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The Many Faces of PPARγ

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In an era marked by the increasing prevalence of obesity, diabetes, and cardiovascular disease, the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) has emerged as a transcriptional regulator of metabolism whose activity can be modulated by direct binding of small molecules. As the master regulator of fat-cell formation, PPARγ is required for the accumulation of adipose tissue and hence contributes to obesity. Yet PPARγ ligands are clinically effective antidiabetic drugs, although side effects limit their utility. Can PPARγ be targeted with greater benefit and with less risk to patients? The answer depends upon the basic biology of PPARγ, and the possibility of selectively modulating the activity of this nuclear receptor in a tissue- and target-gene-specific manner.

The Obesity Pandemic, the Metabolic Syndrome, and PPARγ

An epidemic of obesity is threatening to undermine the health of people living in Westernized societies. Obesity is a major risk factor for insulin resistance, hyperglycemia, abnormal blood lipid profiles, and hypertension, all of which contribute to cardiovascular disease leading to stroke and myocardial infarction (Eckel et al., 2005). Indeed, cardiovascular disease is the major cause of death in the industrialized world, and much of this can be attributed to the excess accumulation of adipose tissue. At the crossroads of obesity, insulin resistance, and cardiovascular disease is the nuclear receptor PPARγ, which is required for adipose tissue formation but is also a target of insulin-sensitizing drugs for treating diabetes.

Obesity and Insulin Resistance

We will briefly review the pathophysiology of insulin resistance associated with obesity before considering the role of PPARγ. In normal physiology, adipose tissue stores energy in the form of triglycerides that can be broken down (lipolysis) to release free fatty acids. In obese individuals, adipose tissue is characterized by hypertrophic adipocytes that are less responsive to insulin and have a higher basal rate of fatty-acid release. This leads to increased fatty-acid concentrations in the serum and ectopic fat accumulation in nonadipose tissues such as liver and muscle. Whole-body insulin sensitivity correlates with myocellular lipid content and free fatty-acid concentrations, illustrating the deleterious metabolic consequences of nonadipose lipid storage (Boden et al., 1994). Adipose tissue also functions as an endocrine organ, secreting many polypeptides that regulate metabolism, including insulin sensitizers such as adiponectin and insulin resistance factors such as resistin and TNFα (Kershaw and Flier, 2004). Insulin resistance associated with obesity is exacerbated by pathophysiological changes in the secretion of these factors.

PPARγ

PPARγ is a member of the nuclear receptor family that includes 48 human transcription factors whose activity is regulated by direct binding of steroid and thyroid hormones, vitamins, lipid metabolites, and xenobiotics (Chawla et al., 2001b). Binding of PPARγ to specific DNA sequences requires heterodimerization with a second member of the nuclear receptor family, retinoic X receptor (RXR). Binding of agonist ligands to PPARγ triggers a conformation change that attracts transcriptional coactivators, including members of the steroid receptor coactivator (SRC) family (McKenna and O'Malley, 2002). In the absence of ligand, PPARγ has the potential to actively silence genes to which it is bound by recruiting transcriptional corepressor complexes containing nuclear receptor corepressor (N-CoR) or SMRT (silencing mediator of retinoid and thyroid receptors). The transcriptional coactivators and corepressors exist in multiprotein complexes including histone-modifying enzymes, such as histone acetyltransferases (notably p300/CBP) and histone deacetylases (notably HDAC 3), respectively. The activity of these histone-modifying enzymes affects gene transcription by altering chromatin structure (McKenna and O'Malley, 2002). More detailed information about the identification, structure, and function of PPARγ and its closest relatives, PPARs α and β (also known as δ), can be found elsewhere (Desvergne and Wahli, 1999a).

