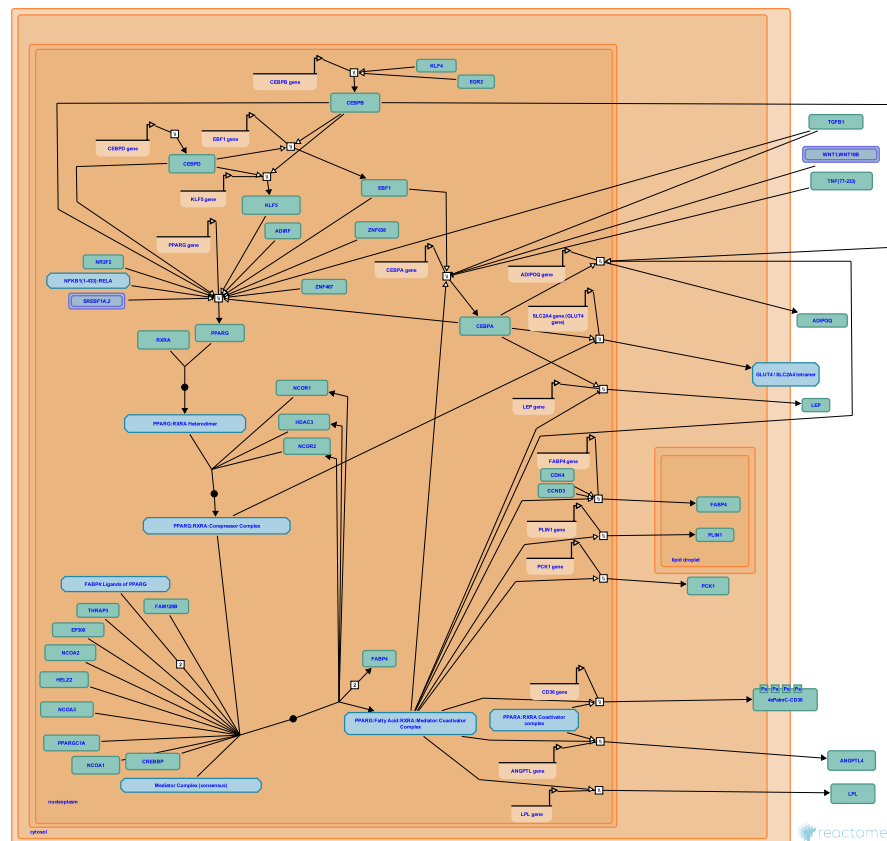


# Transcriptional regulation of white adipocyte differentiation



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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

- 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: 76

This document contains 1 pathway and 18 reactions ([see Table of Contents](#))



CEBPB and CEBPD act directly on the Peroxisome Proliferator-activated Receptor Gamma (PPARG) gene by binding its promoter and activating transcription. CEBPB and CEBPD also directly activate the EBF1 gene (and possibly other EBFs) and KLF5 (Jimenez et al. 2007, Oishi 2005). The EBF1 and KLF5 proteins, in turn bind, and activate the PPARG promoter. Other hormones, such as insulin, affect PPARG expression and other transcription factors, such as ADD1/SREBP1c, bind the PPARG promoter. This is an area of ongoing research.

During adipogenesis the PPARG gene is transcribed to yield 2 variants. The adipogenic variant 2 mRNA encodes 30 additional amino acids at the N-terminus compared to the widely expressed variant 1 mRNA.

PPARG encodes a type II nuclear hormone receptor (remains in the nucleus in the absence of ligand) that forms a heterodimer with the Retinoid X Receptor Alpha (RXRA). The heterodimer was initially identified as a complex regulating the aP2/FABP4 gene and named ARF6 (Tontonoz et al. 1994).

The PPARG:RXRA heterodimer binds a recognition sequence that consists of two hexanucleotide motifs (DR1 motifs) separated by 1 nucleotide. Binding occurs even in the absence of ligands, such as fatty acids, that activate PPARG. In the absence of activating ligands, the PPARG:RXRA complex recruits repressors of transcription such as SMRT/NCoR2, NCoR1, and HDAC3 (Tontonoz and Spiegelman 2008).

Each molecule of PPARG can bind 2 molecules of activating ligands. Although, the identity of the endogenous ligands of PPARG is unknown, exogenous activators include fatty acids and the thiazolidinedione class of antidiabetic drugs (reviewed in Berger et al. 2005, Heikkinen et al. 2007, Lemberger et al. 1996). The most potent activators of PPARG in vitro are oxidized derivatives of unsaturated fatty acids. Upon binding activating ligands PPARG causes a rearrangement of adjacent factors: Corepressors such as SMRT/NCoR2 are lost and coactivators such as TIF2, PRIP, CBP, and p300 are recruited (Tontonoz and Spiegelman). PPARG also binds directly to the TRAP220 subunit of the TRAP/Mediator complex that recruits RNA polymerase II. Thus binding of activating ligand by PPARG causes transcription of PPARG target genes.

Targets of PPARG include genes involved in differentiation (PGAR/HFARP, Perilipin, aP2/FABP4, CEBPA), fatty acid transport (LPL, FAT/CD36), carbohydrate metabolism (PEPCK-C, AQP7, GK, GLUT4 (SLC2A4)), and energy homeostasis (LEPTIN and ADIPONECTIN) (Perera et al. 2006).

Within 10 days of differentiation CEBPB and CEBPD are no longer located at the PPARG promoter. Instead CEBPA is present. EBF1 and PPARG bind the CEBPA promoter and activate transcription of CEBPA, one of the key transcription factors in adipogenesis. A current hypothesis posits a self-reinforcing loop that maintains PPARG expression and the differentiated state: PPARG activates CEBPA and CEBPA activates PPARG. Additionally EBF1 (and possibly other EBFs) activates CEBPA, CEBPA activates EBF1, and EBF1 activates PPARG.

## Literature references

- Wdziekonski, B., Mohsen-Kanson, T., Villageois, P., Dani, C. (2011). The generation and the manipulation of human multipotent adipose-derived stem cells. *Methods Mol Biol*, 702, 419-27. ↗
- Tontonoz, P., Graves, RA., Budavari, AI., Erdjument-Bromage, H., Lui, M., Hu, E. et al. (1994). Adipocyte-specific transcription factor ARF6 is a heterodimeric complex of two nuclear hormone receptors, PPAR gamma and RXR alpha. *Nucleic Acids Res*, 22, 5628-34. ↗
- Rosen, ED., MacDougald, OA. (2006). Adipocyte differentiation from the inside out. *Nat Rev Mol Cell Biol*, 7, 885-96. ↗
- Berger, JP., Akiyama, TE., Meinke, PT. (2005). PPARs: therapeutic targets for metabolic disease. *Trends Pharmacol Sci*, 26, 244-51. ↗

Lane, MD., Tang, QQ., Jiang, MS. (1999). Role of the CCAAT enhancer binding proteins (C/EBPs) in adipocyte differentiation. *Biochem Biophys Res Commun*, 266, 677-83. [↗](#)

## Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
2009-05-15	Authored	May, B.
2009-05-27	Reviewed	D'Eustachio, P.
2011-02-10	Reviewed	Sethi, JK.

