very low density lipoproteins (Me1, Scd1);
- 4) genes encoding apolipoproteins (Apoa1, Apoa2, Apoa5);
- 5) genes involved in triglyceride clearance (Angptl4);
- 6) genes involved in glycerol metabolism (Gpd1 in mouse);
- 7) genes involved in glucose metabolism (Pdk4);
- 8) genes involved in peroxisome proliferation (Pex11a);
- 9) genes involved in lipid storage (Plin, Adfp).

Many other genes are known to be regulated by PPAR-alpha but whether their regulation is direct or indirect remains to be found. These genes include: ACACA, FAS, SREBP1, FADS1, DGAT1, ABCA1, PLTP, ABCB4, UGT2B4, SULT2A1, Pnpla2, Acsl1, Slc27a4, many Acot genes, and others (reviewed in Rakhshandehroo et al. 2010).

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Qi, C., Reddy, JK., Zhu, Y. (2000). Peroxisome proliferator-activated receptors, coactivators, and downstream targets. *Cell Biochem Biophys*, 32, 187-204. [↗](#)

Kersten, S. (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. *PPAR Res*, 2008, 132960. [↗](#)

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