Natural Ligands of PPARγ

A variety of substances have been suggested to be natural ligands for PPARγ, including fatty acids and eicosanoids (Desvergne and Wahli, 1999b), components of oxidized low-density lipoproteins (Nagy et al., 1998), and oxidized alkyl phospholipids including lysophosphatidic acid (McIntyre et al., 2003) and nitrolinoleic acid (Schopfer et al., 2005). The prostaglandin J2 derivative, 15-deoxy-Δ12,14-PGJ2, does not naturally exist at sufficient concentrations to activate PPARγ in mammalian cells (Bell-Parikh et al.,

2003) and affects cellular pathways other than PPARγ (Straus et al., 2000). Moreover, recent studies have provided functional evidence for an unidentified ligand that is produced only transiently during adipocyte differentiation (Tzameli et al., 2004). Overall, despite intensive research efforts, it remains to be determined whether PPARγ has a highly specific natural ligand or whether it operates as a physiological lipid sensor activated by the combined concentration of weakly activating fatty acids and eicosanoids.

PPARγ and Adipocyte Differentiation

Fat cells develop from a fibroblast-like preadipocyte to a mature, lipid-enriched adipocyte. The underlying transcriptional regulatory network that controls the maturation of adipocytes has been the focus of intense research and is reviewed elsewhere (MacDougald and Mandrup, 2002). Here we focus on the central role of PPARγ in this process. The highest levels of PPARγ are expressed in adipose tissue (Chawla et al., 1994; Tontonoz et al., 1994a). In 1994, Spiegelman and colleagues discovered that expression and activation of PPARγ was sufficient to induce adipogenesis (Tontonoz et al., 1994b). The essential role of PPARγ in adipogenesis has been clearly demonstrated in functional and genetic knockdown experiments (Barak et al., 1999; Rosen et al., 1999).

Two PPARγ isoforms created by differential promoter usage and splicing (γ1 and γ2) are found in adipocytes. PPARγ2, harboring an additional 30 amino acids at its N-terminal end, is expressed specifically in adipocytes, whereas PPARγ1 is also relatively abundant in macrophages, colon epithelia, and endothelium (Marx et al., 1999; Ricote et al., 1998; Sarraf et al., 1998). Liver and muscle express PPARγ1 at much lower levels, although tissue-specific gene disruption suggests that PPARγ1 expression in these tissues may be functionally relevant (Hevener et al., 2003; Matsusue et al., 2003; Norris et al., 2003). Selective in vivo disruption of the PPARγ2 isoform has metabolic consequences, with reduced adipose tissue mass observed in some, but not all, studies (Koutnikova et al., 2003; Medina-Gomez et al., 2005; Zhang et al., 2004). Posttranscriptional modification can also modulate the activity of both PPARγ isoforms. For example, phosphorylation of serine residue 112 in the N terminus of PPARγ2 reduces its transcriptional activity (Hu et al., 1996) and promotes sumoylation on lysine 107, which further lowers its ability to act as a transcriptional activator (Yamashita et al., 2004).

PPARγ and Adipocyte Metabolism

In addition to its importance in adipogenesis, PPARγ plays an important role in regulating lipid metabolism in mature adipocytes. Much of what is known about this role of PPARγ, and indeed many other aspects of its biology, followed the discovery that thiazolidinedione (TZD) antidiabetic drugs are high-affinity agonist ligands for PPARγ (Lehmann et al., 1995). TZDs appear to coordinately activate gene expression leading to an increase in net lipid partitioning into adipocytes. Target genes directly regulated by PPARγ that are involved in this pathway include lipoprotein lipase (Schoonjans et al., 1996), fatty-acid transport protein (Frohnert et al., 1999), and oxidized LDL receptor 1 (Chui