## Expression of CEBPB in adipogenesis ↗

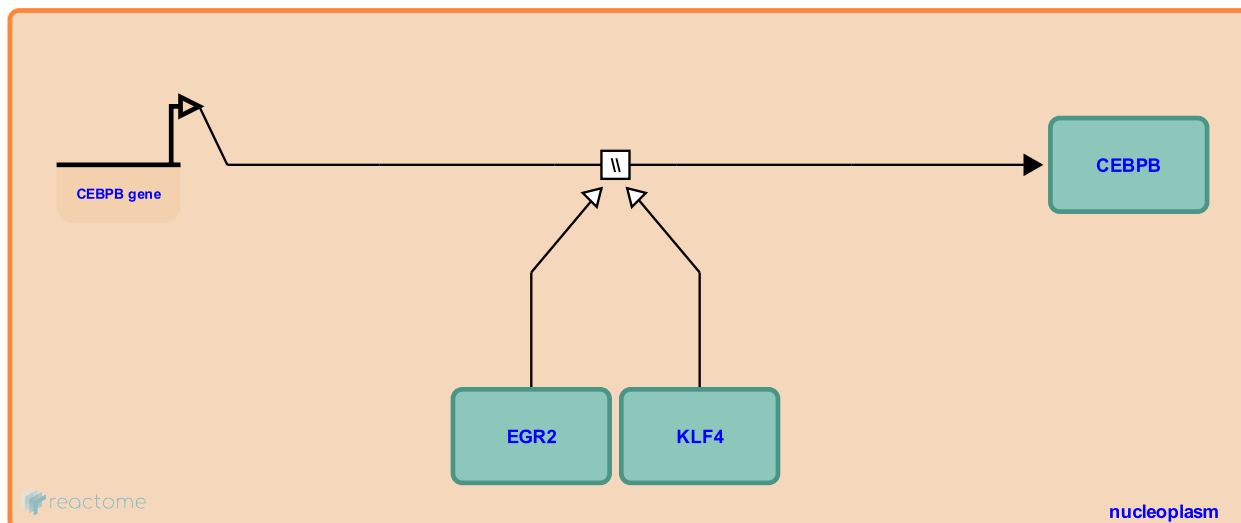
**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-381337

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** [Expression of Cebpb \(Mus musculus\)](#)



Expression of the CEBPB and CEBPD transcription factors is induced by at least three factors:

- 1) Mitogens such as those present in fetal serum act via the Krox20 transcription factor to activate expression of CEBPB.
- 2) Glucocorticoids activate expression of CEBPD.
- 3) Hormones or drugs that increase intracellular cAMP act via pCREB to activate expression of CEBPB.

The detailed mechanisms of activation are not yet known.

**Followed by:** [Expression of PPARG](#), [Expression of EBF1](#), [Expression of KLF5](#), [Expression of Adiponectin](#)

### Literature references

Farmer, SR. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. ↗

### Editions

2008-11-20	Edited	Gopinathrao, G., May, B.
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## Expression of CEBPD [↗](#)

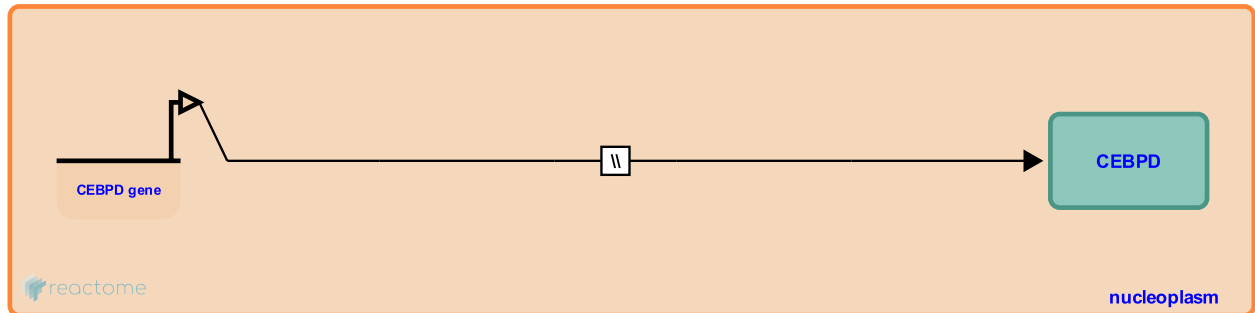
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**Stable identifier:** R-HSA-977392

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** [Expression of Cebpd \(Mus musculus\)](#)



Expression of the CEBPB and CEBPD transcription factors is induced by at least three factors:

- 1) Mitogens such as those present in fetal serum act via the Krox20 transcription factor to activate expression of CEBPB.
- 2) Glucocorticoids activate expression of CEBPD.
- 3) Hormones or drugs that increase intracellular cAMP act via pCREB to activate expression of CEBPB.

The detailed mechanisms of activation are not yet known.

**Followed by:** [Expression of EBF1](#), [Expression of KLF5](#), [Expression of PPARG](#)

## Literature references

Farmer, SR. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. [↗](#)

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2011-02-10	Reviewed	Sethi, JK.

## Expression of KLF5 [↗](#)

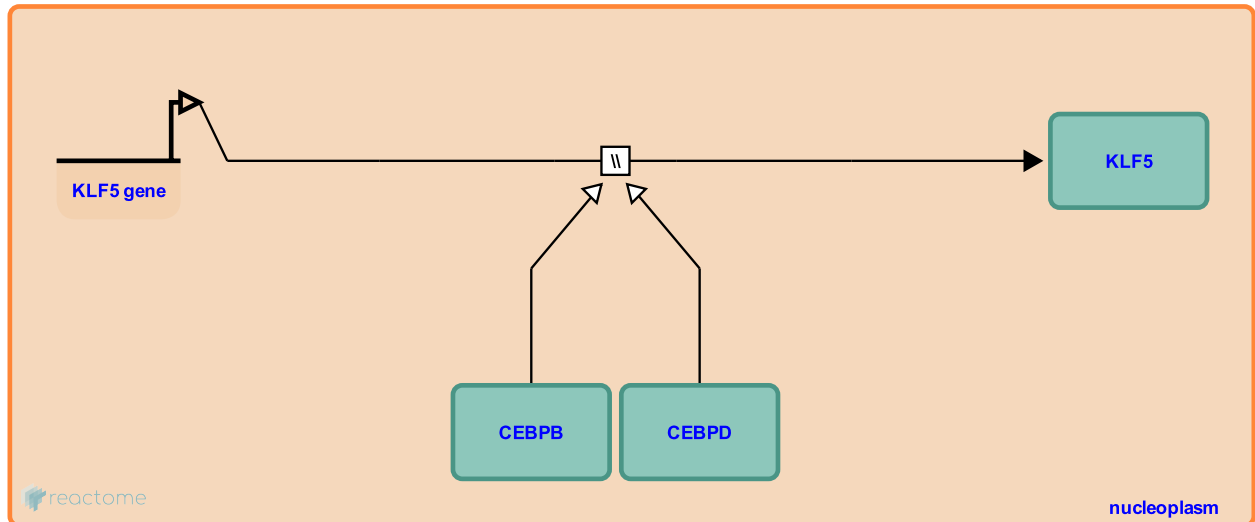
**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-381377

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** [Expression of Klf5 \(Mus musculus\)](#)



Increased expression of KLF5 occurs after activation of the transcription factors CEBPB and CEBPD during differentiation and activation of KLF5 depends on CEBPB and CEBPD. Both CEBPB and CEBPD bind the promoter of the KLF5 gene upstream of the site of transcription initiation and activate transcription of KLF5.

**Preceded by:** [Expression of CEBPB in adipogenesis](#), [Expression of CEBPD](#)

**Followed by:** [Expression of PPARG](#)

## Literature references

Farmer, SR. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. [↗](#)

## Editions

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## Expression of EBF1 ↗

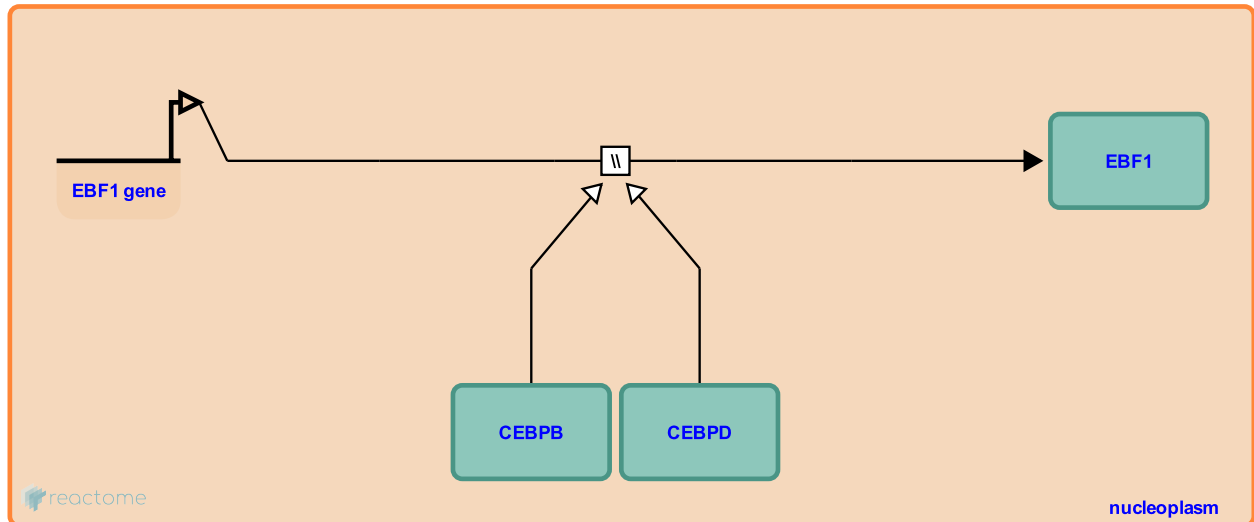
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**Stable identifier:** R-HSA-977271

