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


Reactome database release: 79

This document contains 1 pathway and 18 reactions (see Table of Contents)
Adipogenesis is the process of cell differentiation by which preadipocytes become adipocytes. During this process the preadipocytes cease to proliferate, begin to accumulate lipid droplets and develop morphologic and biochemical characteristics of mature adipocytes such as hormone responsive lipogenic and lipolytic programs. The most intensively studied model system for adipogenesis is differentiation of the mouse 3T3-L1 preadipocyte cell line by an induction cocktail of containing mitogens (insulin/IGF1), glucocorticoid (dexamethasone), an inducer of cAMP (IBMX), and fetal serum (Cao et al. 1991, reviewed in Farmer 2006). More recently additional cellular models have become available to study adipogenesis that involve almost all stages of development (reviewed in Rosen and MacDougald 2006). In vivo knockout mice lacking putative adipogenic factors have also been extensively studied. Human pathways are traditionally inferred from those discovered in mouse but are now beginning to be validated in cellular models derived from human adipose progenitors (Fischer-Posovszky et al. 2008, Wdziekonski et al. 2011).

Adipogenesis is controlled by a cascade of transcription factors (Yeh et al. 1995, reviewed in Farmer 2006, Gesta et al. 2007). One of the first observable events during adipocyte differentiation is a transient increase in expression of the CEBPB (CCAAT/Enhancer Binding Protein Beta, C/EBPB) and CEBPD (C/EBPD) transcription factors (Cao et al. 1991, reviewed in Lane et al. 1999). This occurs prior to the accumulation of lipid droplets. However, it is the subsequent inductions of CEBPA and PPARG that are critical for morphological, biochemical and functional adipocytes.

Ectopic expression of CEBPB alone is capable of inducing substantial adipocyte differentiation in fibroblasts while CEBPD has a minimal effect. CEBPB is upregulated in response to intracellular cAMP (possibly via pCREB) and serum mitogens (possibly via Krox20). CEBPD is upregulated in response to glucocorticoids. The exact mechanisms that upregulate the CEBPs are not fully known.
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, 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**


## Editions

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Expression of CEBPB in adipogenesis

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