# Peroxisome proliferator-activated receptor γ, the ultimate liaison between fat and transcription

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The peroxisome proliferator-activated receptor gamma (PPARγ) is nuclear receptor that controls the expression of a large number of genes involved in adipocyte differentiation, lipid storage and insulin sensitization. PPARγ is bound and activated by fatty acid derivatives and prostaglandin J2. In addition, thiazolidinediones, non-steroidal anti-inflammatory drugs are synthetic ligands and agonists of this receptor. This review addresses the role of PPARγ in obesity and diabetes.

**Adipogenesis: Adipose tissue: Gene expression: Fatty acids: Insulin resistance: Nuclear receptors: Thiazolidinediones: Type 2 diabetes: Transcription**

Peroxisome proliferator-activated receptors (PPARs) compose a subfamily of the nuclear hormone receptor. Three distinct PPARs, termed α, δ (also called β, NUC-1 or FAAR) and γ, each encoded by a separate gene and showing a distinct tissue distribution pattern, have been described. Activated PPARs heterodimerize with another nuclear receptor, retinoid X receptor (RXR), and alter the transcription of numerous target genes after binding to specific response elements or PPREs. Since they are activated by various fatty acid metabolites as well as several drugs used in the treatment of metabolic disorders, PPARs translate nutritional, pharmacological and metabolic stimuli into changes in the expression of genes. In this review, we will focus our discussion on PPARγ, the most important PPAR species in adipose tissue. PPARγ plays crucial roles in adipogenesis and insulin sensitization and is activated by prostaglandin J2, certain fatty acid derivatives, thiazolidinedione anti-diabetic compounds, and a number of non-steroidal anti-inflammatory drugs. Recently, a number of additional functions were attributed to PPARγ, which suggested a more pleiotropic role affecting multiple fundamental pathways in the cell with wide ranging biomedical implications. In this review, we will focus on the metabolic functions of PPARγ. For more general information relating to the other PPARs and other aspects of PPARγ function, we refer to one of the several reviews on this topic for more exhaustive coverage (Desvergne & Wahli, 1994; Schoonjans *et al.* 1997).

## PPARγ, a pivotal role in adipocyte differentiation and fatty acid metabolism

The molecular mechanisms that control adipocyte differentiation from adipose precursor cells (adipoblasts) are complex and are affected by numerous signaling pathways (for review see Fajas *et al.* 1998). It is currently thought that adipogenesis as well as the maintenance of the fully differentiated adipocyte phenotype requires an interplay between the PPARγ/RXR heterodimer and two other groups of transcription factors: the CCAATT enhancer binding proteins (C/EBP) and ADD-1/SREBP-1 (reviewed by Fajas *et al.* 1998). These transcription factors could also play a role in the pathology of adipose tissue such as seen in obesity or lipodystrophy.

Although all of these transcription factors can independently induce adipocyte differentiation *in vitro*, they act synergistically *in vivo*. During the initial phases of adipogenesis C/EBPβ and δ are induced in response to adipogenic hormones such as insulin or glucocorticoids (Wu *et al.* 1996). Both C/EBPs then induce the transcription of PPARγ2, via interaction with a C/EBP site in the PPARγ2 promoter (Fajas *et al.* 1997). PPARγ2 in its turn then induces the expression of PPARγ1 (Saladin *et al.* 1999). Another protein which is also induced during early adipocyte differentiation is the basic helix-loop-helix protein ADD-1/SREBP-1 (Kim & Spiegelman, 1996). This transcription factor, which plays a pivotal role in

**Abbreviations:** BMI, body mass index; C/EBP, CCAATT enhancer binding proteins; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; TNFα, tumor necrosis factor α; TZD, thiazolidinedione.

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cholesterol homeostasis, also regulates the expression of several genes in fatty acid metabolism, and hence it is suggested that ADD-1/SREBP-1 might control the generation of PPARγ ligands which in their turn enhance the transcriptional activity of PPARγ (Lopez *et al.* 1996; Shimano *et al.* 1996). Furthermore, our recent work showed that ADD-1/SREBP-1, as well as the related basic helix-loop-helix factor, SREBP-2, can induce PPARγ transcription through response elements in the PPARγ1 and γ3 promoters (Fajas *et al.* 1999). These interactions between cholesterol (ADD-1/SREBP) and fatty acid signaling (PPARγ) point to an interplay of these two lipids in adipocyte biology. Terminal adipocyte differentiation requires furthermore the concerted action of PPARγ and C/EBPα (Tontonoz *et al.* 1994*b*) which appears only relatively late in the differentiation process. PPARγ controls not only the expression of C/EBPα, but this last factor on its turn also induces PPARγ gene expression, via interaction with C/EBP response elements present in the human PPARγ promoter (Saladin *et al.* 1999).