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** [Expression of Ebf1 \(Mus musculus\)](#)



The gene encoding transcription factor EBF1 is transcribed to yield mRNA and the mRNA is translated to yield protein in pre-adipocytes and adipocytes. Transcription of EBF1 is enhanced by CEBPB and CEBPD, which bind the EBF1 promoter.

**Preceded by:** [Expression of CEBPB in adipogenesis](#), [Expression of CEBPD](#)

**Followed by:** [Expression of CEBPA](#), [Expression of PPARG](#)

### Editions

2009-05-27	Reviewed	D'Eustachio, P.
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## Expression of PPARG ↗

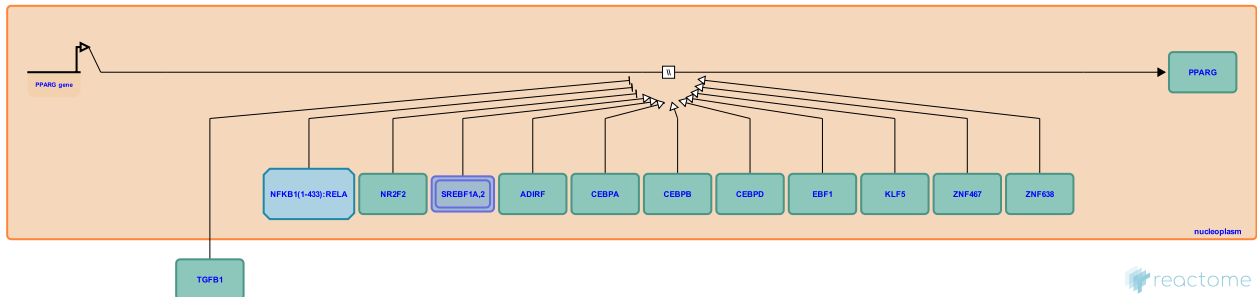
**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-381283

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** [Expression of Pparg \(Mus musculus\)](#)



The transcription factors CEBPB, CEBPD, and KLF5 simultaneously bind the PPARG promoter and synergistically activate transcription of the PPARG gene. These three factors activate transcription after initial stimulation of adipocyte differentiation but then are replaced by CEBPA within 10 days. CEBPA and other factors may be responsible for long term maintenance of PPARG expression and the differentiated state.

Pre-adipose tissue contains both the widely expressed PPARG isoform 1 mRNA and the more tissue-specific PPARG isoform 2. The PPARG isoform 2 mRNA is translated to yield PPARG isoform 2 protein, which has 505 amino acid residues (57 KDa) and is the longest of the 4 observed variants. Isoform 2 is specific to preadipose and adipose tissue (Mukherjee et al. 1997). Confusingly, the longest variant is called isoform 1 in some publications.

In mouse, by 10 days after induction of adipocyte differentiation Cebpa, but neither Cebpb nor Cebpd, is detectable at the Pparg promoter. While adipocyte differentiation can proceed without Cebpa, adipocytes differentiated from Cebpa-knockout cells are insulin insensitive due to a defect in Glut4 (Slc2a4) vesicle trafficking.

The adipogenesis regulatory factor (ADIRF, aka AFRO, APM2, C10orf116) promotes adipogenic differentiation and stimulates transcription initiation of master adipogenesis factors like PPARG and CEBPA (Ni et al. 2013).

**Preceded by:** [Expression of CEBPB in adipogenesis](#), [Expression of KLF5](#), [Expression of EBF1](#), [Expression of CEBPD](#)

**Followed by:** [Formation of PPARG:RXRA heterodimer \(ARF6 complex\)](#)

## Literature references

Mukherjee, R., Jow, L., Croston, GE., Paterniti JR, Jr. (1997). Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms PPARGgamma2 versus PPARGgamma1 and activation with retinoid X receptor agonists and antagonists. *J Biol Chem*, 272, 8071-6. ↗

Sewter, CP., Blows, F., Vidal-Puig, A., O'Rahilly, S. (2002). Regional differences in the response of human pre-adipocytes to PPARGgamma and RXRalpha agonists. *Diabetes*, 51, 718-23. ↗

Farmer, SR. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. ↗

Ni, Y., Ji, C., Wang, B., Qiu, J., Wang, J., Guo, X. (2013). A Novel pro-adipogenesis factor abundant in adipose tissues and over-expressed in obesity acts upstream of PPAR $\gamma$  and C/EBP $\alpha$ . *J. Bioenerg. Biomembr.*, 45, 219-28. [↗](#)

## Editions

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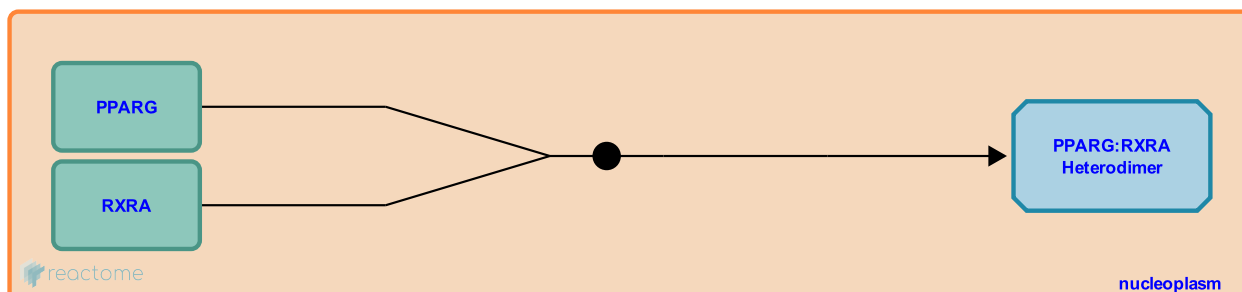
## Formation of PPARG:RXRA heterodimer (ARF6 complex) ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-381262

**Type:** binding

**Compartments:** nucleoplasm



PPARG binds the Retinoic acid X Receptor RXRA to form a heterodimer that has transcriptional activation activity. The complex was initially called ARF6 when discovered. PPARG binds RXRA via the C-terminus and AF-2 regions of PPARG.

