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Abstract—The three peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of the nuclear hormone receptor superfamily. They share a high degree of structural homology with all members of the superfamily, particularly in the DNA-binding domain and ligand- and cofactor-binding domain. Many cellular and systemic roles have been attributed to these receptors, reaching far beyond the stimulation of peroxisome proliferation in rodents after which they were initially named. PPARs exhibit broad, isotype-specific tissue expression patterns. PPAR α is expressed at high levels in organs with significant catabolism of fatty acids. PPAR β/δ has the broadest expression pattern, and the levels of expression in certain tissues depend on the extent of cell proliferation and differentiation. PPAR γ is expressed as two isoforms, of which PPAR γ 2 is found at high levels in the adipose tissues, whereas PPAR γ 1 has a broader expression pattern. Transcrip-

tional regulation by PPARs requires heterodimerization with the retinoid X receptor (RXR). When activated by a ligand, the dimer modulates transcription via binding to a specific DNA sequence element called a peroxisome proliferator response element (PPRE) in the promoter region of target genes. A wide variety of natural or synthetic compounds was identified as PPAR ligands. Among the synthetic ligands, the lipid-lowering drugs, fibrates, and the insulin sensitizers, thiazolidinediones, are PPAR α and PPAR γ agonists, respectively, which underscores the important role of PPARs as therapeutic targets. Transcriptional control by PPAR/RXR heterodimers also requires interaction with coregulator complexes. Thus, selective action of PPARs *in vivo* results from the interplay at a given time point between expression levels of each of the three PPAR and RXR isotypes, affinity for a specific promoter PPRE, and ligand and cofactor availabilities.

Introduction

Peroxisome proliferator-activated receptors (PPARs)¹ are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. PPAR α

(NR1C1) (Nuclear Receptors Nomenclature Committee, 1999) was first described as a receptor that is activated by peroxisome proliferators, hence its name (Issemann and Green, 1990). Two additional related isotypes, PPAR β/δ (NR1C2) and PPAR γ (NR1C3), were then found and characterized (Dreyer et al., 1992). The PPAR β/δ isotype was called PPAR β when it was first isolated from a *Xenopus* oocyte library (Dreyer et al., 1992). Because the mammalian PPAR β protein sequence was not highly homologous to the *Xenopus* PPAR β protein sequences, it was named PPAR δ when identified in the mouse with the view that there may be four members of this nuclear receptor family (Kliwer et al., 1994). PPAR β was also designated FAAR (fatty acid

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¹ Abbreviations: PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; DR, direct repeat; PPRE, peroxisome proliferator response element; LBD, ligand-binding domain; HDL-C, high-density lipoprotein cholesterol.

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activated receptor) (Amri et al., 1995) in rats and NUC1 in humans (Schmidt et al., 1992). Sequencing of mammalian genomes indicated that there are only three PPAR isotypes. Characterization of PPARs in the chick and comparison with the PPARs of mouse and *Xenopus* demonstrated that the mammalian PPAR δ is the ortholog of the amphibian PPAR β . For reasons of clarity, we propose that this receptor be designated herein as PPAR β/δ . Each of the PPAR isotypes is encoded in a separate gene, and, to date, many cellular and systemic roles have been attributed to these receptors, reaching far beyond the stimulation of peroxisome proliferation in rodents after which they were initially named (Desvergne and Wahli, 1999). In line with their various developmental and physiological functions, PPARs exhibit broad, but isotype-specific, tissue expression patterns (Kliwer et al., 1994; Braissant et al., 1996). PPAR α is expressed at high levels in organs that carry out significant catabolism of fatty acids such as the brown adipose tissue, liver, heart, kidney, and intestine (Mandard et al., 2004). Of the three isotypes, PPAR β/δ has the broadest expression pattern, and the levels of expression in certain tissues depend on the extent of cell proliferation and differentiation. Important functions have been assigned to this isotype in the skin, gut, placenta, skeletal muscle, adipose tissue, and brain (Braissant et al., 1996; Bastie et al., 1999; Peters et al., 2000; Michalik et al., 2001; Barak et al., 2002). PPAR γ is expressed as two isoforms, $\gamma 1$ and $\gamma 2$, that differ at their N terminus. PPAR $\gamma 2$ is found at high levels in the different adipose tissues (Dreyer et al., 1992; Chawla et al., 1994; Tontonoz et al., 1994b), whereas PPAR $\gamma 1$ has a broader expression pattern that extends to settings such as the gut, brain, vascular cells, and specific kinds of immune and inflammatory cells (Tontonoz et al., 1994a; Zhu et al., 1995).

In contrast to steroid hormone receptors, which act as homodimers, transcriptional regulation by PPARs requires heterodimerization with the retinoid X receptor (RXR; NR2B), which belongs to the same receptor superfamily (Kliwer et al., 1992; Keller et al., 1993). This PPAR/RXR heterodimer can form in the absence of a ligand. When activated by a ligand, it modulates transcription via binding to a specific DNA sequence element frequently called a peroxisome proliferator response element (PPRE) (Dreyer et al., 1992; Kliwer et al., 1992; Tugwood et al., 1992; Feige et al., 2005). This response element, generally of the direct repeat 1 (DR-1) type, is composed of two half-sites that occur as a direct repetition of the consensus sequence AGGTCA with a single nucleotide spacing between the two repeats. The PPRE is usually present in one or multiple copies in the promoter region of target genes but may also be located in the proximal transcribed region of certain PPAR-responsive genes (Di-Poi et al., 2002). PPAR and RXR bind to the 5' and 3' half-sites of this element, respectively, and

the 5'-flanking region mediates the selectivity of binding between different PPAR isotypes (DiRenzo et al., 1997; Ijpenberg et al., 1997; Juge-Aubry et al., 1997). Transcriptional control by PPAR/RXR heterodimers requires interaction with coregulator complexes—either a coactivator for stimulation or a corepressor for inhibition of target gene expression (Dowell et al., 1999; Stanley et al., 2003; Guan et al., 2005; Yu et al., 2005). Selective action of a given PPAR isotype in vivo probably results from a complex interplay at a given time point between expression levels of each of the three PPAR and RXR isotypes, affinity for a specific promoter PPRE, ligand and cofactor availability, and possibly other transcription factor binding in the vicinity of the PPRE.

