

# Current concepts of PPAR- $\gamma$ signaling in diabetes mellitus

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**Peroxisome proliferator-activated receptors (PPARs,  $\alpha$ ,  $\delta$  and  $\gamma$ ) constitute a distinct subfamily of the superfamily of nuclear receptors that are activated by naturally occurring fatty acids or fatty acid derivatives. Recently, there is an increased interest in PPAR $\gamma$  research because they (a) are key regulators of adipocyte differentiation and energy source and (b) are cellular targets of thiazolidinedione drugs, which are used to treat Type 2 diabetes by decreasing insulin resistance. Additionally, PPAR $\gamma$  has emerged to be a powerful player in general transcriptional control of numerous cellular processes, with implications in diabetes and obesity, cell cycle control, carcinogenesis, inflammation, atherosclerosis and immunomodulation. This review focuses on some of the recent research on the pivotal role of PPAR $\gamma$  in insulin resistance and Type 2 diabetes.**

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## Peroxisome proliferator-activated receptor

The peroxisome is a subcellular organelle whose functions extend well beyond the removal of molecular oxygen and later breakdown of hydrogen peroxide, to include glycerolipid synthesis, cholesterol biosynthesis and breakdown, and fatty-acid oxidation. The fact that proliferation of peroxisomes induced in rodents is associated with a multitude of biochemical changes has been for a long time contrasted with the uncertainty about the underlying mechanisms of peroxisome proliferation. Essentially, the discovery of the first peroxisome proliferator-activated receptor (PPAR) by Issemann and Green<sup>1</sup> was the key to the present understanding of peroxisome proliferation and its growing medical significance. Subsequently, several PPAR isotypes ( $\alpha$ ,  $\beta$  or  $\delta$  and  $\gamma$ ) have been found in vertebrate species<sup>2</sup>, e.g. *Xenopus*, mouse, hamster and human. Based on DNA and protein sequence analyses, PPARs have been assigned to the subfamily of nuclear receptors that include the thyroid hormone receptors and the retinoic acid receptors.

## PPAR $\gamma$ and insulin resistance/Type 2 diabetes

A more pleiotropic role has been recently assigned to PPAR $\gamma$  as it influences multiple fundamental pathways in the cell with wide-ranging biomedical implications<sup>3,4</sup>. In particular, studies looking into the molecular basis of insulin resistance have focused on the PPAR $\gamma$ , as they increase our understanding of the pathophysiology of Type 2 diabetes and also lead to the development of newer anti-diabetic agents. Type 2 diabetes is a major medical problem, the incidence of which is escalating rapidly in developing countries, with India harbouring the largest ever number of diabetics in the world<sup>5</sup>. Insulin resistance is one of the principal defects underlying the development of Type 2 diabetes and Asian Indians are considered to be more insulin-resistant<sup>6-9</sup>. Additionally, the prevalence of micro and macrovascular complications associated with diabetes is also increasing in epidemic proportions<sup>10-14</sup>. There is a general consensus that targetting insulin resistance early in the course of the disease may help achieve optimal glycemic control, halt disease progression, and probably even prevent the diabetic complications. This view has been strengthened by the recent trials of thiazolidinedione group of drugs that treat diabetes by increasing the sensitivity of insulin's action, primarily acting through PPAR $\gamma$  signaling.

## Cellular abundance of PPAR $\gamma$

Although PPAR $\gamma$  expression is detected in the nucleus of many cells, only adipose tissue, large intestine and haematopoietic cells express the highest levels of PPAR $\gamma$  mRNA and protein<sup>15</sup>. Human muscle tissue expresses only trace amounts of PPAR $\gamma$  under basal conditions. However, PPAR $\gamma$  mRNA has been identified in skeletal muscle and is found to be increased in obese subjects with insulin resistance<sup>16,17</sup>. The expression of PPAR $\gamma$  mRNA or protein or both in adipose tissue changes under the influence of a number of metabolic and hormonal variables. While short-term changes in food intake do not affect the expression of human PPAR $\gamma$ , hypocaloric diets for a longer period result in its down regulation<sup>18</sup>. In rodents, PPAR $\gamma$  is down regulated by fasting and insulin-dependent diabetes melli-

