Modulation of the Transcriptional Activity of Peroxisome Proliferator-Activated Receptor Gamma by Protein-Protein Interactions and Post-Translational Modifications

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Peroxisome proliferator-activated receptor gamma (PPARγ) belongs to a nuclear receptor superfamily; members of which play key roles in the control of body metabolism principally by acting on adipose tissue. Ligands of PPARγ, such as thiazolidinediones, are widely used in the treatment of metabolic syndromes and type 2 diabetes mellitus (T2DM). Although these drugs have potential benefits in the treatment of T2DM, they also cause unwanted side effects. Thus, understanding the molecular mechanisms governing the transcriptional activity of PPARγ is of prime importance in the development of new selective drugs or drugs with fewer side effects. Recent advancements in molecular biology have made it possible to obtain a deeper understanding of the role of PPARγ in body homeostasis. The transcriptional activity of PPARγ is subject to regulation either by interacting proteins or by modification of the protein itself. New interacting partners of PPARγ with new functions are being unveiled. In addition, post-translational modification by various cellular signals contributes to fine-tuning of the transcriptional activities of PPARγ. In this review, we will summarize recent advancements in our understanding of the post-translational modifications of, and proteins interacting with, PPARγ, both of which affect its transcriptional activities in relation to adipogenesis.

Key Words: PPARγ, coregulator, post-translational modifications, transcriptional activity, adipogenesis, metabolic syndrome

INTRODUCTION

Structure and function of peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPARs) are known to be lipid sensors, and their ligands are used in the treatment of type 2 diabetes mellitus (T2DM) and other metabolic syndromes. PPARs are a family of nuclear receptors that act as transcription factors, controlling the genes involved in energy homeostasis.1 PPARs share a high degree of structural homology with other types of nuclear hormone receptors.2 PPARs comprise a DNA-binding domain (DBD), an agonist-independent activation domain (AF-1), and an agonist-dependent activation domain
(AF-2), which contains the ligand-binding domain (LBD). PPARs heterodimerize with the retinoid X receptor (RXR)-α and activate the expression of target genes by binding to the PPAR response element (PPRE).

The PPAR family has three isoforms; PPARα, γ, and β/δ. PPARα is expressed mainly in the liver, heart, kidney, brown adipose tissue (BAT), and skeletal muscle, and participates in fatty acid oxidation (β- and α-oxidation). The PPARβ/δ isoform is expressed ubiquitously and is involved in fatty acid oxidation in muscle. PPARγ is expressed predominantly in adipose tissue and plays key roles in lipogenesis and adipocyte differentiation. It also stimulates glucose oxidation and decreases plasma free fatty acid level. PPARγ consists of two isotypes; PPARγ1 is expressed in adipocytes, skeletal muscle, liver, and heart, whereas PPARγ2 is mostly found in adipose tissue. PPARγ2 plays a more important role than does PPARγ1 in adipogenesis.

**Physiological significance of PPARγ**

PPARγ was first identified as a trans-acting factor binding to a gene encoding a fat-specific enhancer of aP2 (adipocyte-specific fatty acid binding protein). Homozygous PPARγ knockout mice exhibit an embryonic lethal phenotype due to placental dysfunction. Heterozygous PPARγ deficient mice are resistant to high-fat diet-induced insulin resistance due to adipocyte hypertrophy and increased leptin expression. The ectopic expression of PPARγ was found to enhance the differentiation of preadipocytes into adipocytes, with PPARγ acting as an essential factor for differentiation. In addition, PPARγ is known to block the clonal expansion that occurs via mitosis, an essential stage of adipocyte differentiation.

Thiazolidinediones (TZDs) are a class of compounds that function as ligands of PPARγ. These compounds improve insulin sensitivity in vivo and have been introduced as therapeutic agents for the treatment of T2DM. TZDs increase the expression of PPARγ and its transcriptional activity in adipose tissue, resulting in the upregulation of the expression of genes involved in the metabolism of lipids, carbohydrates, steroids, and amino acids. TZDs increase insulin sensitivity by upregulating the expression of multiple genes, such as adiponectin, Cbl-associated protein, insulin receptor substrate 2, and glucose transporter 4. TZDs also promote fatty acid storage and lipid metabolism, such as fatty acid translocase (CD36), perilipin, fatty acid binding protein 4 (Fabp4/ap2), lipoprotein lipase, acyl-CoA synthase, phosphoenol pyruvate carboxykinase (PEPCK), and glycerol kinase (GyK).

However, the activation of PPARγ results in the repression of the genes encoding leptin, tumor necrosis factor-α (TNF-α), and interleukin-6. PPARγ decreases serum free fatty acid level and increases the number of small adipocytes, with a concomitant decrease in the number of large adipocytes in white adipose tissue (WAT). In addition to the role of PPARγ in adipose tissue, PPARγ directly activates the genes of the glucose-sensing apparatus in the liver and pancreatic β-cells. TZDs increase the expression of the genes encoding glucokinase (LGK and βGK) and glucose transporter 2 (GLUT2) in the liver and pancreatic β-cells, respectively (see Table 1 for summary). The transcriptional activity of PPARγ is subject to control at various levels; i.e., via modification of the receptor itself or interactions with other proteins.