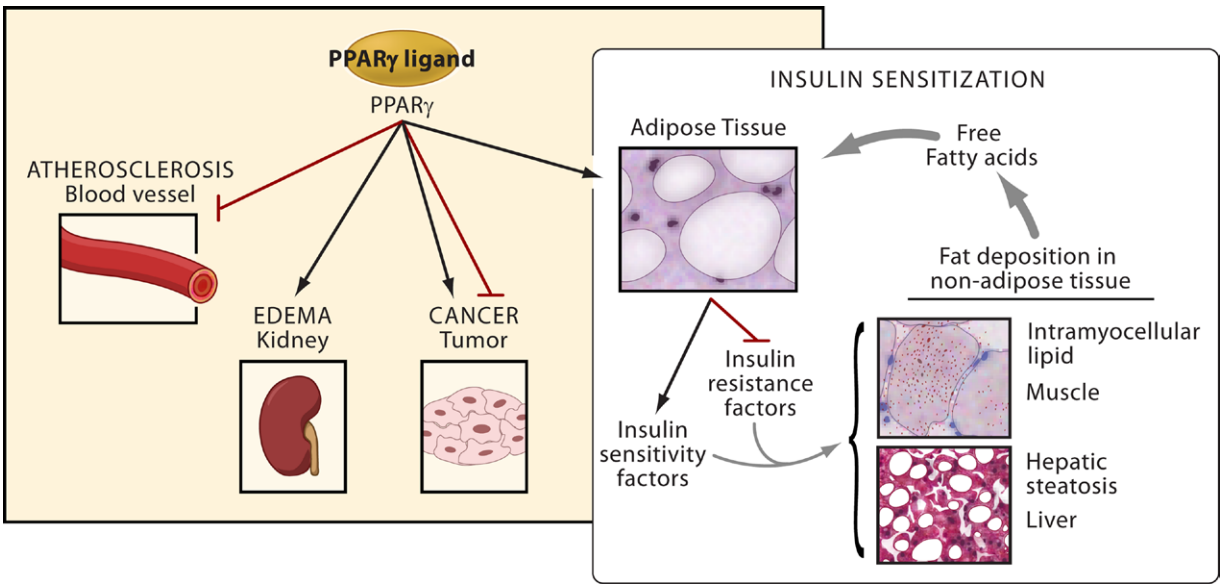

Figure 1. The Many Faces of PPARγ

PPARγ has many activities, leading to complicated and even paradoxical effects on adipocyte biology, insulin action, cardiovascular disease, inflammation, renal function, and tumor biology. Shown are some of the various tissues and processes that PPAR affects. The specific gene targets are discussed in the text. The ultimate therapeutic potential of small molecule regulators depends upon their ability to selectively modulate PPARγ activity in a gene- and tissue-specific manner.

et al., 2005), which all favor adipocyte uptake of circulating fatty acids; phosphoenolpyruvate carboxykinase (Tontonoz et al., 1995; Tordjman et al., 2003), glycerol kinase (Guan et al., 2002), and the glycerol transporter aquaporin 7 (Hibuse et al., 2005), which promote recycling rather than export of intracellular fatty acids. Together, these pathways lead to the net flux of fatty acids from the circulation and other tissues into adipocytes (Figure 1). Although increased fat storage would be expected to boost the size of adipocytes, TZD treatment actually leads to smaller adipocytes (Okuno et al., 1998). This is partly due to increased adipocyte differentiation, leading to new smaller cells. In addition, TZDs induce the coactivator PPARγ-coactivator 1a (PGC-1α), which promotes mitochondrial biogenesis (Wilson-Fritch et al., 2004), leading to an increase in fatty-acid oxidation that further protects against adipocyte hypertrophy.