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tus<sup>19</sup> whereas its expression is induced by a high-fat diet. Interestingly, PPAR $\gamma$  expression is highly enriched in subcutaneous fat in normal weight subjects and its higher expression culminates in visceral adipose tissue in obese subjects<sup>20</sup>. Additional experiments also point out its regulation by insulin, tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) and glucocorticoids<sup>21-23</sup>. Moreover, the tissue specific expression of PPAR $\gamma$  in endothelial<sup>24</sup> and vascular smooth muscle cells<sup>25</sup> suggest their causal and additional influence on vascular tone and elevated blood pressure.

While PPAR $\gamma$  seems to have its primary effects on adipose tissue, it is a paradox how PPAR $\gamma$  agonists improve insulin sensitivity in muscle, where glucose uptake maximally occurs. It is important to note that on a whole-body level, adipose tissue is indispensable for glucose homeostasis, as demonstrated by the link between lipotrophy and insulin resistance<sup>26,27</sup>, suggesting that the adipogenic activity of PPAR $\gamma$  contributes to insulin sensitization. As suggested by Martin *et al.*<sup>28</sup>, the PPAR $\gamma$  agonists induce a 'fatty acid steal' by the adipose tissue. The resulting decreased systemic availability of fatty acids and diminished fatty acid uptake by muscle will improve insulin resistance. In a nutshell, short-term storage of excess energy, secondary to PPAR $\gamma$  activity, ameliorates insulin sensitivity. Nevertheless, the low abundance of PPAR $\gamma$  mRNA and protein in muscle tissue poses a question. Is PPAR $\gamma$  essential for the normal action of insulin and uptake of glucose? According to Auwerx<sup>29</sup>, minute quantities of PPAR $\gamma$  in muscle might, however, be sufficient or alternatively might be induced during treatment with thiazolidinedione, leading to an eventual direct PPAR $\gamma$ -mediated response of the muscle to these insulin sensitizers. Conversely, PPAR $\gamma$  activators may generate an adipocyte-derived signal affecting insulin sensitivity in muscle.

### Mechanisms of PPAR activation and regulation of target gene expression

The mechanisms by which PPAR are activated and thus regulate transcriptional expression of target genes are summarized in Figure 1. When PPAR $\gamma$  is bound by natural ligand or synthetic molecules such as a thiazolidinedione, it becomes activated and complexed with another transcription factor known as the retinoid X receptor (RXR). Transcriptional regulation by PPARs is achieved through PPAR-RXR heterodimers which bind to DNA motifs termed peroxisome proliferative response elements (PPREs) in the promoters of target genes. The whole PPRE consensus sequence exhibits a pattern specific for PPAR-RXR heterodimer<sup>30</sup> and is distinguishable from the responsive elements of other nuclear receptors belonging to oestrogen, vitamin D or