In this review, we will limit our discussion to the regulation of PPARγ activity by various interacting proteins including coregulators, and by post-translational modifications (PTMs) that result in transcriptional regulation of PPARγ target genes.

**INTERACTING PROTEINS MODULATING TRANSCRIPTIONAL ACTIVITIES OF PPARγ**

The transcriptional activity of PPARγ is principally modulated by agonists, which recruit either coactivators or corepressors. In general, ligand-bound PPARγ recruits coactivators, whereas ligand-free PPARγ is bound to corepressors. These coregulators function as histone-modifying enzymes or bridging groups between the basal transcriptional machinery and PPARγ. Moreover, additional proteins are recruited to these coregulators that may affect tissue-specific activities of PPARγ.

**Coactivators of PPARγ**

**Coactivators with histone acetyltransferase activity**

Ligand-bound PPARγ undergoes conformational changes, providing contact sites for LXXLL motifs that are present in coactivators such as p160/steroid receptor coactivator-1 (SRC-1) and p300/CREB-binding protein (CBP). These coactivators have intrinsic histone acetyltransferase activities, which enhance the transcriptional activities of PPARγ. Members of the p160/SRC-1 family including SRC-1 (also known...
as NcoA-1), SRC-2 (also known as TIF2, GRIP-1, or NcoA-2), and SRC-3 (also known as p/CIP, ACTR, RAC-3, AIB-1, or TRAM-1), belong to this category.\textsuperscript{42} SRC-1 knockout (KO) mice showed increased WAT mass and a decrease in the expression of genes involved in thermogenesis in brown adipose tissue (BAT). These KO mice also showed decreased expression of the genes encoding uncoupling protein (UCP-1), PPARγ coactivator-1 (PGC-1α), and acyl-CoA oxidase, as well as those encoding enzymes involved in fatty acid oxidation.\textsuperscript{42} LXXLL motifs in SRC-1 interact directly with the AF-2 domain of PPARγ, recruiting CBP, which is required for PPARγ function.\textsuperscript{43} SRC2−/− mice exhibit increased insulin sensitivity and are resistant to the development of obesity. These mice show increased lipolysis and decreased fatty acid uptake and storage which are related to the reduction of PPARγ activity.\textsuperscript{45} When SRC-3 is deficient, corepressors such as nuclear receptor co-repressor (NCoR) and nuclear receptor interacting protein 1 (NRIIP1 or RIP140) are recruited to the PPRE of the UCP1 gene, resulting in a decrease in its transcription.\textsuperscript{44} SRC-3 and SRC-1 double KO mice are resistant to high-fat diet-induced obesity, due to the decreased expression of PPARγ target genes.\textsuperscript{44} PGC-1α activates PPARγ by increasing the binding of SRC-1 both in vivo and in vitro,\textsuperscript{45} whereas SRC-2 attenuates the formation of the PGC-1α-PPARγ complex by competing with SRC-1.\textsuperscript{46} This study suggests that the ratio of SRC-2/SRC-1 could be a critical metabolic determinant in the development of obesity and insulin resistance.\textsuperscript{42}

CBP/p300 indirectly increases the transcriptional activity of PPARγ through its interaction with PGC-1α. The docking of PGC-1α to PPARγ induces a conformational change in PGC-1α that promotes the binding of SRC-1 and CBP/p300.\textsuperscript{45} SRC-1 is also required for a functional interaction between CBP/p300 and PPARγ.\textsuperscript{43} CBP/p300 not only binds to the AF-2 domain of PPARγ in a ligand-dependent manner but also binds directly to the AF-1 domain in a ligand-independent manner,\textsuperscript{46} increasing the transcriptional activities of PPARγ\textsuperscript{46} and thereby inducing adipogenesis in NIH3T3 fibroblasts.\textsuperscript{57} The recruitment of PPARγ along with CBP/p300 to the aP2 gene promoter results in adipocyte differentiation.\textsuperscript{48}

### TRAP mediator complex

The thyroid hormone receptor-associated protein (TRAP) complex was first discovered in yeast and shown to be essential for RNA polymerase II-dependent transcription. TRAPs were first purified by affinity chromatography from cells overexpressing the thyroid hormone receptor. They are components of the TRAP/vitamin D receptor-interacting protein (DRIP)/activator-recruited cofactor/Mediator (Med) complex, functioning as mediators between RNA polymerase II and CBP/p300 or p160/SRC.\textsuperscript{49} TRAPs also