The enhanced adipocyte differentiation, which ensues from PPARγ activation, translates in to the induction of the expression of adipocyte-specific genes, most of them involved in lipid storage and control of metabolism. Good examples are aP2 (adipocyte protein binding 2) (Tontonoz *et al.* 1994*a*), phosphoenol pyruvate carboxykinase (Tontonoz *et al.* 1995), acyl CoA synthase (Schoonjans *et al.* 1993; Schoonjans *et al.* 1995), fatty acid translocase/CD36 (Tontonoz *et al.* 1998), fatty acid transport protein-1 (Martin *et al.* 1997), and lipoprotein lipase (Schoonjans *et al.* 1996), which are all regulated by PPARγ. The identification of PPREs in the lipoprotein lipase, acyl CoA synthase, fatty acid translocase/CD36 (Tontonoz *et al.* 1998) and fatty acid transport protein-1 (Hui *et al.* 1998), are interesting in this context, since it suggests that PPARγ can influence the generation and/or cellular uptake of its own ligands or activators. We suggest therefore that PPARγ and its target genes play an interdependent role in adipocyte differentiation. This hypothesis is supported by the observation that fatty acids and fatty acid analogues induce the expression of adipocyte-specific genes, enhance adipocyte conversion, and maintain the mature adipocyte phenotype by creating a positive feedforward loop, which involves PPARγ and several of its target genes (such as LPL, ACS, leptin, FAT/CD36 and FATP).

In addition to the above mentioned genes, which are mainly involved in adipocyte metabolism, two cytokines produced by the adipocytes, i.e. leptin and tumor necrosis factor α (TNFα), also appear to be functioning in this adipocyte sustaining positive regulatory loop. Leptin induces a pleiotropic response including control of body weight and energy expenditure (reviewed in Auwerx & Staels, 1998). Leptin gene expression is regulated in an opposite fashion by PPARγ and C/EBPα, the first one reducing its expression (De Vos *et al.* 1996), whereas the second induces its expression (Miller *et al.* 1996). TNFα, is a potent inhibitor of adipocyte differentiation (Torti *et al.* 1985), an effect based in part on the down-regulation of the expression of adipogenic factors such as C/EBPα (Williams *et al.* 1992) and PPARγ (Peraldi *et al.* 1997). Interestingly, obesity characterized by increased adipose tissue mass is associated with increased TNFα expression in adipose tissue. Although the exact role of high TNFα levels in obesity is unclear, it might constitute a regulatory mechanism to limit further increase in adipose tissue mass. This increase in TNFα levels in obesity also interferes with the insulin signaling pathways (Hotamisligil *et al.* 1995) contributing to the insulin resistance characteristic of the obese state (Hotamisligil *et al.* 1996).

## PPARγ, a role in insulin sensitivity and the determination of body mass

Antidiabetic PPARγ agonists, such as thiazolidinediones (TZDs), improve insulin sensitivity in the muscle, an organ where PPARγ is hardly expressed (Fajas *et al.* 1997). Several hypotheses could explain this rather puzzling issue. One hypothesis is that the effects of thiazolidinediones are indirect (Shao & Lazar, 1997), and mediated by adipose tissue where PPARγ is mainly expressed. This effect could be exerted through two different processes. First, PPARγ activators may modulate the expression of adipocyte-derived signals affecting insulin sensitivity in muscle, such as TNFα (Hofmann *et al.* 1994) and leptin (Cohen *et al.* 1996; Liu *et al.* 1997). Second, PPARγ activation could induce a 'fatty acid steal' due to a specific TZD/PPARγ-mediated increase in lipid and fatty acid clearance by adipose tissue, without a concomitant increase in fatty acid delivery to the muscle (Martin *et al.* 1998). The 'trapping' of fatty acids in fat tissue would result in a decreased systemic availability and a diminished fatty acid uptake by the muscle, improving insulin sensitivity according to Randle (Randle *et al.* 1961). The antidiabetic effect of PPARγ agonists, agents that induce adipocyte differentiation, might seem illogical since obesity, the end-result of increased adipogenesis, is associated with insulin resistance. This discrepancy becomes apparent when one takes into account that on a whole body level, adipose tissue is absolutely required for glucose homeostasis in response to insulin. Indeed, human subjects (Moller & Flier, 1991) and transgenic animals with lipoatrophy (Moitra *et al.* 1998; Shimomura *et al.* 1998) are very insulin resistant. This indicates that storage of energy reserves in the adipocytes favors insulin sensitivity, and that the important adipogenic activity of PPARγ contributes to the insulin sensitization of TZDs. Other adipose-independent mechanisms however also contribute to the insulin-sensitizing effects of TZDs since these compounds retain this activity in transgenic mice that lack adipose tissue (Burant *et al.* 1997).