thyroid hormone. PPAR-mediated transcriptional control of genes is regulated by a new functional class of proteins called cofactors (corepressors and coactivators). SMRT (silencing mediator for retinoid and thyroid hormone receptor) is one such corepressor reported to be involved in down-modulating PPAR $\gamma$ -mediated gene transcription<sup>31</sup>. Interestingly, a number of proteins<sup>29,32,33</sup> have been identified and characterized as coactivators of PPAR $\gamma$  such as CREB binding protein (CBP), P300, steroid receptor coactivator (SRC-1), PPAR binding protein (PBP) and PPAR $\gamma$  coactivator-1 (PGC-1). Zhu *et al.*<sup>34</sup> have recently reported a novel coactivator of PPAR $\gamma$ , designated as PPAR interacting protein (PRIP). It has been postulated that these coactivators act as bridges to transmit the nuclear receptor regulatory signals to the cellular transcriptional machinery. In general, unactivated nuclear receptors are complexed with corepressors, which extinguish their transcriptional activity by the recruitment of histone deacetylases. Activation of the receptor then induces a conformational change which results in the dissociation of corepressors and the recruitment of coactivator complexes that contain proteins with histone acetyl transferase activity, which facilitates target gene transcription<sup>35</sup>. Apart from these cofactors, activation of PPAR $\gamma$  can also be depressed by phosphorylation of a seryl residue in its structural region, mediated by mitogen-activated protein (MAP) kinase<sup>36</sup>. In fact, phosphorylation at Ser114 was proposed as a mechanism by which growth factors and insulin, through MAP kinase, decrease PPAR $\gamma$  activity and adipocyte differentiation<sup>37-40</sup>. The final action of PPAR $\gamma$  depends on a variety of factors such as the abundance of the relevant endogenous ligands/activators, numerous co-activators or co-repressors and the expression and function of RXRs, the companion nuclear receptors essential for formation of the active heterodimeric complex (PPAR $\gamma$  + RXR).

### 'Glitazones' as pharmacological insulin sensitizers

The thiazolidinedione class of drugs or glitazones as they are called (troglitazone, pioglitazone, ciglitazone, englitazone and rosiglitazone) are specific high-affinity ligands for PPAR $\gamma$ <sup>41</sup>, and the order of their receptor-binding affinities *in vitro* mirrors their antihyperglycemic activity *in vivo*<sup>42</sup>. PPAR $\gamma$  enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism<sup>43,44</sup>. Particularly, adipocyte differentiation responds well to pharmacological PPAR $\gamma$  ligands. Functional PPREs have been identified in several adipocyte-specific genes (*viz.* phosphoenol pyruvate carboxykinase, aP2, acyl CoA synthase, fatty acid