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**Table 1. Selected PPARγ Target Genes Involved in Metabolism**

| Genes          | PPARγ effect | Organ/cell type | Metabolic effects | Reference |
|----------------|--------------|----------------|-------------------|----------|
| Adiponectin    | Upregulation | Adipocyte      | Decrease in atherogenesis | 18       |
| CAP            | Upregulation | Adipocyte      | Improved insulin sensitivity | 20       |
| IRS2           | Upregulation | Adipocyte      | Anti-diabetic effect | 21       |
| GLUT4          | Upregulation | Adipocyte      | Glucose uptake    | 22, 23   |
| CD36           | Upregulation | Adipocyte      | Fatty acid uptake | 29       |
| aP2            | Upregulation | Adipocyte      | Lipid oxidation   | 25       |
| LPL            | Upregulation | Adipocyte, muscle | Decrease in triglyceride | 23, 30 |
| ACS            | Upregulation | Adipocyte      | Decrease in triglyceride | 31       |
| PCK2           | Upregulation | Adipocyte, muscle | Decrease in triglyceride | 23-25   |
| GyK            | Upregulation | Adipocyte      | Decrease in free fatty acid | 26       |
| Perlipin       | Upregulation | Adipocyte      | Decrease in free fatty acid | 27, 28  |
| Leptin         | Downregulation | Adipocyte | Improved insulin sensitivity | 32, 33  |
| TNF-α          | Downregulation | Adipocyte, liver | Improved insulin sensitivity | 32, 34, 35 |
| IL-6           | Downregulation | Adipocyte, liver | Improved insulin sensitivity | 32, 34, 35 |
| GK             | Upregulation | Liver, pancreatic β-cell | Improved glucose homeostasis | 37, 38  |
| GLUT2          | Upregulation | Liver, pancreatic β-cell | Increase in glucose sensing | 36, 39  |

PPARγ, peroxisome proliferator-activated receptor gamma; CAP, Cbl-associated protein; IRS2, insulin receptor substrate 2; GLUT4, glucose transporter 4; LPL, lipoprotein lipase; GyK, glycerol kinase; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; GLUT2, glucose transporter 2; CD36, fatty acid translocase; ACS, acetyl-CoA synthetase; PCK2, phosphoenolpyruvate carboxykinase 2; GK, glucokinase.
interact with nuclear receptors, such as the vitamin D receptor (VDR), retinoic acid receptor α (RARα), RXRα, PPARγ, and PPARα, in a ligand-dependent manner.\textsuperscript{50} Both TRAP220 and TRAP100 interact with PPARγ through their respective LXXLL motifs.\textsuperscript{50} TRAP220 is also referred to as the PPAR-binding protein/DRIP205/Med1 subunit of the TRAP complex, functioning as a bridging protein between various mediator complexes and nuclear receptors.\textsuperscript{51} TRAP220\textsuperscript{−/−} mice are embryonically lethal at day 11.5, suggesting that TRAP is essential for development. The ligand-dependent transcriptional activity of PPARγ is decreased in TRAP220\textsuperscript{−/−} mouse embryonic fibroblasts (MEFs).\textsuperscript{51} TRAP220\textsuperscript{−/−} MEF cells were not able to induce adipogenic genes via PPARγ. The PPARγ2-TRAP220 interaction is essential for adipogenesis\textsuperscript{52} and increases PPARγ-mediated transactivation of the promoter reporter construct.\textsuperscript{53} Although PPARγ acts by forming heterodimers with RXRα, treatment with the cognate PPARγ and RXRα-selective ligands results in the recruitment of different co-activators. RXRα-specific ligands recruit SRC-1/p160 to PPARγ-RXR, whereas PPARγ ligands recruit TRAP220, but not SRC-1/p160.\textsuperscript{54}

Regulation of PPARγ is achieved by the combinatorial actions of the coactivator and its ligands. Ligand-mediated selective recruitment of the coactivator may be responsible for fine-tuning of target gene expression.

**The switching/sucrose nonfermenting (SWI/SNF) chromatin remodeling complex**

The mating type SWI/SNF complex is an ATP-dependent chromatin remodeling enzyme that activates transcription by promoting the access of transcription factors to their cognate binding sites.\textsuperscript{55} The core components of the complex include either the Brg1 or Brm ATPases and several Brg1/Brm-associated factors (BAFs). Brg1 and/or Brm can interact with a number of different transcriptional regulatory proteins. For example, CCAAT-enhancer binding protein alpha (C/EBPα), a critical factor for adipogenesis, is known to interact with hBrm.\textsuperscript{57}

The Brg1/Brm-associated factors (BAFs) family is an accessory subunit of the SWI/SNF complex, acting as a connector between transcription factors and SWI/SNF complexes.\textsuperscript{59} BAF180 binds PPARγ-RXRα. The factor contains six bromodomains that bind selectively to acetylated histone tails, an important protein modification for targeting the co-activator complex to chromatin.\textsuperscript{59} In addition, the presence of Brg1 and Brm in the PPARγ promoter suggests that these coregulator complexes may contribute to adipogenesis. Transcriptional regulation by PPARγ during adipogenesis critically depends on the SWI/SNF complex, which plays a key role in the formation of preinitiation complexes.\textsuperscript{60} BAF60c2 (a BAF of 60 kDa, subunit 2) is also known to interact with the LBD of PPARγ. The N-terminal of BAF60c binds to the C-terminal of PPARγ, and the C-terminal of BAF60c interacts with the N-terminal of PPARγ in a ligand-independent manner. BAF acts as an anchor between SWI/SNF complexes and PPARγ. BAF60c increases the transcriptional activity of PPARγ in the presence of ligand but does not affect adipocyte differentiation.\textsuperscript{59}