PPARγ and Insulin Sensitivity

Before they were identified as PPARγ ligands, TZDs were found to be effective for treating type 2 diabetes as they directly reduced the systemic insulin resistance of peripheral tissues (Nolan et al., 1994). Currently, two TZD compounds, rosiglitazone and pioglitazone, are prescribed clinically for this purpose. Evidence that PPARγ is the insulin-sensitizing target of TZD action includes a strong correlation between receptor binding and agonism and the biological potency of the glucose-lowering effect in vivo, as well as antidiabetic activity of non-TZD-related PPARγ agonists (Berger et al., 1999). Genetic studies are also consistent with a role of PPARγ in glucose homeostasis. Mice with increased PPARγ activity due to a mutation that prevents phosphorylation on serine 112 are protected from obesity-associated insulin resistance (Rangwala et al., 2003), whereas mice lacking PPARγ in fat, muscle, or liver are predisposed to developing insulin resistance (He et al., 2003; Hevener et al., 2003; Matsusue et al., 2003; Norris et al., 2003). In humans, rare patients with dominant-negative mutations in PPARγ are severely insulin resistant (Barroso et al., 1999), whereas carriers of a Pro12Ala polymorphism in the *PPARγ* gene display improved glucose homeostasis (Deeb et al., 1998).

Despite the broad metabolic relevance of PPARγ in different organs, adipose tissue is likely to be the primary target site for the glucose-lowering actions of TZDs. In addition to the observation that PPARγ expression is greatest in adipocytes, mice lacking adipose tissue (Chao et al., 2000) or adipose PPARγ (He et al., 2003) are refractory to the insulin-sensitizing effects of TZDs. Also, TZDs retain their glucose-lowering capacities in PPARγ-specific knockout models of the liver and muscle, the two main glucose-disposing organs (Matsusue et al., 2003; Norris et al., 2003), although muscle PPARγ appears to contribute in one mouse model (Hevener et al., 2003).

The mechanism by which TZD activation of adipocyte PPARγ leads to insulin sensitivity is of much interest. Although TZDs directly modulate adipocyte glucose uptake, glucose disposal into adipose tissue contributes only modestly to the hypoglycemic effects of insulin. Therefore, it is apparent that TZD action must also alter communication between adipose tissue and the muscle and liver, the main insulin-sensitive organs. Remarkably, TZDs induce expression of the insulin-sensitizing factor, adiponectin, and simultaneously reduce adipocyte expression of several insulin resistance-promoting polypeptides. This causes the lowering of serum fatty-acid levels by promoting flux into adipose tissue as described above and reducing adipocyte production of cortisol (reviewed in Rangwala and Lazar, 2004) (Figure 1). All of these effects promote insulin sensitivity.

PPARγ and Body Weight

The success of TZDs as a therapy for type 2 diabetes is paradoxical, as they target PPARγ, an adipogenic transcription factor, yet adiposity is a major risk factor for type 2 diabetes. The ability of TZDs to alter the secretion of factors derived from adipocytes and reduce free fatty-acid levels plausibly explains their benefit. Yet one unwanted side effect of TZD treatment is modest weight gain. Part of the weight gain is explained by increased adipogenesis as well as the net flux of fatty acids into adipose tissue, which contributes to the antidiabetic effect. However, TZDs also increase weight via fluid retention and expansion of the extracellular volume, which is especially a problem for patients with preexisting congestive heart failure (Mudaliar et al., 2003). Although the mechanism of TZD-dependent fluid retention is not completely understood, recent advances have focused attention on PPARγ activation in the collecting duct of the kidney (Figure 1), as specific loss of PPARγ in this region prevents fluid retention and weight gain induced by TZD (Guan et al., 2005b; Zhang et al., 2005). The molecular mechanism involves PPARγ-dependent induction of the Na transporter ENaC (Guan et al., 2005b). Interestingly, amiloride, a clinically used diuretic that directly inhibits ENaC, was able to block TZD-dependent weight gain in mice, presenting a potentially specific tool for clinical use (Guan et al., 2005b).

PPARγ in Macrophage Biology and Atherosclerosis

PPARγ is expressed in blood cells and induced during macrophage differentiation (Ricote et al., 1998). As affector cells of the innate immune system, macrophages combine pathogen-clearing capacities with immune modulatory function. Attenuated lipid derivates like oxidized LDL are part of the pattern recognition code that triggers phagocytosis (Li and Glass, 2002). The absence of feedback mechanisms limiting lipid uptake can result in massive intracellular cholesterol accumulation in a lipid-saturated environment, which creates the foamy appearance of macrophages seen in atherosclerotic lesions. This process involves PPARγ, as well as many of its target genes, with functional implications for lipid utilization (Wellen and Hotamisligil, 2003).