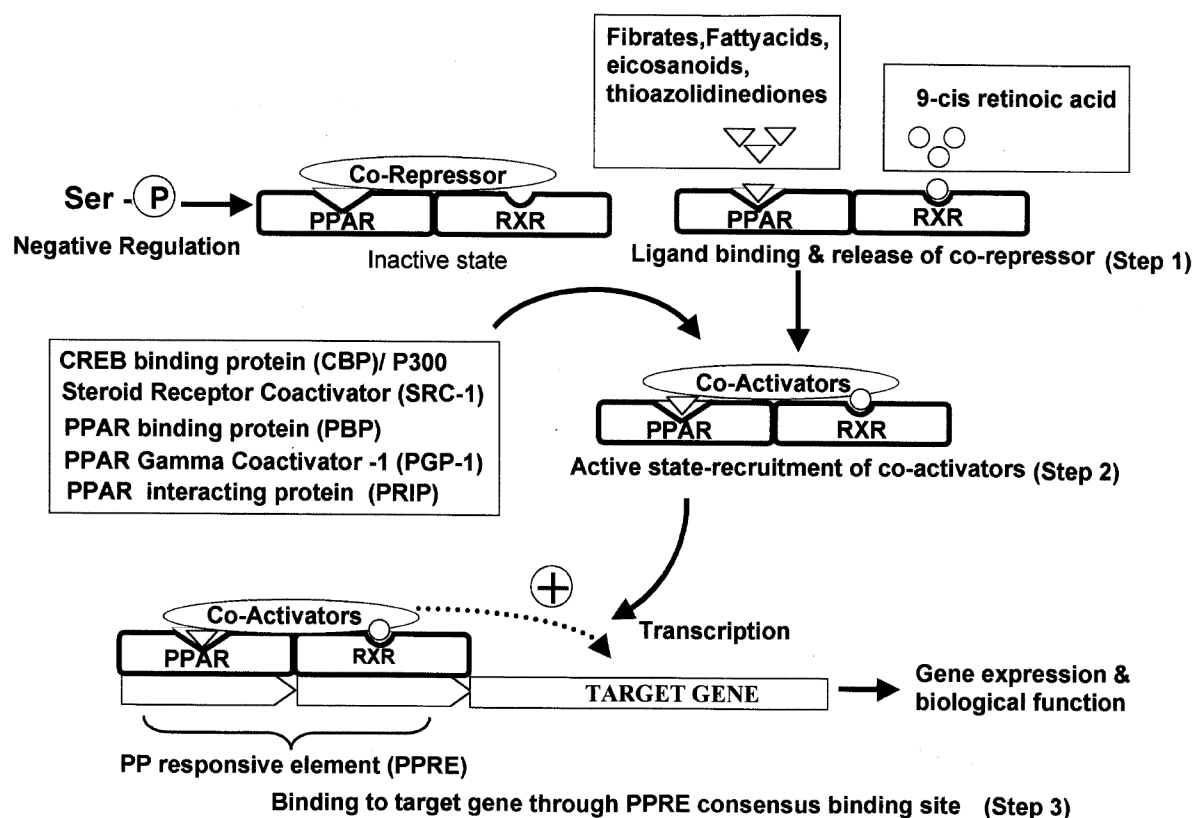


Figure 1. Mechanism of PPAR activation and transcriptional regulation of target genes.

transport protein-1, and lipoprotein lipase) and the fact that all of them regulated by PPAR $\gamma$  provide evidence that PPAR $\gamma$  and its target genes have an interdependent role in adipocyte differentiation<sup>45</sup>. Leptin gene expression is shown regulated by PPAR $\gamma$ <sup>46-48</sup> and the decrease in circulating leptin concentrations after PPAR $\gamma$  activation seem to be associated with an increase in food intake, which provides substrates, subsequently to be stored in the adipocytes. Whereas, TNF $\alpha$  exerts an anti-adipogenic action in part by the down-regulation of the expression of adipogenic factors including PPAR $\gamma$ <sup>22,23,49</sup>, activation of PPAR $\gamma$  stimulates adipogenesis and blocks the inhibitory effects of TNF $\alpha$  on insulin signaling<sup>49</sup> as well as the TNF $\alpha$ -induced glycerol and non-esterified fatty acid release<sup>50</sup>. Thus, stimulation of PPAR $\gamma$  may decrease the release by the adipocytes of various signaling molecules, such as free fatty acids, leptin, and TNF $\alpha$ , all of which are able to counteract the hypoglycemic action of insulin<sup>44</sup>. In addition to their role in adipocyte differentiation, glitazones also profoundly affect lipid metabolism. They increase the lipolysis of triglycerides in very-low-density lipoproteins (VLDL) and thereby reduce triglyceride and increase HDL-cholesterol levels<sup>51,52</sup>. Moreover, increased glucose uptake and mRNA expressions of the glucose transporter

isoforms (GLUT1 and GLUT4) were induced by glitazones through PPAR $\gamma$  activation<sup>53</sup>.

Stimulation of PPAR $\gamma$  with thiazolidinediones in 3T3-L1 adipocytes or in diabetic rodents lead to increased c-Cbl-associating protein (CAP) expression and increased insulin-stimulated c-Cbl phosphorylation that correlates well with increased insulin sensitivity both *in vitro* and *in vivo*<sup>54</sup>. The restricted expression of CAP in cells metabolically sensitive to insulin suggests an important potential role in insulin action. Administration of troglitazone to Zucker (fa/fa) rats markedly increased the expression of the major CAP isoform in adipose tissue. This effect was sustained for up to 12 weeks of treatment and accompanied the ability of troglitazone to prevent the onset of diabetes and its complications. Thus, CAP is the first PPAR $\gamma$ -sensitive gene identified that participates in insulin signaling and may play a role in glitazone-induced insulin sensitization. In support of this, Baumann *et al.*<sup>55</sup> have recently cloned and characterized a functional PPRE in the promoter of the CAP gene. Interestingly, the antidiabetic drug troglitazone has been demonstrated to differentially activate PPAR- $\gamma$  (either full or as a partial agonist) in a manner dependent on the cellular environment<sup>56</sup>. The observation that ligands can have distinct effects on the receptor raises