Classification of PPARs in the Nuclear Receptor Family

In the nomenclature system for the nuclear receptor superfamily, which divides the superfamily into six subfamilies and 26 groups of receptors, PPARs belong to subfamily 1 (Nuclear Receptors Nomenclature Committee, 1999). This subfamily, which is the largest in the entire superfamily, comprises 11 groups of receptors (TR, RAR, PPAR, REV-ERB, E78, RZR/ROR, *Caenorhabditis* CNR14, ECR, VDR, *Drosophila* DHR96 orphan receptor, and the nematode NHR1 orphan receptor from *Onchocerca volvulus*) composed of a total of 27 individual genes.

Chromosomal Distribution

Vertebrate gene families in which three paralogous genes are found, as is the case for the PPARs, are relatively frequent. In a phylogenetic tree, PPAR γ is the most divergent isotype, whereas the PPAR α and PPAR β/δ isotypes are more closely related (Laudet, 1997). It is thought that during the evolution of PPARs, the first gene duplication occurred between amphioxus and lamprey, giving rise to PPAR γ . The second gene, which was then duplicated after the lamprey-gnathostome split, gave rise to PPAR α and PPAR β/δ . This suggests that the PPAR α -PPAR β/δ duplication is specific to gnathostomes, as was also proposed for TR α and TR β (Escriva et al., 2002). The sequencing of the mouse and human genomes revealed the exact position of the three isotypes on different chromosomes. The relatively important difference in protein length between PPAR β/δ and the two other isotypes originates mainly in the A/B domain, which is shorter in the former.

Functional Roles

Consistent with its distribution in tissues with high catabolic rates of fatty acids and high peroxisomal activity, the major role of PPAR α is the regulation of energy homeostasis (Lefebvre et al., 2006). In the liver especially, PPAR α activates fatty acid catabolism, stimu-

lates gluconeogenesis and ketone body synthesis, and is involved in the control of lipoprotein assembly (Staels et al., 1995; Vu-Dac et al., 1995; Kersten et al., 1999; Reddy and Hashimoto, 2001). PPAR α also stimulates heme synthesis and cholesterol catabolism. Furthermore, it attenuates inflammatory responses and participates in the control of amino acid metabolism and urea synthesis (Devchand et al., 1996; Staels et al., 1998; Kersten et al., 2001). Increased fatty acid oxidation by activated PPAR α lowers circulating triglyceride levels, liver and muscle steatosis, and reduces adiposity, which improves insulin sensitivity (Guerre-Millo et al., 2000; Chou et al., 2002; Kim et al., 2003). Not surprisingly, fibrate drugs such as gemfibrozil, clofibrate, and fenofibrate that are widely used to treat hypertriglyceridemia are activators of PPAR α . In addition, PPAR α agonists have demonstrated significant anti-inflammatory activities that seem to play a role in their protective actions within the cardiovascular system (Berger et al., 2005).

PPAR β/δ is necessary for placental and gut development and is also involved in the control of energy homeostasis by stimulating genes involved in fatty acid catabolism and adaptive thermogenesis (Peters et al., 2000; Barak et al., 2002; Wang et al., 2003; Nadra et al., 2006; Varnat et al., 2006). In addition, PPAR β/δ has an important role in the control of cell proliferation, differentiation, and survival and is involved in tissue repair (Tan et al., 2001; Di-Poi et al., 2002; Letavernier et al., 2005; Michalik and Wahli, 2006). In animal models, PPAR β/δ agonists retard weight increase under high-fat diet conditions and therefore maintain insulin sensitivity probably by stimulating skeletal muscle fatty acid metabolism and thermogenesis (Wang et al., 2003).

PPAR γ is a pivotal actor in adipose tissue differentiation and in maintaining adipocyte specific functions, such as lipid storage in the white adipose tissue and energy dissipation in the brown adipose tissue (Tontonoz et al., 1993, 1994b; Rosen et al., 2000; He et al., 2003; Koutnikova et al., 2003). Furthermore, it is required for the survival of differentiated adipocytes (Imai et al., 2004). In addition, PPAR γ is involved in glucose metabolism through an improvement of insulin sensitivity and thus represents a molecular link between lipid and carbohydrate metabolism (Kubota et al., 1999; Rosen et al., 1999; Wu et al., 1999; Rieusset et al., 2002; Savage et al., 2003). Like PPAR α , PPAR γ activation seems to limit inflammation, adding to the interest in its possible role in limiting atherosclerosis and/or diabetes (Ricote et al., 1998). Among the synthetic compounds that selectively activate PPAR γ , the thiazolidinediones are insulin sensitizers used to treat the hyperglycemia of type 2 diabetes (Mayerson et al., 2002; Bajaj et al., 2003; Bays et al., 2004). The clinical use of these agonists and the discovery of both rare and severely deleterious dominant-negative mutations that lead to a stereotyped syn-

drome of partial lipodystrophy and severe insulin resistance, as well as more common sequence variants with a much smaller impact on receptor function, have increased our understanding of the functions of PPAR γ in humans (Semple et al., 2006). Finally, growing evidence implicates PPAR γ , as well as the two other isoforms, in tumor development in different tissues, although whether PPAR activation promotes or limits this process remains under debate and may depend on specific conditions (Michalik et al., 2004; Peters et al., 2005; Burdick et al., 2006).

Structural Features of the Ligand-Binding Domain

All three PPAR isoforms have a protein domain organization similar to most members of the superfamily. The best-characterized domains are the DNA-binding domain and ligand-binding domain (LBD). Although the latter is generally less well conserved than the former, X-ray crystal structure analyses have revealed a tridimensional fold of the PPAR LBD that is similar to other nuclear receptors. The PPAR LBD consists of 12 α -helices that form the characteristic three-layer antiparallel α -helical sandwich with a small four-stranded sheet. This structure delineates a large Y-shape hydrophobic pocket, the ligand-binding cavity (Nolte et al., 1998; Uppenberg et al., 1998; Xu et al., 1999, 2001; Gampe et al., 2000), which is larger in PPARs than in other receptors. This feature may contribute to the ability of PPARs to bind a wide range of synthetic and natural lipophilic compounds with an acidic head group. Comparison of the ligand-binding pocket of the three PPAR isoforms has revealed the following interesting characteristics (Xu et al., 2001). The PPAR β/δ ligand-binding pocket is significantly smaller than the corresponding PPAR α and PPAR γ pockets, which are similar to each other in shape and size. This difference might explain why fewer PPAR β/δ ligands have been reported compared with PPAR α and PPAR γ and may indicate that the size of the pocket contributes to the ligand-binding specificity of this isoform. The PPAR α pocket is more lipophilic than the two others, which suggests a possible explanation for why certain potent PPAR γ ligands do not bind PPAR α and why PPAR α can bind the more lipophilic-saturated fatty acids. Finally, it is important to note that single amino acid differences in the pockets can be major determinants of ligand isoform selectivity.