In macrophages, PPARγ-dependent lipid uptake and storage were initially suggested to increase foam-cell formation and, potentially, atherosclerosis (Nagy et al., 1998). Despite these concerns, however, TZD treatment proved

vasoprotective and reduced atherosclerosis in mouse models (Li et al., 2000a) (Figure 1). Furthermore, transplantation of PPARγ null bone marrow to mice lacking LDL that are therefore atherosclerosis prone further demonstrated a direct athero-protective role of PPARγ in the macrophage (Chawla et al., 2001a). Retrospective human studies have also suggested an athero-protective effect of TZDs (Minamikawa et al., 1998), and a recent, prospective trial demonstrated that TZD therapy protected patients with type 2 diabetes, albeit modestly, from cardiovascular events (Dormandy et al., 2005). The solution to the paradox of PPARγ increasing lipid uptake in macrophages without increasing atherosclerotic risk has focused on the activation of lipid efflux pathways, such as reverse cholesterol transport, that prevent atherosclerotic lipid accumulation (Chawla et al., 2001a; Chinetti et al., 2001).

PPARγ and Inflammation

An alternative and primarily lipid-independent explanation for the antiatherosclerotic effects of TZDs are the anti-inflammatory capacities of PPARγ (Li et al., 2004). TZDs inhibit the expression of various inflammatory proteins like iNOS, TNFα, and MMP9 in macrophages (Li et al., 2000b) and are beneficial in disorders such as inflammatory bowel disease (Su et al., 1999). Several anti-inflammatory mechanisms have been suggested, including inhibition of NF-κB, AP1, and STAT transcription factors by PPARγ (Welch et al., 2003). Although nuclear receptors repress target genes in the absence of ligand by recruiting corepressors, the molecular mechanism for transcriptional repression by nuclear receptors in response to the binding of ligands remains poorly understood. One possibility involves the reciprocal inhibition of differential transcription systems through limited availability of shared cofactors, sometimes referred to as squelching. A recent report by Glass and colleagues suggests an alternative mechanism, wherein a functionally distinct pool of PPARγ is susceptible to ligand-dependent sumoylation at lysine 365, leading to recruitment to and stabilization of N-CoR complexes at the promoters of proinflammatory genes thereby repressing them (Pascual et al., 2005). It remains to be determined whether TZDs downregulate adipocytokine gene expression by the same mechanisms.

PPARγ and Cancer

In addition to its metabolic and anti-inflammatory properties, PPARγ has been implicated both as a tumor suppressor and tumor promoter (Figure 1). It is expressed in many cancers, including colon, breast, and prostate, and PPARγ ligands are generally antiproliferative in these settings (Grommes et al., 2004). However, although PPARγ has characteristics of a colon cancer tumor suppressor (Sarraf et al., 1999), colon tumors with mutations in the APC gene appear to be an exception as TZDs promote growth in these tumors (Lefebvre et al., 1998; Saez et al., 1998). Furthermore, although the data are not in the peer-reviewed literature, reports of hemangiosarcoma and other tumors in rodents treated with PPARγ ligands has led the US Food and Drug Administration to require two-year pre-clinical cancer surveillance studies before approving any new drug whose target is PPARγ (J. El-Hage, Preclinical and Clinical Safety Assessments for PPAR Agonists, http://www.fda.gov/cder/present/DIA2004/elhage_files/frame.htm).