**Preceded by:** [Expression of PPARG](#)

**Followed by:** [PPARG:RXRA heterodimer binds to PPARG corepressors](#)

### Literature references

Chandra, V., Huang, P., Hamuro, Y., Raghuram, S., Wang, Y., Burris, TP. et al. (2008). Structure of the intact PPARG-gamma-RXR- nuclear receptor complex on DNA. *Nature*, 456, 350-6. ↗

Lu, J., Chen, M., Stanley, SE., Li, E. (2008). Effect of heterodimer partner RXRalpha on PPARGgamma activation function-2 helix in solution. *Biochem Biophys Res Commun*, 365, 42-6. ↗

Farmer, SR. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. ↗

### Editions

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## PPARG:RXRA heterodimer binds to PPARG corepressors ↗

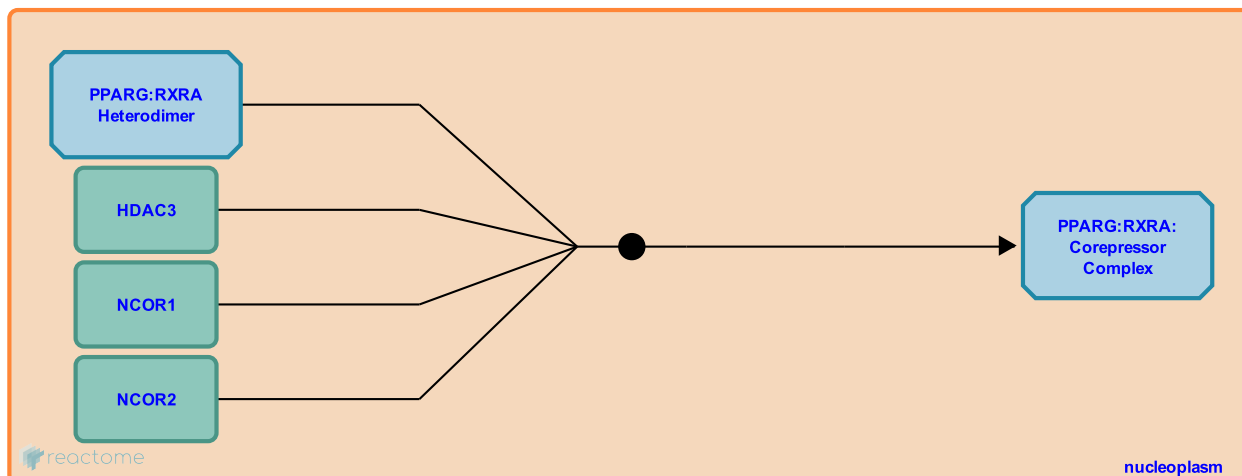
**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-381290

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** [Pparg:Rxra heterodimer binds to PPARG corepressors \(Mus musculus\)](#)



The PPARG:RXRA heterodimer binds specific the PPRE element, two 6-bp DR-1 motifs separated by 1 nucleotide, in the promoters of target genes such as aP2/FABP4 even in the absence of fatty acid ligands that activate PPARG. When activating ligands of PPARG are absent PPARG:RXRA recruits corepressors such as NCoR2(SMRT), NCoR, and HDAC3 to maintain the target gene in an inactive state.

**Preceded by:** [Formation of PPARG:RXRA heterodimer \(ARF6 complex\)](#)

**Followed by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

### Literature references

Lemberger, T., Desvergne, B., Wahli, W. (1996). Peroxisome proliferator-activated receptors: a nuclear receptor signaling pathway in lipid physiology. *Annu Rev Cell Dev Biol*, 12, 335-63. ↗

Farmer, SR. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. ↗

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## PPARG:RXRA heterodimer binds to fatty acid-like ligands ↗

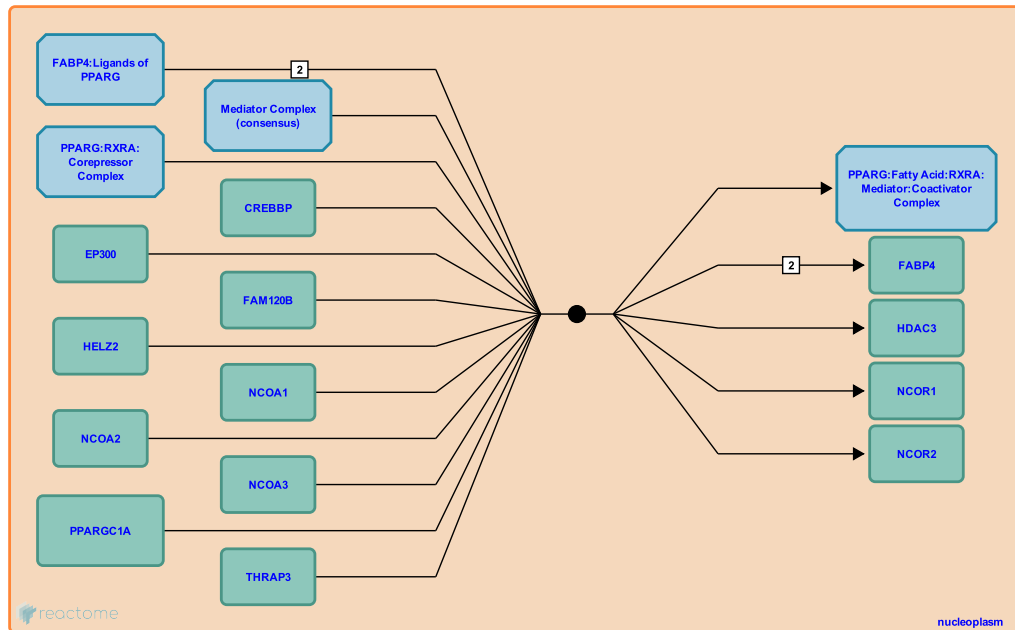
**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-381309

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** [Pparg:Rxra heterodimer binds to fatty acids \(Mus musculus\)](#)



PPARG can be activated in cell cultures by adding ligands such as polyunsaturated fatty acids and certain prostanoids (prostaglandins). Endogenous fatty acids are relatively poor activators. Which ligands are most responsible for PPARG activation in the body has not yet been established. Generally, oxidized fatty acids such as 9(S)-hydroxyoctadeca-10,12-dienoic acid (9(S)-HODE) and 13(S)-HODE are more effective activators than are endogenous fatty acids. The thiazolidinedione (TZD) class of antidiabetic drugs are agonist ligands for PPARG (Lambe and Tugwood 1996).

FABP4 delivers ligands to PPARG directly. Binding of activator ligands to PPARG causes loss of corepressors such as SMRT/NCoR2, NCoR1, and HDAC3 and gain of interactions with the basal transcription machinery (Yoo et al. 2006). The TRAP220/MED1/DRIP205 subunit of the TRAP/Mediator (DRIP) complex binds directly to the LXXLL motif of PPARG and TRAP/Mediator is necessary for full transcriptional activation of target genes (Ge et al. 2008). PPARG also interacts with the MED14 subunit of the Mediator complex (Grontved et al. 2010).

Other coactivators, including NCOA1/SRC-1, NCOA2/TIF2/GRIP1, CBP, HAT/p300, and PRIP, interact with PPARG in a ligand-dependent way and enhance transcription (Gellman et al. 1999, Wallberg et al. 2003, Yang et al. 2000, Ge et al. 2002, Puigserver et al. 1999, Bugge et al. 2009, Steger et al. 2010).

The target genes of PPARG encode proteins involved in adipocyte differentiation (PPARG/ANGPTL4, PLIN, and aP2/FABP4), carbohydrate metabolism (PEPCK-C), and fatty acid transport (FAT/CD36, LPL).

**Preceded by:** [PPARG:RXRA heterodimer binds to PPARG corepressors](#)

**Followed by:** [Expression of Lipoprotein lipase \(LPL\)](#), [Expression of FABP4 \(aP2\)](#), [Expression of ANGPTL4](#), [Expression of Phosphoenolpyruvate carboxykinase 1 \(PEPCK-C\)](#), [Expression of Perilipin \(PLIN\)](#), [Expres-](#)

## Literature references

- Gelman, L., Zhou, G., Fajas, L., Raspé, E., Fruchart, J.C., Auwerx, J. (1999). p300 interacts with the N- and C-terminal part of PPARgamma2 in a ligand-independent and -dependent manner, respectively. *J Biol Chem*, 274, 7681-8. [↗](#)
- Lambe, K.G., Tugwood, J.D. (1996). A human peroxisome-proliferator-activated receptor-gamma is activated by inducers of adipogenesis, including thiazolidinedione drugs. *Eur J Biochem*, 239, 1-7. [↗](#)
- Mukherjee, R., Jow, L., Croston, G.E., Paterniti JR, Jr. (1997). Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms PPARgamma2 versus PPARgamma1 and activation with retinoid X receptor agonists and antagonists. *J Biol Chem*, 272, 8071-6. [↗](#)
- Farmer, S.R. (2006). Transcriptional control of adipocyte formation. *Cell Metab*, 4, 263-73. [↗](#)
- Lemberger, T., Desvergne, B., Wahli, W. (1996). Peroxisome proliferator-activated receptors: a nuclear receptor signaling pathway in lipid physiology. *Annu Rev Cell Dev Biol*, 12, 335-63. [↗](#)