**Other interacting proteins**

ADP-ribosylation factor (ARF6), a key regulator of the aP2 gene, is a novel transcription factor that is purified from BAT.\textsuperscript{60} ARF6 binding sites are present in the aP2 and PEPCK gene promoters.\textsuperscript{25,61} The PPARγ/RXRα heterodimer interacts with ARF6 during adipogenesis.\textsuperscript{60}

Menin, encoded by the multiple endocrine neoplasia type 1 (MEN1) tumor suppressor gene, is involved in activation of gene transcription as a component of the mixed-lineage leukemia (MLL) 1/MLL2 (also known as KMT2A/B) protein complexes, and exhibits methyltransferase (HMT) activity.\textsuperscript{62} Ectopic expression of menin increases the transcription of PPARγ target genes, and knock down of menin inhibits the differentiation of 3T3L1 preadipocytes into mature adipocytes. Menin interacts directly with the AF-2 domain of PPARγ and enhances PPARγ-mediated transcriptional activities in a ligand-dependent fashion. Menin increases histone H3K4 methylation in the PPARγ target gene, Fabp4, through a direct interaction with the AF-2 domain of PPARγ.\textsuperscript{62}

Multiprotein bridging factor-1 (MBF-1) is a cofactor that was first identified in *Bombyx mori* (Bm). It has been shown to interact with LXRα or PPARγ, and stimulate their ligand-dependent transcriptional activities.\textsuperscript{63} MBF-1 does not have either histone acetyltransferase or methyltransferase activity but interacts with transcription factor IID (TFIID). MBF-1 acts as a bridging protein between PPARγ and TFIID, increasing the transcriptional activity of PPARγ. Since MBF-1 is also known to interact with LXRα and liver receptor homolog 1 (LRH-1), a detailed investigation of the role of MBF-1 is important to understand its function in the context of lipid metabolism. The central domain of MBF-1 is necessary and critical for interaction with LRH-1, LXRα, and PPARγ.\textsuperscript{64}
PPARγ and thromboxane synthase (TXS) are expressed in macrophages; therefore, they may be involved in atherosclerosis. PPARγ binds to nuclear factor E2-related factor 2 (NRF2), which results in decreasing TXS gene expression by preventing the binding of NRF2 to the TXS gene. The suppression of TXS gene expression by PPARγ was increased by treatment with 15-deoxy-Δ12,14-prostaglandin J2 and troglitazone.65 TXS is increased in an inflammatory model of hydronephrosis, which is characterized by infiltration of macrophages into the kidney, and produces thromboxane.66,67 Thromboxane inhibitors are shown to suppress the progression of experimental diabetic nephropathy in rats68 and ameliorate microalbuminuria in patients with T2DM.69 Hence, PPARγ ligands could be used as drugs for treating renal complications of T2DM.

PPAR-interacting protein (PRIP, also known as RAP250/ASC-2/TRBP/NRC) is expressed in the reproductogenic organs (testis, prostate, and ovary) and identified as a novel, direct interacting coactivator of PPARα, RXRα, PPARα, RARα, estrogen receptor (ER), and thyroid hormone receptor β.70,71 Knock out of PRIP resulted in embryonic lethality and vascular dysfunction of the placenta.72 PRIP-/- MEFs exhibit repression of the transcriptional activity of RXRα rather than PPARα activity. Although PRIP was isolated in the yeast two-hybrid screen using PPARα as a bait, PRIP has a preference for RXRα over its heterodimeric partner, PPARγ.73

PPARγ-DBD interacting protein 1 (PDIP1) was isolated using the yeast two-hybrid system with the DBD and hinge regions of human PPARγ as bait. Two isoforms (α and β) of the PDIP1 gene are generated by alternative splicing. PDIP1 α and β increase the PPARγ-mediated transactivation of the PPRE, and treatment with PDIP1 siRNA significantly reduced the transcriptional activity of PPARγ. Because PDIP1 shows an expression pattern similar to that of CBP and TRAP220 during adipocyte differentiation, it might be involved in PPARγ-mediated adipogenesis.74

PGC-1α also binds to DBD and hinge regions of PPARγ in a ligand-independent fashion, similar to PDIP.75 PGC-1α was isolated from a BAT cDNA library and has been shown to increase the transcriptional activity of PPARγ on the UCP-1 gene. UCP-1 increases mitochondrial DNA content and β-oxidation.75 PGC-1α-deficient mice exhibit a reduced number of mitochondria and lower respiratory capacity, and fail to maintain core body temperature following exposure to cold.76 Overexpression of PGC-1α in WAT resulted in phenotypic changes into BAT.77,78 This phenotypic change provides a defense mechanism against obesity.79 In adipocytes, PPARγ acts as a master regulator of adipogenesis upregulating the aP2 and GyK genes. However, aP2 expression is increased in mature adipocytes whereas that of the GyK gene is not. PPARγ-mediated induction of GyK requires the recruitment of the PPARγ ligand and PGC-1α to PPARγ to replace corepressors with coactivators. In contrast, aP2 gene expression by PPARγ does not require its ligands. Differential regulation of target genes by ligands may determine the selective recruitment of coregulators.80 The interaction between PGC-1α and PPARγ induces a conformational change in PGC-1α, facilitating the recruitment of SRC-1 and CBP/p300.81 Although PGC-1α is known to interact with various nuclear receptors, PGC-1α is an essential cofactor for the transactivation of PPARγ, acting as a hub linking nutritional and hormonal signals to energy metabolism.82