Ligand-dependent activation of PPARs stabilizes the LBD in a relatively compact and rigid structure in which helix 12 is in a conformation that promotes binding of coactivator proteins and thus has a critical function in the stimulation of target genes (Nolte et al., 1998; Nagy and Schwabe, 2004). Usually nucleosome remodeling, for example by histone deacetylation and repositioning, is necessary to allow formation of the transcription preinitiation complex. Alternatively, corepressors in-

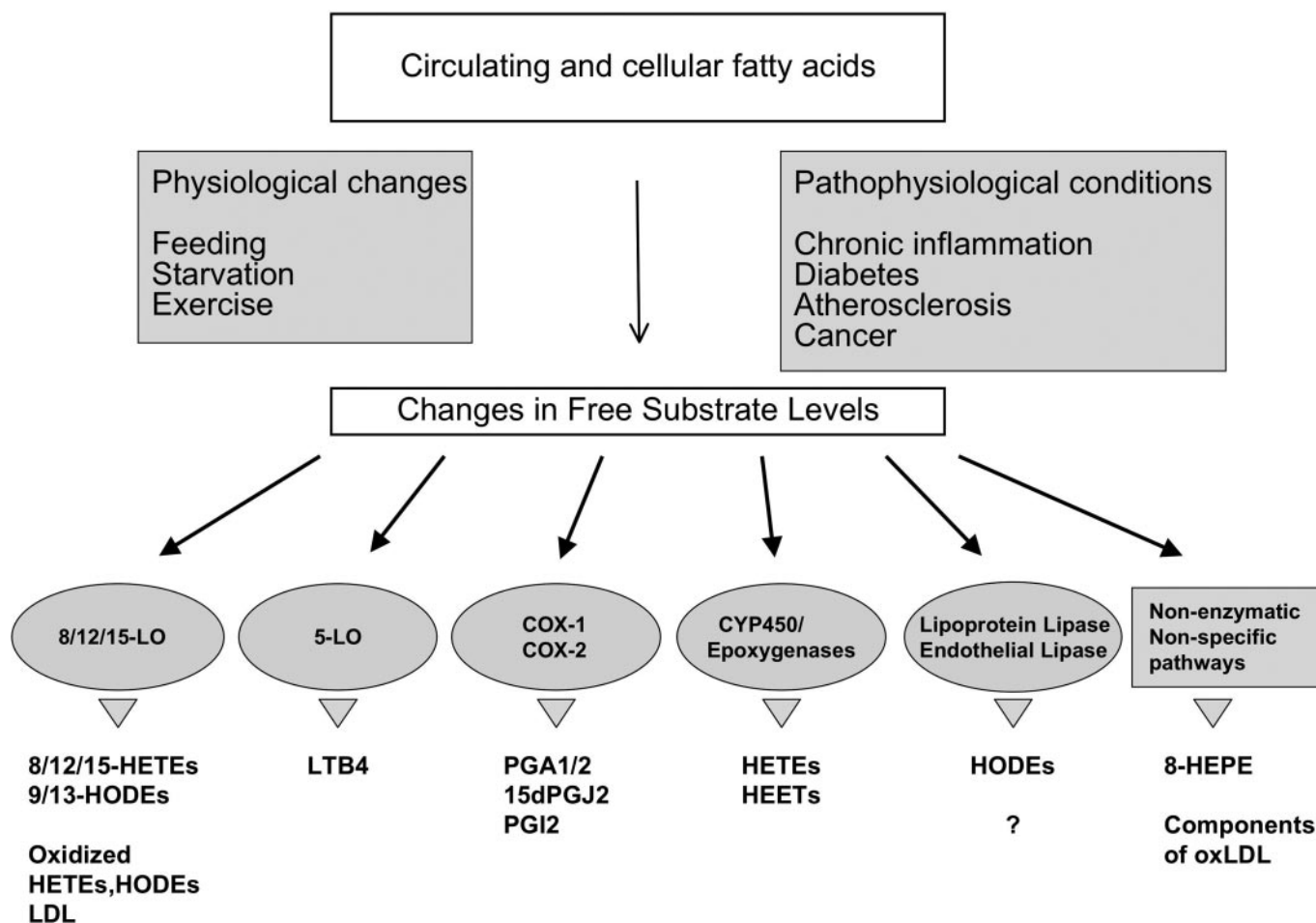


FIG. 1. Endogenous pathways for PPAR ligand production. Unsaturated fatty acids can act both as ligands and as substrates for ligand-generating enzymes, such as the 8/12/15- and 5-lipoxygenases (LOs), the cyclooxygenases (COX-1 and COX-2), the cytochrome (CYP)/epoxygenases, or the lipoprotein and endothelial lipases. In addition, ligands can be generated by nonspecific/nonenzymatic pathways. The levels of substrates available depend on physiological and pathophysiological conditions.

hibit the activity of the receptors in the absence of a ligand or upon antagonist treatment. Often, the repressive effects depend on the recruitment of histone deacetylases, but sometimes direct contacts with the basal transcription machinery are also possible (Glass and Rosenfeld, 2000; McKenna and O'Malley, 2002; Hebbar and Archer, 2003).

Endogenous Ligands

The prevalent point of view today is that PPARs act as lipid sensors that translate changes in lipid/fatty acid levels from the diet or from food deprivation into metabolic activity, leading to either fatty acid catabolism or lipid storage. The endogenous ligands or mediators of these changes have not been characterized but are probably generated by fatty acid metabolism. Their activities are likely to be influenced by their binding specificities toward the different PPARs and by cell-, tissue-, or organ-specific effects (Bishop-Bailey and Wray, 2003; Desvergne et al., 2004; Evans et al., 2004).