the possibility that different PPAR $\gamma$  ligands induce different sets of genes in a tissue specific way to translate distinct downstream biological effects. This explains why thiazolidinediones, besides their metabolic activities, have effects as diverse as the control of host defence, cell proliferation and tumorigenesis<sup>57</sup>.

One attractive feature of the thiazolidinedione insulin sensitizers is their synergism with glucose-lowering drugs (metformin, sulphonylurea or insulin) that have a different mechanism of action<sup>51,58</sup>. When added to current treatment in patients whose glycemic control remained unsatisfactory despite sulphonylureas, metformin, insulin, or a combination of these agents, glitazones seem to be very effective, as judged by decreases in serum levels of glucose, insulin and HbA1c<sup>59,60</sup>.

While thiazolidinediones more specifically enhance insulin sensitivity, they also potently promote adipocyte differentiation and often increase total fat mass<sup>61</sup>. Because obesity is a major cause of insulin resistance, this presents an apparent paradox. In the absence of controlled long-term studies, it is not clear whether glitazones induce progressive weight increase in patients. However, one should consider the reported observations in humans that treatment with thiazolidinediones results in a redistribution of body fat from visceral to subcutaneous depots<sup>61-63</sup>. Thus, as suggested by Montague and O'Rahilly<sup>64</sup> treatment with thiazolidinediones may induce anatomical distribution of adipose tissue with the redistribution of body fat away from 'dangerous' intra-abdominal sites and toward 'safer' subcutaneous ones.

The arrival of novel thiazolidinediones (KRP-297, JTT-501, NC-2100, NIP-223, MCC-555, L-764486, CS-011) is also promising in that they encounter some of the unfavourable effects of simple agonists like troglitazone<sup>65-67</sup>. Additionally, there is progress in the discovery and development of structurally novel class of tyrosine-based PPAR- $\gamma$  modulators with antidiabetic activity. The compound GI262570 is, in particular, claimed to be the most potent PPAR- $\gamma$  agonist reported to date<sup>68,69</sup>. GI262570 is prepared from naturally occurring (L)-tyrosine and does not contain the 2,4-thiazolidinedione structure common to the glitazone class of insulin-sensitizing agents. In addition, unlike the glitazones, GI262570 is a single enantiomer and is not prone to racemization at physiological pH.

### Sequence variants of PPAR $\gamma$ and the ultimate phenotypes

Requirement of proper PPAR $\gamma$  signaling for ensuing normal insulin sensitivity is highlighted by recent genetic studies. Barroso *et al.*<sup>70</sup> have reported the identification of two loss-of-function mutations of PPAR $\gamma$  that

are associated with severe insulin resistance and Type 2 diabetes in humans. Although such mutations are rare, they have shown that the people affected by loss-of-function PPAR $\gamma$  mutations share common characteristics of the 'insulin resistance syndrome' minus obesity. Typically insulin resistance syndrome is characterized by obesity along with insulin resistance, diabetes, high blood pressure, dyslipidemia and acanthosis nigricans. Interestingly, reduced PPAR $\gamma$  signaling seems to cause insulin resistance in the absence of obesity. This study contrasts sharply with the symptoms of gain-of-function mutation of PPAR $\gamma$ , reported by Ristow *et al.*<sup>71</sup>, wherein increased PPAR $\gamma$  signaling was found associated with human obesity. Unexpectedly, the degree of obesity in the study of Ristow *et al.*<sup>71</sup> has no association with Type 2 diabetes or hyperinsulinemia, and possibly defines a specific subclass of obesity.