Corepressors of PPARγ

Nuclear receptor co-repressor (NCoR) and silencing mediator of retinoid and thyroid hormone receptor (SMRT)
The PPARγ antagonist T0070907 covalently binds to PPARγ at Cys135 in helix 3, and was shown to decrease PPARγ activity in a cell-based reporter assay. T0070907 blocks the recruitment of the coactivator and promotes the recruitment of NCoR to PPARγ.82 In the absence of ligand, NCoR and silencing mediator of retinoid and thyroid hormone receptor (SMRT) are recruited to PPARγ, resulting in a decrease in its transcriptional activity. In cells treated with pioglitazone, SMRT and NCoR dissociate from PPARγ. In addition, treatment with siRNA against SMRT and NCoR increased adipogenesis and the accumulation of lipid droplets in 3T3L1 adipocytes.83

NAD-dependent deacetylase sirtuin-1 (SIRT1) is known to be responsible for calorie restriction and mobilizing WAT. SIRT1 activation by resveratrol decreases fat accumulation in differentiated adipocytes. SIRT1 represses PPARγ transcriptional activity by recruiting NCoR and SMRT.84 Since a reduction in fat accumulation is sufficient to extend life span in mice,85 the role of SIRT1 in fat mobilization constitutes a possible molecular pathway connecting calorie restriction to life extension.86

Adipocyte-specific NCoR knockout (AKO) mice exhibit an increase in the expression of PPARγ-responsive genes and a decrease in cyclin-dependent kinase (Cdks)-mediated PPARγ Ser273 phosphorylation, resulting in constitutive activation of these genes. Although AKO mice show an increase in adiposity, they also exhibit improved systemic in-
sulin sensitivity and glucose tolerance, and decreased adipose tissue inflammation. These studies suggest that the dominant function of adipocyte NCoR is to transrepress PPARγ and promote Cdk5-mediated PPARγ phosphorylation, similar to the effects of TZDs.  

Other interacting proteins

RIP140 is a liver protein that interacts with the AF-2 domain of PPARγ and also with PPARγ. BRL49653, a PPARγ ligand, strengthens the interaction between PPARγ and RIP140.  

Because RIP140 is generally known to inhibit nuclear receptor activity through competition with SRC-1, transrepression of PPARγ by RIP140 occurs indirectly.  

Although RIP140 inhibits the transcriptional activity of PPARγ, it does not affect adipogenesis. However, RIP140 KO mice showed increased UCP1 gene expression and resistance to high-fat diet-induced obesity and hepatic steatosis.

The forkhead transcription factor Foxo1 was identified as a PPARγ-interacting protein that disrupts the binding of PPARγ to the target gene. In addition, PPARγ plays a negative role in the transactivation of Foxo1, suggesting that there is a reciprocal interaction between these factors. Ectopic expression of the constitutively active form of Foxo1 in preadipocytes prevents adipogenesis and heterozygous Foxo1 KO mice are less susceptible to diet-induced insulin resistance.

The retinoblastoma protein (Rb) plays a negative role during mitotic clonal expansion in the cell cycle by increasing the transactivation of C/EBP. PPARγ has been shown to interact directly with Rb in 3T3L1 adipocytes, recruiting histone deacetylase HDAC3 which attenuates adipogenic gene expression. Dissociation of the PPARγ-Rb-HDAC3 complex by phosphorylation of Rb or inhibition of HDAC3 activity resulted in the activation of PPARγ.

Lipin1 is known to be expressed in adipose tissue. The null mice of lipin1 show lipodystrophy with severely reduced adipose tissue mass. Lipin1 is increased in the later stages of adipocyte differentiation and increases transcriptional activity of PPARγ2 through direct protein-protein interaction.

Small heterodimer partner (SHP) is an atypical orphan nuclear receptor that inhibits gluconeogenesis by interacting with Foxo1, hepatocyte nuclear factor 4, or C/EBPα. SHP is also known to increase PPARγ activity by interacting with PPARγ in a ligand-independent manner. SHP competes with NCoR for binding to the DBD/hinge region of PPARγ. It has been suggested that SHP may act as an endogenous activator of PPARγ. However, a contradictory report states that SHP represses the transcriptional activity of PPARγ and does not interact with PPARγ. SHP decreases LGK gene expression by inhibiting the transcriptional activity of LXRα and PPARγ via interaction with their common partner, RXRα. Thus, SHP may play a role in fine-tuning glucose homeostasis.

The diverse functions of PPARγ cofactors are summarized in Table 2.

### Phosphorylation

Phosphorylation of nuclear receptors is one of the principal modifications determining their transcriptional activities. Adipocyte differentiation is inhibited by growth factors and cytokines, which are known to phosphorylate PPARγ through their respective signaling pathway (Fig. 1). The site of phosphorylation is Ser12 in the N-terminal transactivation domain (AF-1), which is well conserved among species ranging from fish to man.  