The possible pathways that generate lipid mediators from fatty acids, which also serve as PPAR ligands, are

recapitulated in Fig. 1. In addition, specific lipolytic pathways, for example the action of lipoprotein lipase and endothelial lipase, can hydrolyze certain circulating lipoproteins to generate PPAR ligands and PPAR activation (Chawla et al., 2003; Ziouzenkova et al., 2003; Ahmed et al., 2006). Given the variety and distribution pattern in the body of fatty acids and fatty acid derivatives with a wide range of affinity to PPARs, it has been difficult thus far to thoroughly evaluate the contribution of each of these endogenous ligands to the biology of PPARs. However, it is not surprising, based on the characteristics of these endogenous ligands with their broad spectrum of activation efficiency, that PPARs are involved in functions as diverse as lipid and carbohydrate metabolism, immune/inflammatory responses, vascular biology, tissue repair, and cell differentiation and proliferation. The distribution and abundance of the ligands also depend on a variety of pathophysiological situations associated with hyperlipidemia, hypertension, diabetes, chronic inflammation, cancer, and atherosclerosis. It is important to note that some of these endogenous lipid mediators also signal through the classic cell surface

G-protein-linked receptors and therefore have many PPAR-independent effects.

Synthetic Modulators and Pharmacology of PPARs

Because of their various metabolic and therapeutic actions, PPARs have become major drug targets (Berger et al., 2005; Staels and Fruchart, 2005). As clinical data continue to accumulate regarding current and emerging PPAR modulators, an important distinction must be maintained between the action of PPARs *in vivo* under normal physiologic and natural ligand production conditions and the effects of synthetic PPAR agonists, which may vary as a function of many pharmacologic and other parameters.

PPAR α agonists, such as fibrates, effectively treat dyslipidemia and may have significant anti-inflammatory and antiatherosclerotic activity. Associated with their clinical effectiveness, PPAR α agonists decrease plasma triglyceride levels by stimulating lipid uptake and catabolism and augment HDL-C levels by increasing the production, in the liver, of the apolipoproteins A-I and A-II, which are major components of HDL-C (Bays and Stein, 2003). PPAR α agonists have also demonstrated anti-inflammatory effects in experimental animal models. In line with the expression of PPAR α in vascular cells, PPAR α agonists most likely have direct protective effects at the atherosclerotic lesion itself (Marx et al., 2004). Major clinical studies revealed that these ligands reduce the incidence of cardiovascular events and that their cardioprotective efficacy is higher in dyslipidemic patients with diabetes or hyperinsulinemia, in which the cardiovascular diseases are the major cause of mortality (Steiner et al., 2001; Rubins et al., 2002; Israelian-Konarakaki and Reaven, 2005).

The first PPAR β/δ -selective agonists were shown to augment HDL-C in diabetic mice as well as in obese rhesus monkeys, in which they decrease elevated levels of triglycerides and insulin (Leibowitz et al., 2000; Oliver et al., 2001). Further studies confirmed the functions of PPAR β/δ in regulating energy homeostasis and lipid metabolism (Muio et al., 2002; Dressel et al., 2003; Luquet et al., 2003; Tanaka et al., 2003; Bedu et al., 2005). Thus, agonists of this PPAR isotype might be useful for treating insulin resistance, dyslipidemia, and obesity. Furthermore, the involvement of PPAR β/δ in the control of tissue-repair mechanisms makes it a potential target for improving impaired healing in different organs (Tan et al., 2004; Letavernier et al., 2005).

The thiazolidinediones pioglitazone and rosiglitazone are PPAR γ agonists that have clinical antidiabetic efficacy mainly through their actions in adipose tissues (Xu et al., 1999; Berger and Moller, 2002; Knouff and Auwerx, 2004). The fact that genetic PPAR γ variants in humans are associated with insulin resistance and lipodystrophy provides clear genetic evidence for the role of this receptor in

glucose homeostasis and adipogenesis in humans (Agarwal and Garg, 2006). PPAR γ agonists have also been shown to have potent antiatherogenic effects in animal models (Li et al., 2000; Chen et al., 2001; Collins et al., 2001), and emerging data suggest protective effects in humans (Pfutzner et al., 2005). Unfortunately, PPAR γ agonists can have untoward clinical effects as well, including weight gain due to increased adiposity, edema, hemodilution, and plasma-volume expansion, which preclude their clinical application in patients with heart failure (Arakawa et al., 2004; Rangwala and Lazar, 2004; Staels, 2005). Reversible congestive heart failure, which can occur with these agents, does not seem to be due to changes in myocyte function but rather to an inability to tolerate the fluid retention that can occur as a side effect with these drugs. Recent research has concentrated on the development of efficacious PPAR γ -selective modulators that show improved tolerance, but their superior therapeutic window in the treatment of diabetic patients remains to be demonstrated (Berger et al., 2003). In general, diabetic patients suffer from both hyperglycemia and dyslipidemia with their associated complications, such as peripheral neuropathy, kidney failure, retinopathy, and atherosclerosis, culminating in myocardial infarction and stroke (Plutzky, 2000a,b, 2003). Therefore, it was thought that dual PPAR α and PPAR γ agonists and possibly PPAR α , β/δ , and γ agonists might provide broadly beneficial metabolic effects on these patients through a simultaneous treatment of hyperglycemia and dyslipidemia (Knouff and Auwerx, 2004; Staels and Fruchart, 2005; Tenenbaum et al., 2005). Such compounds are presently being evaluated clinically, and some dual agonists have progressed to phase III clinical trials. Further research on PPAR biology will increase our comprehension of their physiological and pharmacological characteristics and provide additional knowledge for the development of superior ligands with improved therapeutic indices. A major concern of those attempting to develop novel PPAR-targeted drugs is to obtain agents that differ from present compounds that have been shown to promote carcinogenesis in rodents. The U.S. Food and Drug Administration has issued guidelines requiring that PPAR ligand clinical trials exceeding 6 months must be preceded by the successful completion of 2-year carcinogenicity tests in rodents. In spite of this regulatory requirement, research in the area of PPAR modulators continues vigorously, challenged by today's global epidemic of obesity (more than 1 billion adults are currently overweight, and at least 300 million are clinically obese), which is a major contributor to chronic diseases, including diabetes, cardiovascular diseases, hypertension and stroke, and certain forms of cancer for which efficacious treatments with novel PPAR modulators are anticipated.

Tables 1 through 3 summarize the major molecular, physiological, and pharmacological properties of PPAR α , PPAR β/δ , and PPAR γ , respectively.