Insulin resistance is especially likely to occur when excess fat is deposited within the abdominal cavity. This reduces the insulin sensitivity of fat cells and also of other tissues including skeletal muscle and liver. But how might expanding adipose stores impair PPAR $\gamma$  function? Expanding adipose stores may alter the availability of free fatty acids and modify the PPAR ligand binding interactions. The two PPAR $\gamma$  mutations reported by Barroso *et al.*<sup>70</sup> lead to amino-acid substitution in regions of the molecule involved in ligand binding. These changes disrupt the ligand binding process and are associated with insulin resistance and normal body weight in humans. By contrast, the obesity-inducing PPAR $\gamma$  mutation reported by Ristow *et al.*<sup>71</sup> results in an amino-acid substitution adjacent to the serine phosphorylation site. Serine phosphorylation at the site of 114 in the human PPAR $\gamma$  gene suggests a mechanism of negative regulation to limit adipocyte differentiation and lipid accumulation<sup>37,39</sup>. The mutations described by Ristow *et al.*<sup>71</sup> impair this phosphorylation site, increase PPAR $\gamma$  signaling and establish a causal association with obesity.

Though the above studies indicate that 'too much or too little PPAR $\gamma$  signaling is not good', the relation of PPAR $\gamma$  variation to obesity and insulin resistance is not so simple. Recent studies also demonstrate that a much more common Pro12Ala PPAR $\gamma$ 2 sequence variant has been variably associated with either increased<sup>72</sup> or decreased<sup>73,74</sup> body mass index (BMI) and improved insulin sensitivity. Additional complexity arose from studies that reveal no association of Pro12Ala substitution with BMI and insulin sensitivity<sup>75</sup>. These results suggest that the physiological consequences of the Pro12Ala polymorphism could be different in the lean and obese states. This has been shown in a Danish study where Pro12Ala sequence variation was associated with lower BMI among lean subjects and higher BMI among obese subjects<sup>76</sup>. Interestingly, the Pro12Ala polymorphism in PPAR $\gamma$ 2 was shown to protect against Type 2 diabetes

in the Japanese<sup>77</sup>. These apparently conflicting results highlight the gene–environment interactions in the determination of the phenotype.

### Significance of PPAR $\gamma$ in Indians

Several studies on Asian Indians have shown that they are characterized by higher insulin resistance, early onset Type 2 diabetes and hypertension without having a strong association of obesity<sup>11,78–82</sup>. Will it mean that we could expect more loss-of-function mutations of PPAR $\gamma$  in Indians? Although disease-causing mutations of PPAR $\gamma$  are rare, insulin resistance syndrome may also result from impaired PPAR $\gamma$  signaling in the absence of a mutation. Since a number of free fatty acids are PPAR $\gamma$  ligands<sup>25,83</sup>, their alterations in the presence or absence of obesity could reduce PPAR $\gamma$  signaling and lead to insulin resistance. Additionally, the notion that PPAR $\gamma$  is referred to as a ‘thrifty genotype’<sup>29</sup> may be very well tested in Indians. The ‘thrifty genotype’ hypothesis put forward by Neel<sup>84</sup> is stated as follows: ‘Among populations exposed to a varying supply of food, it is advantageous to be metabolically thrifty and store a high proportion of energy intake as fat during time of plenty, as insurance against times of famine’. When individuals with the thrifty genotype are confronted with a continuous supply of energy-dense processed foods, coupled with a reduction in physical activity, as is the case with urban Indians now, one could expect to see more prevalence of obesity, impaired glucose tolerance and Type 2 diabetes and indeed this is so<sup>11–14,85</sup>. The enhanced adipocyte differentiation which ensues from PPAR $\gamma$  activation, supports the view that PPAR $\gamma$  coordinates the thrifty response and urges the need for studying PPAR $\gamma$  in Indians as this could explain partly the heterogeneity of insulin resistance and Type 2 diabetes in Indians. It is also important in the context of overwhelming response among patients to the thiazolidinedione and non-thiazolidinedione PPAR agonists in the treatment of insulin resistance and Type 2 diabetes<sup>43,86–88</sup>.