Phosphorylation by mitogen-activated protein kinase (MAPK) results in a decrease in transcriptional activity and adipogenesis. MAPK is activated by extracellular signal-regulated kinase 1/2 (ERK1/2) that is stimulated by growth factors such as epidermal growth factor, platelet-derived growth factor, transforming growth factor-β, insulin, or the prostaglandin PGF2α.

Insulin plays a key role in adipogenesis. Although preadipocytes express a limited number of insulin receptors, the cells require insulin or insulin-like growth factor-1 for optimal differentiation. After maturation, large numbers of insulin receptors are expressed, transmitting insulin signals for the induction of lipogenic genes. Although insulin is a pivotal player in adipogenesis, Ras/MAPK activation by insulin represses PPARγ activity as shown in the growth factor-induced phosphorylation of PPARγ at Ser112.

Specifically, downstream tyrosine kinase-1 (Dok1), a multi-site adapter molecule in insulin receptor signaling, acts as a negative regulator of MAPK. In mice fed a high-fat diet, Dok1 expression is markedly increased in WAT. A lower mass of WAT is seen in Dok1-deficient mice than in wild-type mice, and the level of PPARγ phosphory-
Trichothiodystrophy (TTD) is a rare autosomal recessive disease caused by mutations in the xeroderma pigmentosum (XP) group-D (XPD) gene. The clinical manifestations include immature sexual development, mental retardation, skeletal abnormalities, and dwarfism. A number of patients with TTD exhibit a lack of subcutaneous fat tissue mass. XPD helicase is a subunit of the transcriptional复合物，包括TIF1γ,bestrophin,Brg1/Brm,SWI2/SNF2,SMC1,SMC3,SMC4,SMC5,SMC6,SMC8, and SMG1. These factors play a role in maintaining the number of mitochondria, respiratory capacity, and body temperature in BAT.

| Role | Coregulators | Metabolic effects | Reference |
|------|--------------|-------------------|-----------|
| SRC-1 | Essential for functional interaction between CBP/p300 and PPARγ | Increases the binding of SRC-1 and CBP/p300 to PPARγ | 43 |
| PGC-1α | Increases the transcriptional activity of PPARγ on the UCP-1 gene | Plays a role in maintaining the number of mitochondria, respiratory capacity, body temperature in BAT | 45, 75, 76 |
| CBP/p300 | Binds to the AF-2 domain of PPARγ (ligand-dependent) | Binds to the AF-1 domain to PPARγ (ligand-independent) | 46-48 |
| TRAP220 | Increases PPARγ transcriptional activity | Essential for PPARγ-mediated adipogenesis | 51, 52 |
| AFR6 | Regulates the expression of aP2 and PEPCK gene | Interacts with PPARγ/RXRα during adipogenesis | 25, 60, 61 |
| Menin | Increases histone H3K4 methylation at the PPARγ target gene, Fabp4 | Directly interacts with the PPARγ AF-2 domain | 62 |
| MBF-1 | Acts as a bridging protein between PPARγ and TFIID | | 64 |
| NRF2 | Decreases TXS gene expression by forming complex with PPARγ | | 65 |
| PRIP | Critical for embryonic development and survival | Represses the transcriptional activity of RXRα | 73 |
| PDIP | Increases the PPARγ-mediated transactivation | | 74 |
| SHP | Compete with NCoR in binding to the DBD/hinge region of PPARγ | Endogenous activator of PPARγ | 99 |
| Lipin1 | Increases the transcriptional activity of PPARγ | | 96 |
| NCoR | Decreases the transcriptional activity of PPARγ | | 83, 86 |
| SMRT | Decreases adipogenesis and lipid accumulation | Interacts with PPARγ and increases the ability of PPARγ to associate with Cdk5 | 83, 86 |
| Sirt1 | Decreases lipid accumulation in differentiated adipocytes | Represses transcriptional activity of PPARγ by recruiting NCoR and SMRT | 84 |
| RIP140 | Decreases the transcriptional activity of PPARγ by competing with SRC-1 | Does not affect adipocyte differentiation | 88, 89 |
| Foxo1 | Disrupts binding of PPARγ to the target genes | | 90 |
| Rb | Recruits histone deacetylase HDAC3 and decreases the expression of adipogenic genes | | 93 |
| SHP | Represses the PPARγ/RXRα transactivation by interacting with RXRα | | 100 |

PPARγ, peroxisome proliferator-activated receptor gamma; SRC-1, steroid receptor coactivator-1; PGC-1α, PPAR coactivator-1; CBP, CREB-binding protein; TRAP, thyroid hormone receptor-associated protein; BAF, Brg1/Brm-associated factor; MBF-1, multiprotein bridging factor-1; NRF2, nuclear factor E2-related factor 2; PRIP, PPAR-interacting protein; PDIP, PPARγDBD interacting protein; SHP, small heterodimer partner; NCoR, nuclear corepressor; SMRT, silencing mediator of retinoid and thyroid hormone receptor; Rb, retinoblastoma protein; SHP, small heterodimer partner; DBD, DNA-binding domain; UCP, uncoupling protein; BAT, brown adipose tissue; AF-1, agonist-independent activation domain; AF-2, agonist-dependent activation domain; LBD, ligand-binding domain; PEPCK, phosphoenol pyruvate carboxykinase; RXR, retinoid X receptor; TFIID, transcription factor IID; TXS, thromboxane synthase; Cdk5, cyclin-dependent kinase; ARF6, ADP-ribosylation factor; RIP140, receptor-interacting protein 140.