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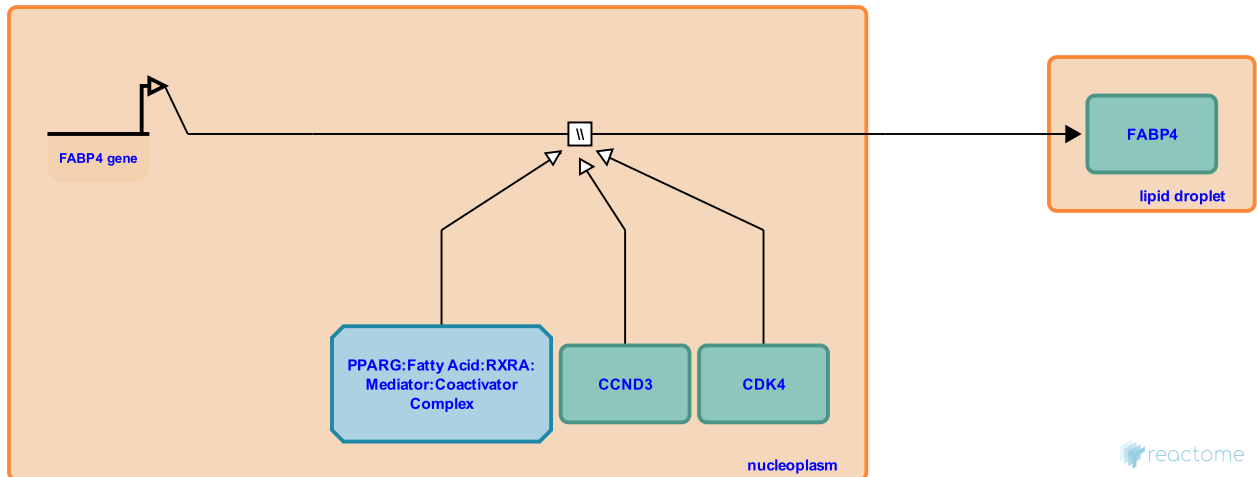
## Expression of FABP4 (aP2) ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560510

**Type:** omitted

**Compartments:** nucleoplasm, lipid droplet



The FABP4 gene is transcribed to yield mRNA and the mRNA is translated to yield protein. Expression of FABP4 is activated during adipogenesis.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

## Literature references

- Boiteux, G., Lascombe, I., Roche, E., Plissonnier, ML., Clairotte, A., Bittard, H. et al. (2009). A-FABP, a candidate progression marker of human transitional cell carcinoma of the bladder, is differentially regulated by PPAR in urothelial cancer cells. *Int J Cancer*, 124, 1820-8. ↗
- Rival, Y., Stennevin, A., Puech, L., Rouquette, A., Cathala, C., Lestienne, F. et al. (2004). Human adipocyte fatty acid-binding protein (aP2) gene promoter-driven reporter assay discriminates nonlipogenic peroxisome proliferator-activated receptor gamma ligands. *J Pharmacol Exp Ther*, 311, 467-75. ↗
- Morganstein, DL., Wu, P., Mane, MR., Fisk, NM., White, R., Parker, MG. (2010). Human fetal mesenchymal stem cells differentiate into brown and white adipocytes: a role for ERRalpha in human UCP1 expression. *Cell Res*. ↗
- Pelton, PD., Zhou, L., Demarest, KT., Burris, TP. (1999). PPARgamma activation induces the expression of the adipocyte fatty acid binding protein gene in human monocytes. *Biochem Biophys Res Commun*, 261, 456-8. ↗

## Editions

2009-05-27	Reviewed	D'Eustachio, P.
2010-03-23	Authored, Edited	May, B.
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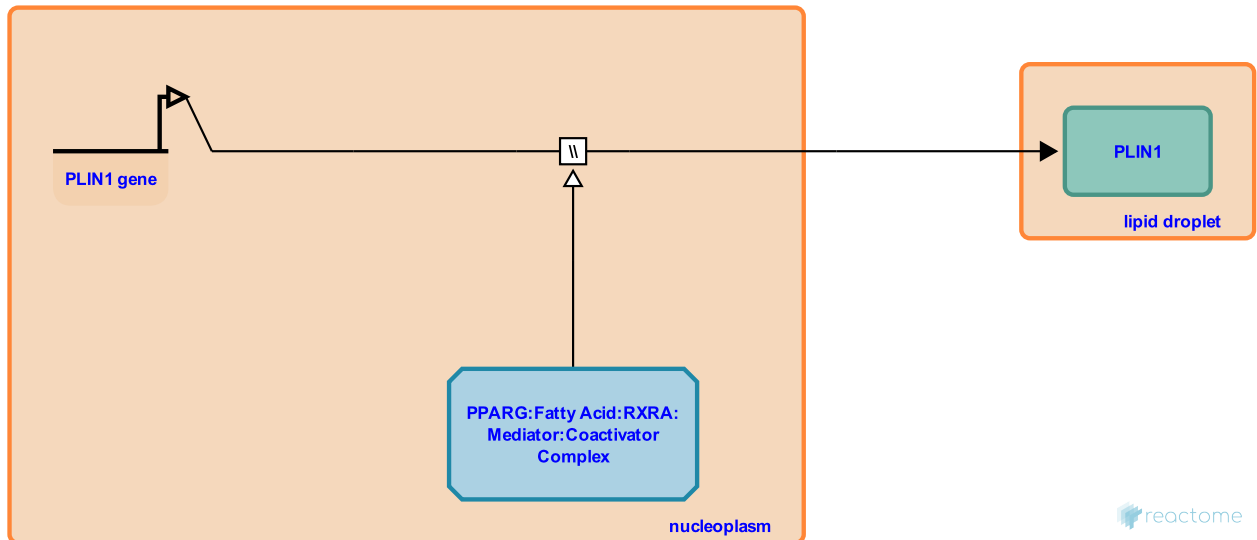
## Expression of Perilipin (PLIN) ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560493

**Type:** omitted

**Compartments:** nucleoplasm, lipid droplet



The Perilipin (PLIN) gene is transcribed to yield mRNA and the mRNA is translated to yield protein. Expression of Perilipin is upregulated during adipogenesis.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

### Literature references

Perera, RJ., Marcusson, EG., Koo, S., Kang, X., Kim, Y., White, N. et al. (2006). Identification of novel PPARgamma target genes in primary human adipocytes. *Gene*, 369, 90-9. ↗