Selective PPARγ Modulation

The unique ability of PPARγ ligands to improve insulin resistance is clearly tempered by side effects that limit their clinical use. In the case of another nuclear receptor, estrogen receptor α (ERα), similar considerations have led to the development of *s*elective *e*strogen *r*eceptor *m*odulators (SERMs), which have improved therapeutic index in breast cancer and osteoporosis because they regulate ERα activity in a tissue- and gene-selective manner. Examination of the properties of PPARγ in adipocytes suggests that it may be possible to selectively modulate PPARγ activity in an analogous fashion. For example, PPARγ is required for the expression of the adipocyte-specific fatty-acid binding protein aP2 (Tontonoz et al., 1994a). In mature adipocytes, even in the absence of a pharmaceutical ligand, PPARγ binds to the aP2 promoter along with coactivator proteins (Chui et al., 2005; Guan et al., 2005a). Whether this is due to constitutive activity of PPARγ or to the presence of an endogenous ligand is not clear. Yet, in the same cells, other PPARγ target genes such as glycerol kinase and OLR-1 require an exogenous ligand for activation (Chui et al., 2005; Guan et al., 2005a). In the absence of TZD or other potent synthetic ligand, PPARγ recruits corepressors to these genes. This observation may be related to the surprisingly improved insulin sensitivity of PPARγ heterozygote null mice (Kubota et al., 1999; Miles et al., 2000), whose PPARγ target genes in adipose tissue might be derepressed by the reduced content of PPARγ in the absence of exogenous ligand.

Differential modulation of PPARγ activity is also apparent from the effects of a form of this protein rendered constitutively active by fusion to the powerful VP16 transactivation domain. This VP16-PPARγ is sufficient to turn on the adipogenic gene program yet differs from PPARγ bound to a ligand because, unlike TZDs, it does not transrepress genes such as the insulin resistance factor resistin (Li and Lazar, 2002). PPARγ activity can also be selectively modulated at the level of coactivator availability. For example, the SRC-family coactivator TIF2 (or SRC-2) preferentially regulates fat storage in white adipose tissue, whereas in brown adipose tissue the related SRC-1 works in concert with PGC-1α to facilitate induction of uncoupling protein 1 and the stimulation of oxidative metabolism (Picard et al., 2002). Of note, tissue-selective cofactor recruitment is also a hallmark of SERMs (Shang and Brown, 2002).

Several PPARγ ligands that function as partial agonists (maximal efficacy is less than that of full agonists even at saturating concentrations) appear to be effective insulin sensitizers with less effect on adipocyte differentiation. One such compound is MCC-555, whose ability to stimulate PPARγ activity is highly context specific (Reginato et al., 1998). In addition to only modestly activating target genes,

some partial agonists, such as FMOC-L-leucine (Rocchi et al., 2001), may have gene-specific effects related to differential coactivator recruitment. Thus, partial agonists can selectively modulate PPARγ activity by creating interfaces that affect coactivator binding qualitatively as well as quantitatively. In addition, as the corepressors and coactivators interface with overlapping surfaces on the receptor (Hu and Lazar, 1999; Xu et al., 2002), partial agonism may also result from ligand inducing an intermediate conformation that is recognized by both classes of cofactors. Moreover, partial agonists may have full transrepression activity (Pascual et al., 2005), thereby providing a distinct mechanism of selective modulation of PPARγ activity. Partial activation can also be achieved by preventing the phosphorylation of PPARγ, which increases insulin sensitivity without weight gain (Rangwala et al., 2003).

Conclusion and Future Prospects

PPARγ indeed has many faces. It is the master regulator of adipocyte differentiation yet promotes insulin sensitivity. It enhances macrophage lipid uptake as well as lipid export and has anti-inflammatory effects. It is generally antiproliferative yet has been suggested to exacerbate the growth of certain tumors. Hence, targeting this receptor for therapeutic purposes while minimizing side effects represents a great challenge. Nevertheless, it is clear that selective PPARγ modulation of desired gene sets can be achieved by targeting corepressor interactions, separating transactivation from transrepression, and favoring specific subsets of coactivators. The specific modulation of these properties of PPARγ should allow optimization of tissue and target gene specificity, thereby enhancing therapeutic efficacy, particularly for metabolic diseases, while reducing undesired side effects that are limitations for the PPARγ compounds currently in the clinic.

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