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REFERENCES

- Agarwal AK and Garg A (2006) Genetic basis of lipodystrophies and management of metabolic complications. *Annu Rev Med* **57**:297–311.
- Ahmed W, Orasanu G, Nehra V, Asatryan L, Rader DJ, Ziouzenkova O, and Plutzky J (2006) High-density lipoprotein hydrolysis by endothelial lipase activates PPARalpha: a candidate mechanism for high-density lipoprotein-mediated repression of leukocyte adhesion. *Circ Res* **98**:490–498.
- Amri EZ, Bonino F, Ailhaud G, Abumrad NA, and Grimaldi PA (1995) Cloning of a protein that mediates transcriptional effects of fatty acids in preadipocytes. Homology to peroxisome proliferator-activated receptors. *J Biol Chem* **270**:2367–2371.
- Arakawa K, Ishihara T, Aoto M, Inamasu M, Kitamura K, and Saito A (2004) An antidiabetic thiazolidinedione induces eccentric cardiac hypertrophy by cardiac volume overload in rats. *Clin Exp Pharmacol Physiol* **31**:8–13.
- Bajaj M, Suraamornkul S, Pratipanawat T, Hardies LJ, Pratipanawat W, Glass L, Cersosimo E, Miyazaki Y, and DeFronzo RA (2003) Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. *Diabetes* **52**:1364–1370.
- Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, Boland R, and Evans RM (2002) Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. *Proc Natl Acad Sci USA* **99**:303–308.
- Bastie C, Holst D, Gaillard D, Jehl-Pietri C, and Grimaldi PA (1999) Expression of peroxisome proliferator-activated receptor PPARdelta promotes induction of PPARgamma and adipocyte differentiation in 3T3C2 fibroblasts. *J Biol Chem* **274**:21920–21925.
- Bays H, Mandarino L, and DeFronzo RA (2004) Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J Clin Endocrinol Metab* **89**:463–478.
- Bays H and Stein EA (2003) Pharmacotherapy for dyslipidaemia—current therapies and future agents. *Expert Opin Pharmacother* **4**:1901–1938.
- Bedu E, Wahli W, and Desvergne B (2005) Peroxisome proliferator-activated receptor beta/delta as a therapeutic target for metabolic diseases. *Expert Opin Ther Targets* **9**:861–873.
- Berger J and Moller DE (2002) The mechanisms of action of PPARs. *Annu Rev Med* **53**:409–435.
- Berger JP, Akiyama TE, and Meinke PT (2005) PPARs: therapeutic targets for metabolic disease. *Trends Pharmacol Sci* **26**:244–251.
- Berger JP, Petro AE, Macnaul KL, Kelly LJ, Zhang BB, Richards K, Elbrecht A, Johnson BA, Zhou G, Doebber TW, et al. (2003) Distinct properties and advantages of a novel peroxisome proliferator-activated protein [gamma] selective modulator. *Mol Endocrinol* **17**:662–676.
- Bishop-Bailey D and Wray J (2003) Peroxisome proliferator-activated receptors: a critical review on endogenous pathways for ligand generation. *Prostaglandins Other Lipid Mediat* **71**:1–22.
- Braissant O, Foufelle F, Scotto C, Dauca M, and Wahli W (1996) Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. *Endocrinology* **137**:354–366.
- Burdick AD, Kim DJ, Peraza MA, Gonzalez FJ, and Peters JM (2006) The role of peroxisome proliferator-activated receptor-beta/delta in epithelial cell growth and differentiation. *Cell Signal* **18**:9–20.
- Chawla A, Lee CH, Barak Y, He W, Rosenfeld J, Liao D, Han J, Kang H, and Evans RM (2003) PPARdelta is a very low-density lipoprotein sensor in macrophages. *Proc Natl Acad Sci USA* **100**:1268–1273.
- Chawla A, Schwarz EJ, Dimaculangan DD, and Lazar MA (1994) Peroxisome proliferator-activated receptor (PPAR) gamma: adipose-predominant expression and induction early in adipocyte differentiation. *Endocrinology* **135**:798–800.
- Chen Z, Ishibashi S, Perrey S, Osuga J, Gotoda T, Kitamine T, Tamura Y, Okazaki H, Yahagi N, Izuka Y, et al. (2001) Troglitazone inhibits atherosclerosis in apolipoprotein E-knockout mice: pleiotropic effects on CD36 expression and HDL. *Arterioscler Thromb Vasc Biol* **21**:372–377.
- Chou CJ, Haluzik M, Gregory C, Dietz KR, Vinson C, Gavrilova O, and Reitman ML (2002) WY14,643, a peroxisome proliferator-activated receptor alpha (PPARalpha) agonist, improves hepatic and muscle steatosis and reverses insulin resistance in lipotrophic A-ZIP/F-1 mice. *J Biol Chem* **277**:24484–24489.
- Collins AR, Meehan WP, Kintscher U, Jackson S, Wakino S, Noh G, Palinski W, Hsueh WA, and Law RE (2001) Troglitazone inhibits formation of early atherosclerotic lesions in diabetic and nondiabetic low density lipoprotein receptor-deficient mice. *Arterioscler Thromb Vasc Biol* **21**:365–371.
- Desvergne B, Michalik L, and Wahli W (2004) Be fit or be sick: peroxisome proliferator-activated receptors are down the road. *Mol Endocrinol* **18**:1321–1332.
- Desvergne B and Wahli W (1999) Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* **20**:649–688.
- Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, and Wahli W (1996) The PPARalpha-leukotriene B4 pathway to inflammation control. *Nature (Lond)* **384**:39–43.
- Di-Poi N, Tan NS, Michalik L, Wahli W, and Desvergne B (2002) Antiapoptotic role of PPARbeta in keratinocytes via transcriptional control of the Akt1 signaling pathway. *Mol Cell* **10**:721–733.
- DiRenzo J, Soderstrom M, Kurokawa R, Ogliastro MH, Ricote M, Ingrey S, Horlein A, Rosenfeld MG, and Glass CK (1997) Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors. *Mol Cell Biol* **17**:2166–2176.
- Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevriy DJ, and Leid M (1999) Identification of nuclear receptor corepressor as a peroxisome proliferator-activated receptor alpha interacting protein. *J Biol Chem* **274**:15901–15907.
- Dressel U, Allen TL, Pippal JB, Rohde PR, Lau P, and Muscat GE (2003) The peroxisome proliferator-activated receptor beta/delta agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. *Mol Endocrinol* **17**:2477–2493.
- Dreyer C, Krey G, Keller H, Givel F, Helftenbein G, and Wahli W (1992) Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. *Cell* **68**:879–887.
- Escriba H, Manzon L, Youson J, and Laudet V (2002) Analysis of lamprey and hagfish genes reveals a complex history of gene duplications during early vertebrate evolution. *Mol Biol Evol* **19**:1440–1450.
- Evans RM, Barish GD, and Wang YX (2004) PPARs and the complex journey to obesity. *Nat Med* **10**:355–361.
- Feige JN, Gelman L, Tudor C, Engelborghs Y, Wahli W, and Desvergne B (2005) Fluorescence imaging reveals the nuclear behavior of peroxisome proliferator-activated receptor/retinoid X receptor heterodimers in the absence and presence of ligand. *J Biol Chem* **280**:17880–17890.
- Gampe RT Jr, Montana VG, Lambert MH, Miller AB, Bledsoe RK, Milburn MV, Kliewer SA, Willson TM, and Xu HE (2000) Asymmetry in the PPARgamma/RXRalpha crystal structure reveals the molecular basis of heterodimerization among nuclear receptors. *Mol Cell* **5**:545–555.
- Glass CK and Rosenfeld MG (2000) The coregulator exchange in transcriptional functions of nuclear receptors. *Genes Dev* **14**:121–141.
- Guan HP, Ishizuka T, Chui PC, Lehrke M, and Lazar MA (2005) Corepressors selectively control the transcriptional activity of PPARgamma in adipocytes. *Genes Dev* **19**:453–461.
- Guerre-Millo M, Gervois P, Raspe E, Madsen L, Poulain P, Derudas B, Herbert JM, Winegar DA, Willson TM, Fruchart JC, et al. (2000) Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. *J Biol Chem* **275**:16638–16642.
- He W, Barak Y, Hevener A, Olson P, Liao D, Le J, Nelson M, Ong E, Olefsky JM, and Evans RM (2003) Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. *Proc Natl Acad Sci USA* **100**:15712–15717.
- Hebbar PB and Archer TK (2003) Chromatin remodeling by nuclear receptors. *Chromosoma* **111**:495–504.
- Ijpenberg AI, Jeannin E, Wahli W, and Desvergne B (1997) Polarity and specific sequence requirements of peroxisome proliferator-activated receptor (PPAR)/retinoid X receptor heterodimer binding to DNA. A functional analysis of the malic enzyme gene PPAR response element. *J Biol Chem* **272**:20108–20117.
- Imai T, Takakuwa R, Marchand S, Dentz E, Bornert JM, Messaddeq N, Wendling O, Mark M, Desvergne B, Wahli W, et al. (2004) Peroxisome proliferator-activated receptor gamma is required in mature white and brown adipocytes for their survival in the mouse. *Proc Natl Acad Sci USA* **101**:4543–4547.
- Israelian-Konarakis Z and Reaven PD (2005) Peroxisome proliferator-activated receptor-alpha and atherosclerosis: from basic mechanisms to clinical implications. *Cardiology* **103**:1–9.
- Issemann I and Green S (1990) Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature (Lond)* **347**:645–650.
- Juge-Aubry C, Pernin A, Favez T, Burger AG, Wahli W, Meier CA, and Desvergne B (1997) DNA binding properties of peroxisome proliferator-activated receptor subtypes on various natural peroxisome proliferator response elements. Importance of the 5'-flanking region. *J Biol Chem* **272**:25252–25259.
- Keller H, Dreyer C, Medin J, Mahfoudi A, Ozato K, and Wahli W (1993) Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. *Proc Natl Acad Sci USA* **90**:2160–2164.
- Kersten S, Mandarino S, Escher P, Gonzalez FJ, Tafuri S, Desvergne B, and Wahli W (2001) The peroxisome proliferator-activated receptor alpha regulates amino acid metabolism. *FASEB J* **15**:1971–1978.
- Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, and Wahli W (1999) Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. *J Clin Invest* **103**:1489–1498.
- Kim H, Haluzik M, Asghar Z, Yau D, Joseph JW, Fernandez AM, Reitman ML, Yakar S, Stannard B, Heron-Milhavet L, et al. (2003) Peroxisome proliferator-activated receptor-alpha agonist treatment in a transgenic model of type 2 diabetes reverses the lipotoxic state and improves glucose homeostasis. *Diabetes* **52**:1770–1778.
- Kliwer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K, and Evans RM (1994) Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA* **91**:7355–7359.
- Kliwer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
- Knouff C and Auwerx J (2004) Peroxisome proliferator-activated receptor-gamma calls for activation in moderation: lessons from genetics and pharmacology. *Endocr Rev* **25**:899–918.
- Koutnikova H, Cock TA, Watanabe M, Houten SM, Champy MF, Dierich A, and Auwerx J (2003) Compensation by the muscle limits the metabolic consequences of lipodystrophy in PPAR gamma hypomorphic mice. *Proc Natl Acad Sci USA* **100**:14457–14462.
- Kubota N, Terauchi Y, Miki H, Tamemoto H, Yamauchi T, Komada K, Satoh S, Nakano R, Ishii K, Sugiyama T, et al. (1999) PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. *Mol Cell* **4**:597–609.
- Laudet V (1997) Evolution of the nuclear receptor superfamily: early diversification from an ancestral orphan receptor. *J Mol Endocrinol* **19**:207–226.