### Editions

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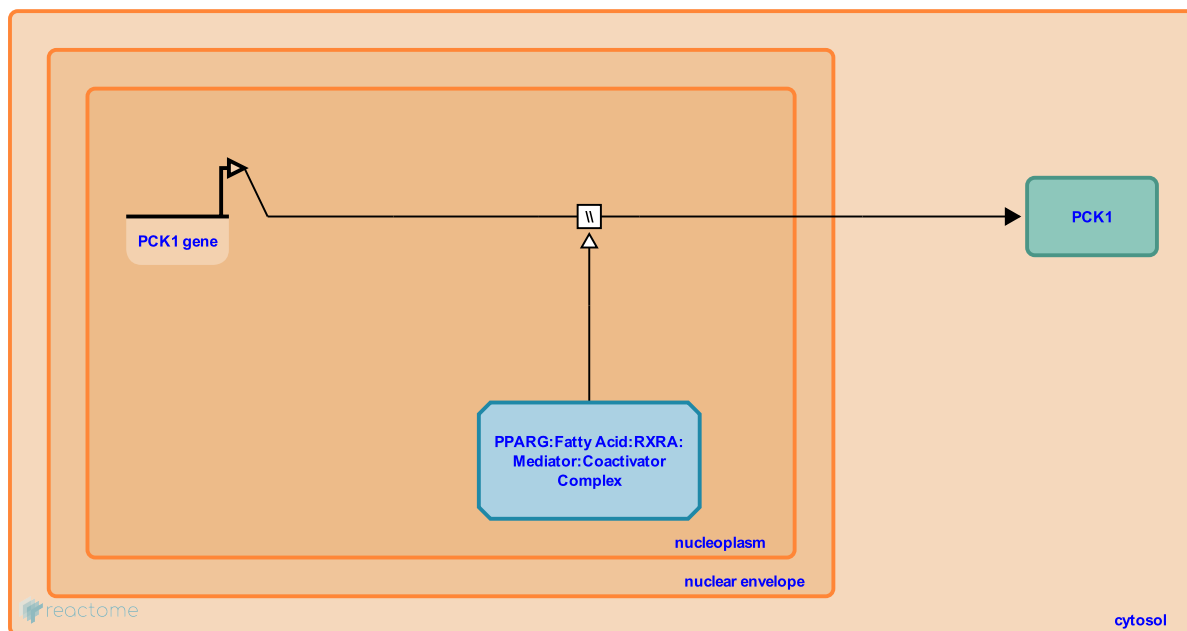
## Expression of Phosphoenolpyruvate carboxykinase 1 (PEPCK-C) ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560472

**Type:** omitted

**Compartments:** nucleoplasm, cytosol



The PEPCK-C gene is transcribed to yield mRNA and the mRNA is translated to yield protein.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

### Literature references

Perera, RJ., Marcusson, EG., Koo, S., Kang, X., Kim, Y., White, N. et al. (2006). Identification of novel PPARgamma target genes in primary human adipocytes. *Gene*, 369, 90-9. ↗

### Editions

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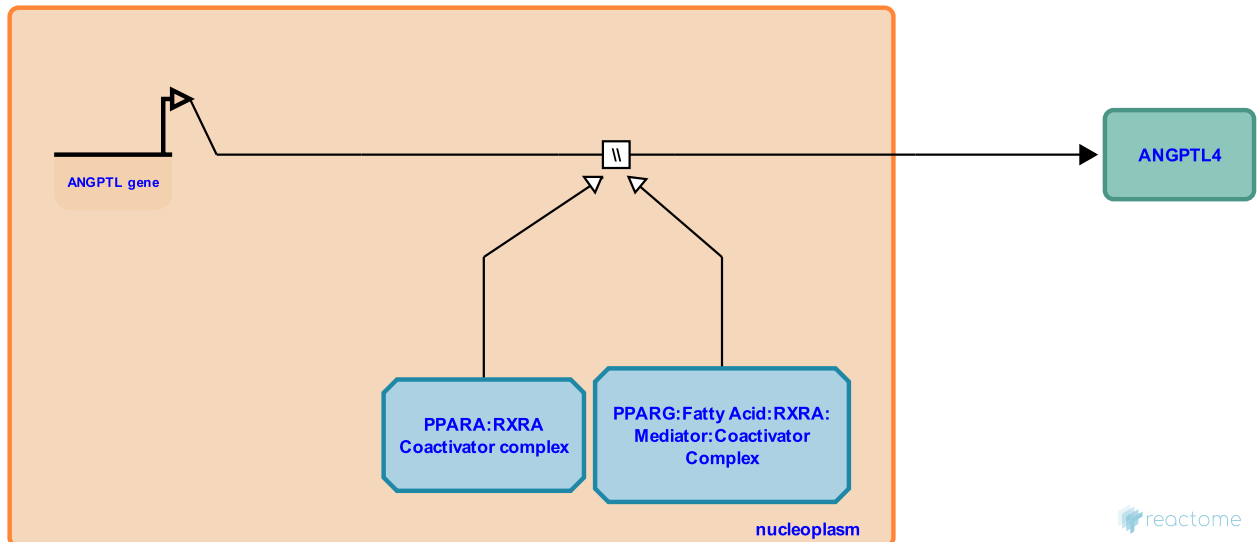
## Expression of ANGPTL4 ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560473

**Type:** omitted

**Compartments:** nucleoplasm, extracellular region



The ANGPTL4 gene is transcribed to yield mRNA and the mRNA is translated to yield protein.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

### Literature references

Tian, L., Zhou, J., Casimiro, MC., Liang, B., Ojeifo, JO., Wang, M. et al. (2009). Activating peroxisome proliferator-activated receptor gamma mutant promotes tumor growth in vivo by enhancing angiogenesis. *Cancer Res*, 69, 9236-44. ↗

Rakhshandehroo, M., Hooiveld, G., Muller, M., Kersten, S. (2009). Comparative analysis of gene regulation by the transcription factor PPARalpha between mouse and human. *PLoS One*, 4, e6796. ↗

### Editions

2009-05-27	Reviewed	D'Eustachio, P.
2009-06-08	Reviewed	Kersten, S.
2010-03-23	Authored, Edited	May, B.
2011-02-10	Reviewed	Sethi, JK.

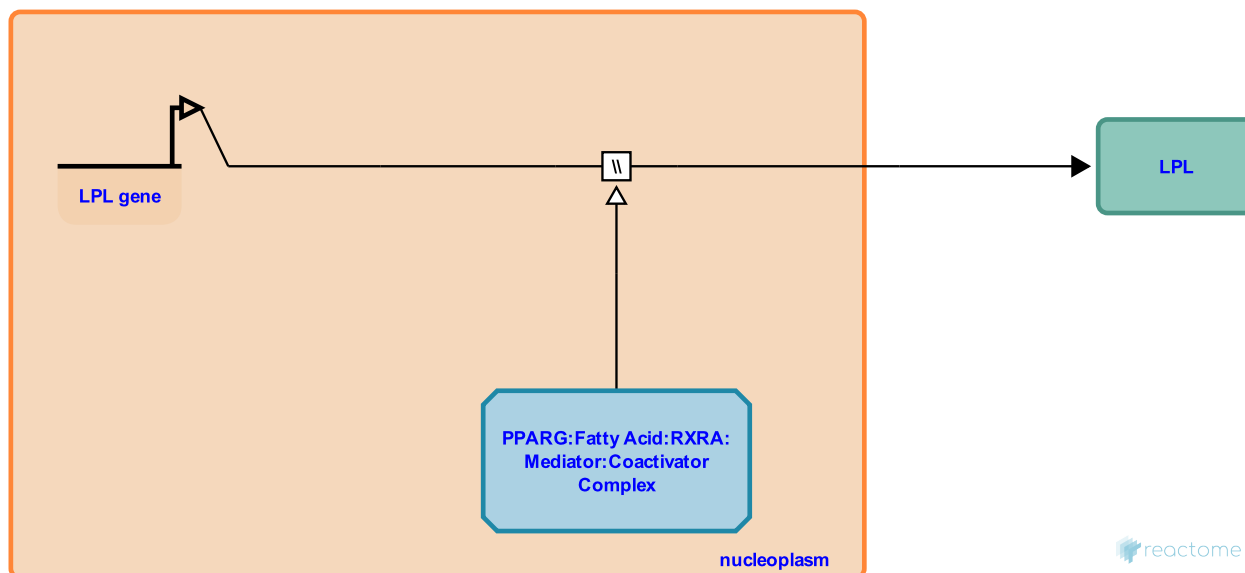
## Expression of Lipoprotein lipase (LPL) ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560498

**Type:** omitted

**Compartments:** nucleoplasm, extracellular region



The LPL gene is transcribed to yield mRNA and the mRNA is translated to yield protein.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

### Literature references

Perera, RJ., Marcusson, EG., Koo, S., Kang, X., Kim, Y., White, N. et al. (2006). Identification of novel PPARgamma target genes in primary human adipocytes. *Gene*, 369, 90-9. ↗

### Editions

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2011-02-10	Reviewed	Sethi, JK.