Modulation of PPARγ Activity

In contrast to the MAPK-mediated phosphorylation of Ser112, the cyclin-dependent kinases Cdk7 and Cdk9 phosphorylate the same Ser112 in PPARγ and increase PPARγ activity.128,129 Trichothiodystrophy (TTD) is a rare autosomal recessive disease caused by mutations in the xerodermia pigmentosum (XP) group-D (XPD) gene. The clinical manifestations include immature sexual development, mental retardation, skeletal abnormalities, and dwarfism. A number of patients with TTD exhibit a lack of subcutaneous fat tissue mass. XPD helicase is a subunit of the transcriptional complex, including TIF1γ, bestrophin, Brg1/Brm, SWI2/SNF2, SMC1, SMC3, SMC4, SMC5, SMC6, SMC8, and SMG1. These factors play a role in maintaining the number of mitochondria, respiratory capacity, and body temperature in BAT.
factor IIH (TFIIH) complex bridging the core-TFIIH [containing particular form of xeroderma pigmentosum B (XPB) helicase] subcomplex and the Cdk-activating kinase containing Cdk7. When the C-terminus of XPD is mutated, XPD helicase cannot perform nucleotide excision repair. In the process of transcription, Cdk7 in the TFIIH complex phosphorylates the C-terminal domain of the largest subunit of RNA polymerase II and nuclear receptors such as ER, VDR, and RARα. PP ARγ phosphorylation by Cdk7 is decreased in XPD patients. The activity of a PP ARγ promoter reporter was rescued by PPARγ-112, a constitutively active form of PPARγ, in fibroblasts isolated from patients with TTD.

In addition, Cdk9, a component of positive transcription elongation factor b, has been shown to participate in adipogenesis by directly interacting with PP ARγ and phosphorylating Ser112. Overexpression of Cdk9 in 3T3L1 cells increased adipogenesis, whereas inhibition of Cdk9 by specific Cdk inhibitors or a dominant-negative Cdk9 mutant inhibited adipogenesis. These data suggest that the transcriptional activity of PP ARγ is either activated or inhibited depending on the types of kinases involved.

In the adipose tissues of mice fed a high-fat diet, phosphorylation of Ser273 by Cdk5 results in a reduction of adiponectin gene expression, without affecting adipogenesis. Cdk5-mediated phosphorylation of PP ARγ is blocked by full agonists such as rosiglitazone or partial agonists such as MRL24 or SR1664.

Partial agonists, like MRL24 and SR1664, have been shown to have excellent anti-diabetic activity without increasing adipogenesis. These compounds are known to block the phosphorylation of Ser273 by Cdk5 and can therefore potentially be used as therapeutic drugs for T2DM without causing weight gain and fluid retention, which are major side effects of full agonist-antidiabetic drugs.

It is worth note that strong PP ARγ activators are not necessary to increase insulin sensitivity. Understanding the regulation of Ser273 phosphorylation in PP ARγ could provide a hint for the development of drugs to treat T2DM that have fewer side effects.

Sumoylation

SUMOylation is one of the post-translational modifications responsible for regulating the stability, nuclear-cytosolic distribution, and activity of transcription factors. Small ubiquitin-like modifier (SUMO) family proteins (SUMO-1, -2, and -3 in mammals) affect the interaction between target proteins and their substrates or the DNA that they bind. SUMO binds to proteins by forming isopeptide bonds between the C-terminal glycine residue of SUMO and the ε-amino group of a lysine in the target protein. Currently, a number of transcription factors including nuclear receptors, such as PPARs, LXR, glucocorticoid receptor, androgen receptor, and RXRα are known to be SUMOylated. Selective modulation of the transcriptional activity of PP ARγ by SUMOylation is now beginning to be understood. The transcriptional activities of PP ARγ isoforms in the presence or absence of ligands are regulated by SUMOylation. PP ARγ2 is SUMOylated by protein inhibitor of activated STAT 1 (PIAS1) or PIASx, belonging to the
PIAS family, regardless of its ligand. PPARγ2 is SUMOylated at Lys^{307} in the AF-1 domain, and at Lys^{305} in the AF-2 domain (equivalent to Lys^{27} and Lys^{365} of PPARγ1, respectively). SUMOylation of PPARγ2 at Lys^{307} negatively regulates the transcriptional activity of PPARγ2, because the 107K→R mutation showed increased transcriptional activity.^{142} This observation is further supported by a promoter reporter assay performed using the variant PPARγ2 107K→R in NIH3T3 fibroblasts.\(^{148,149}\) Furthermore, fibroblast growth factor21 (FGF21)-KO mice exhibit impaired insulin sensitivity in adipocytes and reduced fat mass and adipocyte size. This phenomenon occurs because PPARγ2-induced adipogenesis is inhibited by SUMOylation in WAT. These results indicate that FGF21 is a key regulator of PPARγ2 in the context of SUMOylation.\(^{150}\) In addition, the transcriptional activity of PPARγ2 is increased by overexpressing SUMO1/sentrin/SMT3-specific peptidase 2 (SEN2P), a SUMO-specific protease, in C2C12 myotubes.\(^{147}\) Interestingly, the inhibition of PPARγ2 transcriptional activity by SUMOylation is augmented when PPARγ2 is phosphorylated at Ser^{112},\(^{148,149}\) This indicates an interrelationship between the SUMOylation and phosphorylation of PPARγ2.