- Lefebvre P, Chinetti G, Fruchart JC, and Staels B (2006) Sorting out the roles of PPAR alpha in energy metabolism and vascular homeostasis. *J Clin Invest* **116**:571–580.
- Leibowitz MD, Fievet C, Hennuyer N, Peinado-Onsurbe J, Duez H, Bergera J, Cullinan CA, Sparrow CP, Baffic J, Berger GD, et al. (2000) Activation of PPAR delta alters lipid metabolism in db/db mice. *FEBS Lett* **473**:333–336.
- Letavernier E, Perez J, Joye E, Bellocq A, Fouqueray B, Haymann JP, Heudes D, Wahli W, Desvergne B, and Baud L (2005) Peroxisome proliferator-activated receptor beta/delta exerts a strong protection from ischemic acute renal failure. *J Am Soc Nephrol* **16**:2395–2402.
- Li AC, Brown KK, Silvestre MJ, Willson TM, Palinski W, and Glass CK (2000) Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* **106**:523–531.
- Luquet S, Lopez-Soriano J, Holst D, Fredenrich A, Melki J, Rassoulzadegan M, and Grimaldi PA (2003) Peroxisome proliferator-activated receptor delta controls muscle development and oxidative capability. *FASEB J* **17**:2299–2301.
- Mandard S, Muller M, and Kersten S (2004) Peroxisome proliferator-activated receptor alpha target genes. *Cell Mol Life Sci* **61**:393–416.
- Marx N, Duez H, Fruchart JC, and Staels B (2004) Peroxisome proliferator-activated receptors and atherogenesis: regulators of gene expression in vascular cells. *Circ Res* **94**:1168–1178.
- Mayerson AB, Hundal RS, Dufour S, Lebon V, Befroy D, Cline GW, Enochsson S, Inzucchi SE, Shulman GI, and Petersen KF (2002) The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* **51**:797–802.
- McKenna NJ and O'Malley BW (2002) Combinatorial control of gene expression by nuclear receptors and coregulators. *Cell* **108**:465–474.
- Michalik L, Desvergne B, Tan NS, Basu-Modak S, Escher P, Rieusset J, Peters JM, Kaya G, Gonzalez FJ, Zakany J, et al. (2001) Impaired skin wound healing in peroxisome proliferator-activated receptor (PPAR)alpha and PPARbeta mutant mice. *J Cell Biol* **154**:799–814.
- Michalik L, Desvergne B, and Wahli W (2004) Peroxisome-proliferator-activated receptors and cancers: complex stories. *Nat Rev Cancer* **4**:61–70.
- Michalik L and Wahli W (2006) Involvement of PPAR nuclear receptors in tissue injury and wound repair. *J Clin Invest* **116**:598–606.
- Muio DM, MacLean PS, Lang DB, Li S, Houmard JA, Way JM, Winegar DA, Corton JC, Dohm GL, and Kraus WE (2002) Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) alpha knock-out mice. Evidence for compensatory regulation by PPAR delta. *J Biol Chem* **277**:26089–26097.
- Nadra K, Anghel SI, Joye E, Tan NS, Basu-Modak S, Trono D, Wahli W, and Desvergne B (2006) Differentiation of trophoblast giant cells and their metabolic functions are dependent on peroxisome proliferator-activated receptor beta/delta. *Mol Cell Biol* **26**:3266–3281.
- Nagy L and Schwabe JW (2004) Mechanism of the nuclear receptor molecular switch. *Trends Biochem Sci* **29**:317–324.
- Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, and Milburn MV (1998) Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. *Nature (Lond)* **395**:137–143.
- Nuclear Receptors Nomenclature Committee (1999) A unified nomenclature system for the nuclear receptor superfamily. *Cell* **97**:161–163.
- Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznajdman ML, Lambert MH, et al. (2001) A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci USA* **98**:5306–5311.
- Peters JM, Cheung C, and Gonzalez FJ (2005) Peroxisome proliferator-activated receptor-alpha and liver cancer: where do we stand? *J Mol Med* **83**:774–785.
- Peters JM, Lee SS, Li W, Ward JM, Gavrilova O, Everett C, Reitman ML, Hudson LD, and Gonzalez FJ (2000) Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor beta(delta). *Mol Cell Biol* **20**:5119–5128.
- Pfutzner A, Marx N, Lubben G, Langenfeld M, Walcher D, Konrad T, and Forst T (2005) Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. *J Am Coll Cardiol* **45**:1925–1931.
- Plutzky J (2000a) Emerging concepts in metabolic abnormalities associated with coronary artery disease. *Curr Opin Cardiol* **15**:416–421.
- Plutzky J (2000b) Peroxisome proliferator-activated receptors in vascular biology and atherosclerosis: emerging insights for evolving paradigms. *Curr Atheroscler Rep* **2**:327–335.
- Plutzky J (2003) Peroxisome proliferator-activated receptors as therapeutic targets in inflammation. *J Am Coll Cardiol* **42**:1764–1766.
- Rangwala SM and Lazar MA (2004) Peroxisome proliferator-activated receptor gamma in diabetes and metabolism. *Trends Pharmacol Sci* **25**:331–336.
- Reddy JK and Hashimoto T (2001) Peroxisomal beta-oxidation and peroxisome proliferator-activated receptor alpha: an adaptive metabolic system. *Annu Rev Nutr* **21**:193–230.
- Ricote M, Li AC, Willson TM, Kelly CJ, and Glass CK (1998) The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature (Lond)* **391**:79–82.
- Rieusset J, Touri F, Michalik L, Escher P, Desvergne B, Niesor E, and Wahli W (2002) A new selective peroxisome proliferator-activated receptor gamma antagonist with antiobesity and antidiabetic activity. *Mol Endocrinol* **16**:2628–2644.
- Rosen ED, Sarraf P, Troy AE, Bradwin G, Moore K, Milstone DS, Spiegelman BM, and Mortensen RM (1999) PPAR gamma is required for the differentiation of adipose tissue in vivo and in vitro. *Mol Cell* **4**:611–617.
- Rosen ED, Walkey CJ, Puigserver P, and Spiegelman BM (2000) Transcriptional regulation of adipogenesis. *Genes Dev* **14**:1293–1307.
- Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, Faas FH, and Anderson JW (2002) Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* **162**:2597–2604.
- Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, Williams RL, Umpleby AM, Thomas EL, Bell JD, et al. (2003) Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-gamma. *Diabetes* **52**:910–917.
- Schmidt A, Endo N, Rutledge SJ, Vogel R, Shinar D, and Rodan GA (1992) Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids. *Mol Endocrinol* **6**:1634–1641.
- Seemple RK, Chatterjee VK, and O'Rahilly S (2006) PPAR gamma and human metabolic disease. *J Clin Invest* **116**:581–589.
- Staels B (2005) Fluid retention mediated by renal PPARgamma. *Cell Metab* **2**:77–78.
- Staels B and Fruchart JC (2005) Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* **54**:2460–2470.
- Staels B, Koenig W, Habib A, Merval R, Lebreit M, Torra IP, Delerive P, Fadel A, Chinetti G, Fruchart JC, et al. (1998) Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. *Nature (Lond)* **393**:790–793.
- Staels B, Vu-Dac N, Kosykh VA, Saladin R, Fruchart JC, Dallongeville J, and Auwerx J (1995) Fibrates downregulate apolipoprotein C-III expression independent of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism for the hypolipidemic action of fibrates. *J Clin Invest* **95**:705–712.
- Stanley TB, Leesnitzer LM, Montana VG, Galardi CM, Lambert MH, Holt JA, Xu HE, Moore LB, Blanchard SG, and Stimmel JB (2003) Subtype specific effects of peroxisome proliferator-activated receptor ligands on corepressor affinity. *Biochemistry* **42**:9278–9287.
- Steiner DR, Gonzalez NC, and Wood JG (2001) Leukotriene B(4) promotes reactive oxidant generation and leukocyte adherence during acute hypoxia. *J Appl Physiol* **91**:1160–1167.
- Tan NS, Michalik L, Desvergne B, and Wahli W (2004) Peroxisome proliferator-activated receptor-beta as a target for wound healing drugs. *Expert Opin Ther Targets* **8**:39–48.
- Tan NS, Michalik L, Noy N, Yasmin R, Pacot C, Heim M, Fluhmann B, Desvergne B, and Wahli W (2001) Critical roles of PPARbeta/delta in keratinocyte response to inflammation. *Genes Dev* **15**:3263–3277.
- Tanaka T, Yamamoto J, Iwasaki S, Asaba H, Hamura H, Ikeda Y, Watanabe M, Magoori K, Ioka RX, Tachibana K, et al. (2003) Activation of peroxisome proliferator-activated receptor delta induces fatty acid beta-oxidation in skeletal muscle and attenuates metabolic syndrome. *Proc Natl Acad Sci USA* **100**:15924–15929.
- Tenenbaum A, Motro M, and Fisman EZ (2005) Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. *Cardiovasc Diabetol* **4**:14.
- Tontonoz P, Graves RA, Budavari AI, Erdjument-Bromage H, Lui M, Hu E, Tempst P, and Spiegelman BM (1994a) Adipocyte-specific transcription factor ARF6 is a heterodimeric complex of two nuclear hormone receptors, PPAR gamma and RXR alpha. *Nucleic Acids Res* **22**:5628–5634.
- Tontonoz P, Hu E, Graves RA, Budavari AI, and Spiegelman BM (1994b) mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev* **8**:1224–1234.
- Tontonoz P, Kim JB, Graves RA, and Spiegelman BM (1993) ADD1: a novel helix-loop-helix transcription factor associated with adipocyte determination and differentiation. *Mol Cell Biol* **13**:4753–4759.
- Tugwood JD, Issemann I, Anderson RG, Bundell KR, McPheat WL, and Green S (1992) The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene. *EMBO (Eur Mol Biol Organ)* **11**:433–439.
- Uppenberg J, Svensson C, Jaki M, Bertilsson G, Jendeborg L, and Berkenstam A (1998) Crystal structure of the ligand binding domain of the human nuclear receptor PPARgamma. *J Biol Chem* **273**:31108–31112.
- Varnat F, Bordier-ten Heggeler B, Grisel P, Bouquard N, Corthésy-Theulaz I, Wahli W, and Desvergne B (2006) PPAR beta/delta regulates Paneth cell differentiation via controlling the Hedgehog signaling pathway. *Gastroenterology* **131**:538–553.
- Vu-Dac N, Schoonjans K, Kosykh V, Dallongeville J, Fruchart JC, Staels B, and Auwerx J (1995) Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. *J Clin Invest* **96**:741–750.
- Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, and Evans RM (2003) Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell* **113**:159–170.
- Wu Z, Rosen ED, Brun R, Hauser S, Adelmant G, Troy AE, McKeon C, Darlington GJ, and Spiegelman BM (1999) Cross-regulation of C/EBP alpha and PPAR gamma controls the transcriptional pathway of adipogenesis and insulin sensitivity. *Mol Cell* **3**:151–158.
- Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, et al. (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell* **3**:397–403.
- Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Klierer SA, Gampe RT Jr, McKee DD, et al. (2001) Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA* **98**:13919–13924.
- Yu C, Markan K, Temple KA, Deplewski D, Brady MJ, and Cohen RN (2005) The nuclear receptor corepressors NCoR and SMRT decrease peroxisome proliferator-activated receptor gamma transcriptional activity and repress 3T3-L1 adipogenesis. *J Biol Chem* **280**:13600–13605.
- Zhu Y, Qi C, Korenberg JR, Chen XN, Noya D, Rao MS, and Reddy JK (1995) Structural organization of mouse peroxisome proliferator-activated receptor gamma (mPPAR gamma) gene: alternative promoter use and different splicing yield two mPPAR gamma isoforms. *Proc Natl Acad Sci USA* **92**:7921–7925.
- Ziouzenkova O, Perrey S, Asatryan L, Hwang J, MacNaul KL, Moller DE, Rader DJ, Sevastian A, Zechner R, Hoefler G, et al. (2003) Lipolysis of triglyceride-rich lipoproteins generates PPAR ligands: evidence for an antiinflammatory role for lipoprotein lipase. *Proc Natl Acad Sci USA* **100**:2730–2735.