## Expression of CEBPA ↗

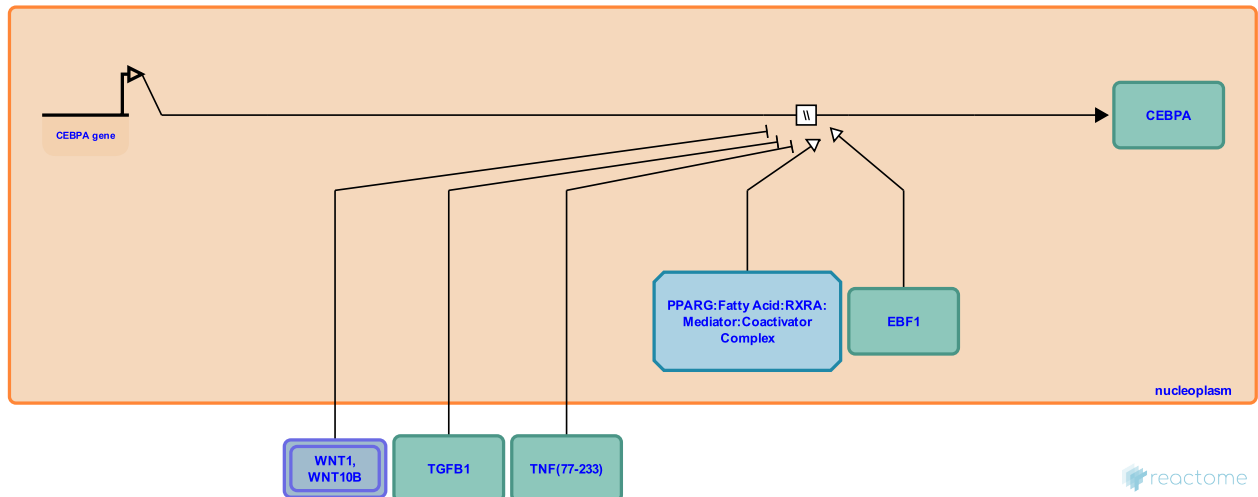
**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560491

**Type:** omitted

**Compartments:** nucleoplasm

**Inferred from:** [Expression of Cebpa \(Mus musculus\)](#)



The CEBPA gene is transcribed to yield mRNA and the mRNA is translated to yield protein.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#), [Expression of EBF1](#)

**Followed by:** [Expression of GLUT4](#), [Expression of Leptin](#), [Expression of Adiponectin](#)

## Literature references

Perera, RJ., Marcusson, EG., Koo, S., Kang, X., Kim, Y., White, N. et al. (2006). Identification of novel PPARgamma target genes in primary human adipocytes. *Gene*, 369, 90-9. ↗

## Editions

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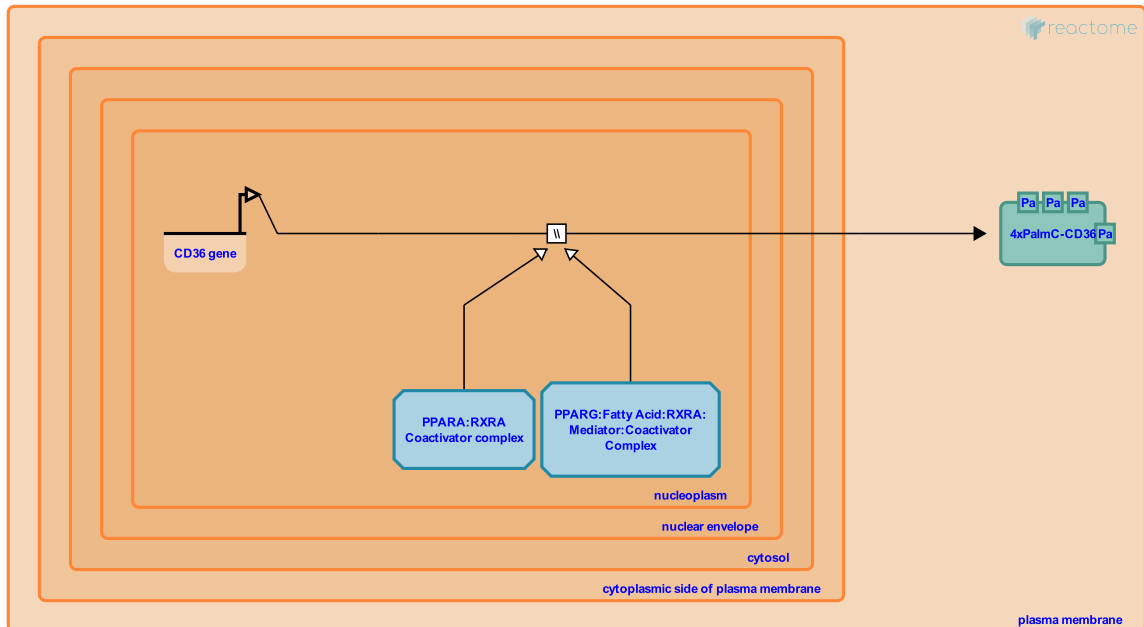
## Expression of CD36 (platelet glycoprotein IV, FAT) ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-560517

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane



The Platelet glycoprotein IV gene (CD36, PAS IV, GPIV) is transcribed to yield mRNA and the mRNA is translated to yield protein.

**Preceded by:** [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#)

### Literature references

Perera, RJ., Marcusson, EG., Koo, S., Kang, X., Kim, Y., White, N. et al. (2006). Identification of novel PPARgamma target genes in primary human adipocytes. *Gene*, 369, 90-9. ↗

### Editions

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2011-02-10	Reviewed	Sethi, JK.

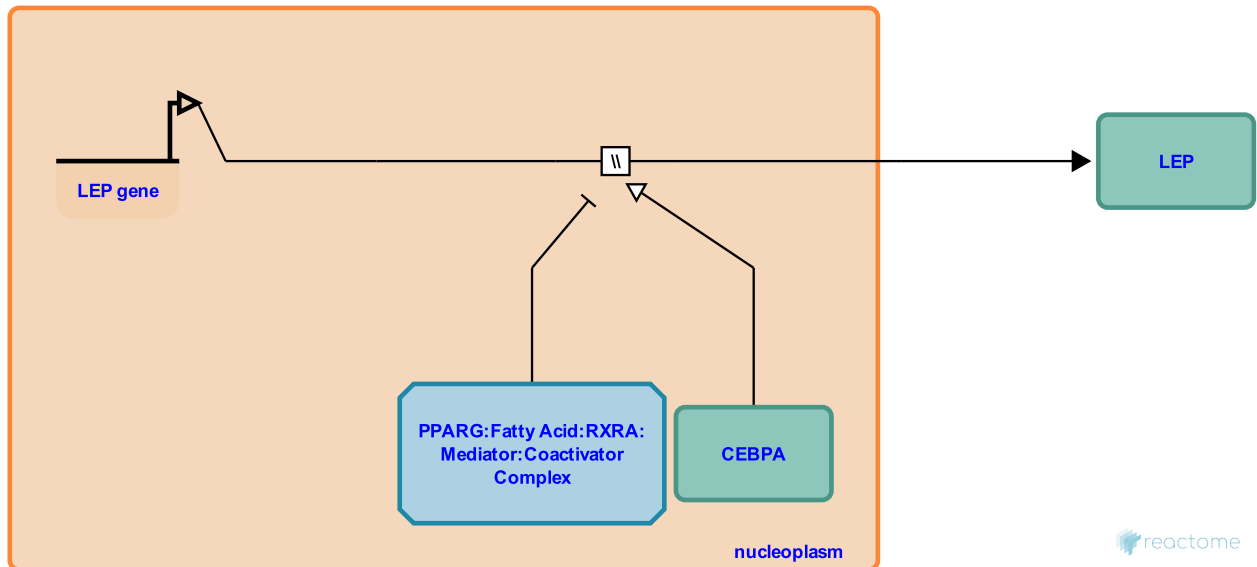
## Expression of Leptin ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-1183003

**Type:** omitted

**Compartments:** nucleoplasm, extracellular region



The Ob gene encoding leptin is transcribed to yield mRNA and translated to yield protein. Expression of leptin is positively regulated by C/EBPalpha (CEBPA, Miller et al. 1996, Melzner et al. 2002) and negatively regulated by PPARG in adipocytes (De Vos et al. 1996).