### Lessons we learn and future directions

Research in PPAR has attained great medical significance because of its multiple effect on metabolic disorders and the fact that developing countries like India are undergoing an epidemiological transition. Combined with genetic predisposition, changes in diet and lifestyle contribute to the huge prevalence of non-communicable diseases and in particular diseases of micro and macrovascular complications of diabetes mellitus<sup>10–13,89</sup>. Dietary modifications play an important role in initiation of insulin resistance syndrome and long chain  $\omega$ -3

fatty acids in phospholipid of skeletal muscles are important for the action of insulin<sup>90</sup>. There is a competition between  $\omega$ -6 and  $\omega$ -3 fatty acids for the enzymes of desaturation and elongation, thus bringing forth high  $\omega$ -6/ $\omega$ -3 ratio as a critical factor in development of insulin resistance and atherosclerosis<sup>91</sup>. The overall diet pattern and in particular, the oil preferred for cooking in India is considerably changing with changes in the ratio of  $\omega$ 6/ $\omega$ 3 fatty acids which may play a role in diabetic micro and macrovascular complications. The identification of fatty acids and their derivatives as ligands for PPAR $\gamma$  emphasize lipids as direct modulators of cellular responses. PPAR $\gamma$  is activated by a range of naturally-occurring substances, including polyunsaturated fatty acids, 15-deoxy-delta prostaglandin J2,  $\alpha$ -linolenic acid, eicosapentaenoic acid, docohexanoic acid and components of oxidized low-density lipoprotein, such as 13-hydroxyoctadecadienoic acid and 15-hydroxy-eicosatetraenoic acid. However, the identities of endogenous ligands for PPAR $\gamma$  and their means of production *in vivo* in sufficient concentrations have not been fully elucidated. Nevertheless, their local concentrations may rise to a threshold for PPAR $\gamma$  activation via other common metabolites. For example, a role of lipoxygenase has been implicated in the generation of endogenous ligands such as eicosanoids and leukotrienes that in turn act as PPAR $\gamma$  activators<sup>92,93</sup>.

No doubt, there is much to be investigated to exploit the modulators of PPAR $\gamma$  for long-term therapeutic use in metabolic diseases. We need to identify novel ways to modulate PPAR $\gamma$  activity without complicating issues such as the enhancement of macrophage foam cell formation<sup>94,95</sup>, stimulation of colon carcinogenesis<sup>96,97</sup> and induction of acute liver dysfunction<sup>98,99</sup>. The restricted expression of certain PPAR $\gamma$  isoforms, such as the adipose-restricted PPAR $\gamma$ 2 form and macrophage-restricted PPAR $\gamma$ 3 form, suggests the feasibility of the development of tissue-specific PPAR $\gamma$  modulators. In fact, PPAR $\gamma$  modulators rather than simple agonists can function better as full or partial agonists or antagonists, depending on cell type and sequence-recognition site. Such agents will have greater medical benefit since they can induce beneficial effects on certain target tissues yet lack activity in other tissues where activation is less desirable. As PPAR $\gamma$  represents an important therapeutic target for the treatment of insulin resistance syndrome, a careful and complete understanding of its exact role in physiology is an absolute requirement. The continued development of pharmacological insulin sensitizers (both new generation thiazolidinediones and non-thiazolidinedione PPAR agonists) also provide us with novel probes to investigate the pathophysiology of Type 2 diabetes with special emphasis on PPAR- $\gamma$  signaling cascade. The ever-increasing pleiotropic role of PPAR $\gamma$  is certain to initiate a new flurry of research in the coming years.

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