The SUMOylation of PPARγ1 at Lys^{365} (equivalent to Lys^{305} of PPARγ2) is important in the regulation of inflammatory gene expression. This SUMOylation mediates the transcriptional repression of inflammatory genes like inducible nitric oxide synthase (iNOS) and TNF-α, which are regulated by nuclear factor kappa B in macrophages.\(^{151,152}\) In the basal state, iNOS gene is repressed by TBL1/TBLR1/HDAC3/NCoR complex. Treatment of lipopolysaccharide (LPS) resulted in the removal of HDAC3/NCoR from the complex in a TBL1/TBLR1 and Ubc5-dependent fashion, allowing activation of iNOS gene.\(^{148}\) When RAW264.7 macrophages or primary cultured macrophages were treated with LPS and rosiglitazone, PPARγ1 was found to be SUMOylated on Lys^{365} by Ubc9, which forms a complex with NCoR/HDAC3 on the promoters of the iNOS gene. Thus, the formation of the NCoR/HDAC3/SUMOylated PPARγ1 complex inhibits the ubiquitination of NCoR/HDAC3, resulting in the repression of the iNOS and TNF-α genes.\(^{151,152}\)

Ligand-dependent SUMOylation of PPARγ1 therefore directly represses the promoters of inflammatory genes by stabilizing the NCoR and HDAC3 complexes. This mechanism demonstrates that the role of Lys^{365} SUMOylation of PPARγ1 is different from that of Lys^{307} SUMOylation of PPARγ2 in that Lys^{365} SUMOylation of PPARγ1 represses the expression of inflammatory genes in the presence of ligand.

**Ubiquitination**

The ubiquitin-proteasome system (UPS) is responsible for the degradation of a variety of intracellular proteins including transcription factors.\(^{153,154}\) Ubiquitin is well conserved between species, binding to target proteins in a sequential manner through the actions of three different cascading enzymes: an ubiquitin-activating enzyme (E1), an ubiquitin-conjugating enzyme (E2), and an ubiquitin protein ligase (E3).\(^{155}\) The polyubiquitinated proteins are recognized and degraded by the 26S proteasome.\(^{156}\) The role of the UPS with respect to transcriptional regulation is well documented.\(^{157}\) In the nucleus of adipocytes, the PPARγ2 protein level is decreased by the action of TZDs.\(^{158}\) Degradation occurs in a ubiquitin-dependent manner in the AF-2 domain of PPARγ.\(^{159}\) However, the AF-1 domains of PPARγ1 and PPARγ2 are degraded by the REGγ proteasome, a type of proteasome that degrades the target substrate in an ubiquitin and ATP-independent fashion.\(^{159,161}\)

Degradation of PPARγ is also regulated by interferon-γ (IFN-γ) in adipocytes. Transcription of PPARγ is decreased by IFN-γ-activated STAT signaling.\(^{162}\) When Ser^{112} of PPARγ, which is known to be phosphorylated by ERK1/2, was replaced with Ala, degradation of the protein was decreased. In addition, U1026, an inhibitor of ERK1/2, decreased IFN-γ-induced PPARγ degradation.\(^{163}\) However, ERK1/2 is not known to be activated by IFN-γ or TZDs; thus, it is assumed that there might be an indirect relationship between the phosphorylation and ubiquitination of PPARγ.\(^{163}\)

TNF-α is well known for its role in insulin resistance.\(^{164}\) Degradation of PPARγ is promoted by TNF-α in adipocytes. Treatment of adipocytes with TNF-α and cycloheximide yielded a 44-kDa sized fragment of PPARγ, which is also seen in the WAT or BAT of diabetic rats. However, the molecular link between this fragment and PPARγ degradation is not known.\(^{165}\) Proteasome-dependent PPARγ degradation is increased by resveratrol, a potent activator of SIRT1; however, the mechanism of SIRT1 requires further investigation.\(^{84,166}\)

### PERSPECTIVE

Regulation of PPARγ activity may be achieved through the interrelationship between agonists, PTM, and coregulators, rather than by the simple action of individual activators or inhibitors. Agonists can induce either coregulator exchange or PTM; the mechanisms of which require further study.
Understanding the mechanistic complexity underlying the interactions of these regulators may help accelerate the development of therapeutic drugs against obesity, T2DM, and metabolic syndromes.

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