**Preceded by:** [Expression of CEBPA](#)

## Literature references

Miller, SG., De Vos, P., Guerre-Millo, M., Wong, K., Hermann, T., Staels, B. et al. (1996). The adipocyte specific transcription factor C/EBPalpha modulates human ob gene expression. *Proc Natl Acad Sci U S A*, 93, 5507-11. ↗

Melzner, I., Scott, V., Dorsch, K., Fischer, P., Wabitsch, M., Bruderlein, S. et al. (2002). Leptin gene expression in human preadipocytes is switched on by maturation-induced demethylation of distinct CpGs in its proximal promoter. *J Biol Chem*, 277, 45420-7. ↗

De Vos, P., Lefebvre, AM., Miller, SG., Guerre-Millo, M., Wong, K., Saladin, R. et al. (1996). Thiazolidinediones repress ob gene expression in rodents via activation of peroxisome proliferator-activated receptor gamma. *J Clin Invest*, 98, 1004-9. ↗

## Editions

2009-05-27	Reviewed	D'Eustachio, P.
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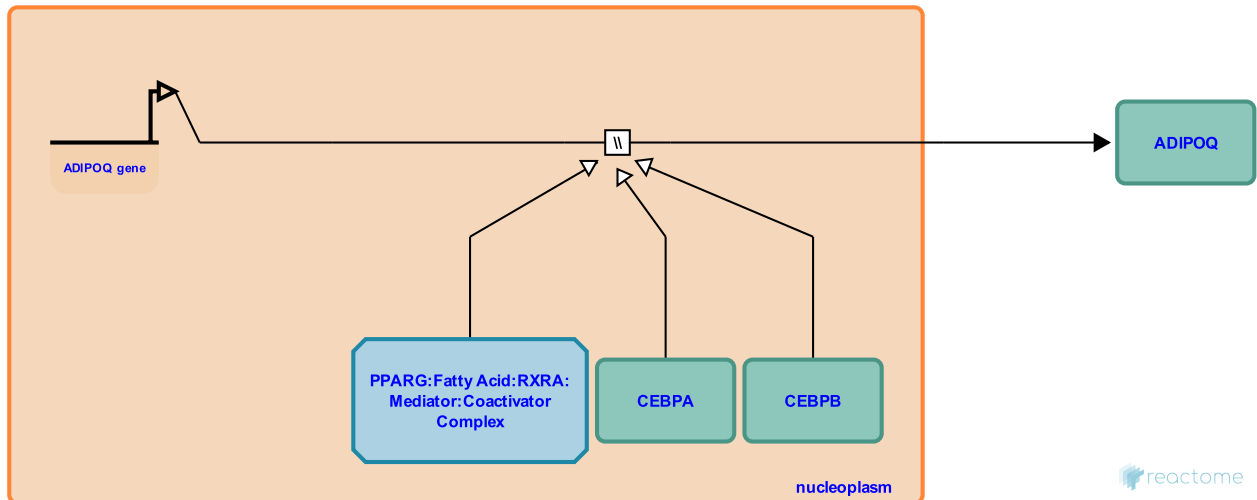
## Expression of Adiponectin ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-1183058

**Type:** omitted

**Compartments:** nucleoplasm, extracellular region



The Adiponectin gene is transcribed to yield mRNA and the mRNA is translated to yield protein. Expression of Adiponectin is upregulated during adipogenesis by C/EBPalpha (CEBPA), PPARG, and CEBPB (Segawa et al. 2009, Qiao et al. 2005, Iwaki et al. 2003, Kita et al. 2005).

**Preceded by:** [Expression of CEBPA](#), [PPARG:RXRA heterodimer binds to fatty acid-like ligands](#), [Expression of CEBPB in adipogenesis](#)

## Literature references

- Segawa, K., Matsuda, M., Fukuhara, A., Morita, K., Okuno, Y., Komuro, R. et al. (2009). Identification of a novel distal enhancer in human adiponectin gene. *J Endocrinol*, 200, 107-16. ↗
- Qiao, L., Maclean, PS., Schaack, J., Orlicky, DJ., Darimont, C., Pagliassotti, M. et al. (2005). C/EBPalpha regulates human adiponectin gene transcription through an intronic enhancer. *Diabetes*, 54, 1744-54. ↗
- Iwaki, M., Matsuda, M., Maeda, N., Funahashi, T., Matsuzawa, Y., Makishima, M. et al. (2003). Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes*, 52, 1655-63. ↗
- Kita, A., Yamasaki, H., Kuwahara, H., Moriuchi, A., Fukushima, K., Kobayashi, M. et al. (2005). Identification of the promoter region required for human adiponectin gene transcription: Association with CCAAT/enhancer binding protein-beta and tumor necrosis factor-alpha. *Biochem Biophys Res Commun*, 331, 484-90. ↗

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2011-02-10	Reviewed	Sethi, JK.



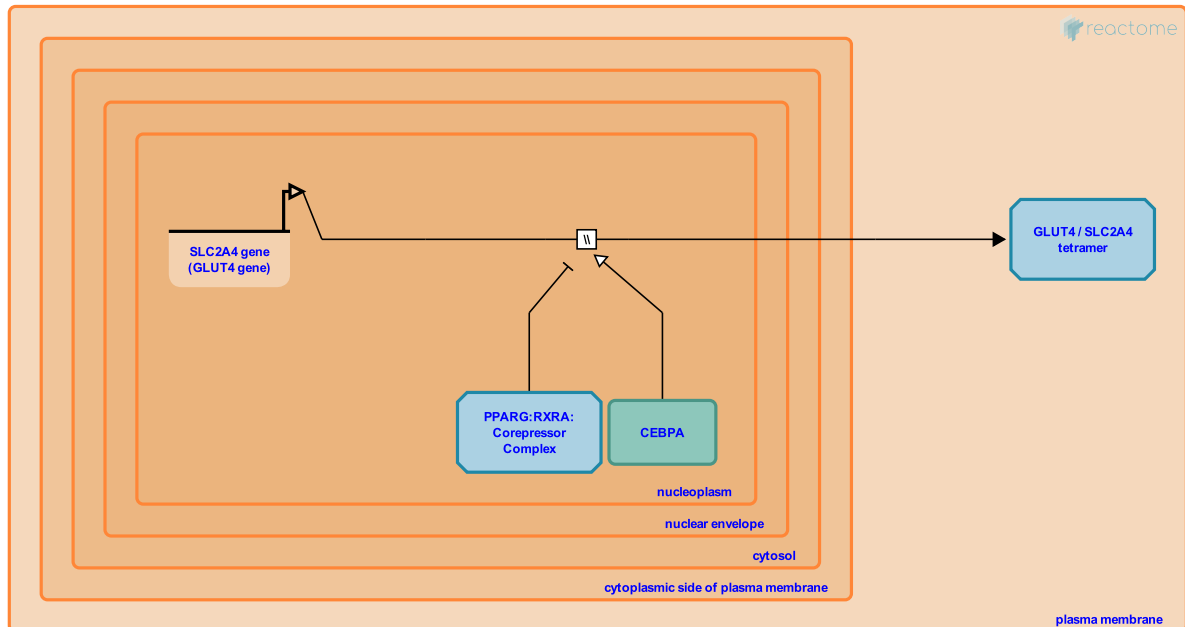
## Expression of GLUT4 ↗

**Location:** [Transcriptional regulation of white adipocyte differentiation](#)

**Stable identifier:** R-HSA-1183032

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane



The GLUT4 (SLC2A4) gene is transcribed to yield mRNA and the mRNA is translated to yield protein.

**Preceded by:** [Expression of CEBPA](#)

## Literature references

Pilch, PF., Wilkinson, W., Garvey, WT., Ciaraldi, TP., Hueckstaedt, TP., Olefsky, JM. (1993). Insulin-responsive human adipocytes express two glucose transporter isoforms and target them to different vesicles. *J Clin Endocrinol Metab*, 77, 286-9. ↗

## Editions

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2011-02-10	Reviewed	Sethi, JK.

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