Another hypothesis to explain the action of TZDs is that it requires a direct effect on insulin sensitive tissues and that the minute quantities of PPARγ in muscle might be sufficient, or alternatively might be induced during TZD treatment, to lead to an eventual direct PPARγ-mediated response of the muscle. Potentially an enrichment of particular cofactors in muscle relative to other tissues could also contribute to a mechanism as such (reviewed in Gelman *et al.* 1999). Furthermore, in parallel to its action on adipose tissue, PPARγ activation might also affect insulin signaling more directly through the regulation of

genes involved in glucose homeostasis. The mRNA encoding for the glucose transporter GLUT-4 (Wu *et al.* 1998) as well as the c-Cbl associated protein (Ribon *et al.* 1998) were recently reported to be induced by PPARγ. c-Cbl associated protein, which is only expressed in cells that are metabolically sensitive to insulin, is involved in insulin-stimulated tyrosine phosphorylation of c-Cbl (Ribon *et al.* 1998). It will await future studies to demonstrate whether the regulation of these genes, which are directly involved in insulin-mediated glucose homeostasis, is mediated via PPAR responsive elements in their promoters.

Twin and family studies suggest that close to 80 % of the variance in body mass index (BMI) is genetically determined (Bouchard & Perusse, 1993; Whitaker *et al.* 1997). Recently, mutations in PPARγ have been described (Beamer *et al.* 1998; Deeb *et al.* 1998; Ristow *et al.* 1998; Vigouroux *et al.* 1998; Yen *et al.* 1997). A rare Pro115Gln mutation in the $NH_2$-terminal ligand-independent activation domain of PPARγ was found in four very obese subjects (Ristow *et al.* 1998). This mutation which results in a more active PPARγ led to increased adipocyte differentiation capacity *in vitro* (Ristow *et al.* 1998). We and others have recently described a much more common Pro12Ala substitution in the PPARγ2-specific exon B (Beamer *et al.* 1998; Deeb *et al.* 1998; Vigouroux *et al.* 1998; Yen *et al.* 1997). The PPARγ2 Ala allele, whose frequency ranges from approximately 0·12 among Caucasians to 0·02 in Japanese Americans (Deeb *et al.* 1998; Yen *et al.* 1997), was associated with a lower BMI, improved insulin sensitivity, and higher plasma HDL cholesterol levels (Deeb *et al.* 1998). The association with insulin sensitivity disappeared when corrected for BMI, indicating that the primary effect of this mutation was on body weight. The PPARγ Ala allele exhibited a reduced ability to transactivate responsive promoters. These results provide together with the observations made on the Pro115Gln substitution strong evidence of a role of PPARγ in the control of adipogenesis *in vivo*, such that a more active PPARγ (Pro115Gln) results in an increased BMI (Ristow *et al.* 1998), whereas the opposite is seen with a less active PPARγ (Pro12Ala) (Deeb *et al.* 1998). These observations appear at odds with two reports which found no association of the Pro12Ala substitution with insulin sensitivity (Beamer *et al.* 1998; Mori *et al.* 1998), and reported an association of the Ala allele with morbid obesity in Caucasians (Beamer *et al.* 1998), suggesting that the physiological consequences of the Pro12Ala polymorphism may be different in the lean and obese states. The recent observation that in Danish males, the Ala allele is associated with lower BMI among lean subjects and with higher BMI among obese subjects is consistent with this hypothesis (Ek *et al.* 1999), and indicate the importance of gene environment interactions in the determination of the phenotype.

The genetic and functional data on the Pro12Ala substitution point to the importance of the PPARγ2 specific B exon in determining the activity of PPARγ more particularly in adipocytes, the only tissue known to express significant amounts of PPARγ2. The function of the $NH_2$-terminal residues of PPARγ2 is unknown. This domain may modulate nuclear import, ligand binding, DNA binding, or transcriptional activation by inducing a conformational change, or it may endow PPARγ2 with unique capacities to interact with co-activators or co-repressors that have been shown to interact with nuclear receptors. Support of the role of the $NH_2$-terminus of PPARγ in transcriptional activity not only comes from the presence of a ligand-independent AF-1 domain in this part of the molecule (Werman *et al.* 1997) but also from its allosteric effects on ligand-dependent transcriptional activity through interdomain communication (Shao *et al.* 1998). The identification and characterization of proteins interacting with the $NH_2$-terminus of PPARγ in the future will point to mechanisms by which this domain affects adipose tissue accumulation and metabolism.

## Conclusion

Despite the fact that PPARγ is today a well characterized nuclear receptor, more detailed knowledge of its function in different specific tissues is indispensable to warrant chronic therapeutic use in metabolic disorders, such as insulin resistance and type 2 diabetes. Better understanding of PPARγ function will involve a thorough knowledge of its role in inflammation, cell cycle and cancer (reviewed in Gelman *et al.* 1999). This enhanced understanding of PPARγ will undoubtedly in the near future lead to an expansion of the therapeutic indication of PPARγ modulators, which will be based upon detailed characterization of the pleiotropic role of this receptor in different systems.

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