TABLE 1
PPAR α

Receptor nomenclature	NR1C1
Receptor code	4.10.1:FA:1:C1
Molecular information	Hs: 468aa, Q07869, chr. 22q13.31 ¹ Rn: 468aa, P37230, chr. 7q34 ² Mm: 468aa, P23204, chr. 15 E2 ³
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AACTAGGNCA A AGGTCA (DR-1, DR-2)
Partners	RXR (physical, functional) DNA binding ⁴
Agonists	GW409544 (8.7), LY-518674 (7.6), LY-510929 (7.55), TZD18 (7.55), LTB4 (7), oleylethanolamide (6.92), LY-465608 (6.8), pirinixic acid (6.22), fatty acids (6), ragaglitazar (6), AD-5061 (5.55), fenofibric acid (4.46) [pIC ₅₀] ⁵⁻²² ; GW7647 (8.22), GW9578 (7.3), TAK-559 (7.17), KRP-297/MK-0767 (6.8), eicosatetraenoic acid (6.7), farglitazar (6.35), reglitazar (5.72), DRF 2519 (~5), pristanic acid (4.4), bezafibrate (4.3), clofibrate (4.25) [pEC ₅₀] ^{6,13,14,18,23-33} , KRP-297/MK-0767 (7.64), 8S-HETE (7), GW2331 (6.8), NS-220* (6.73), [³ H]AD-5061* (5.5) [pK _d] ^{9,17,18,34-38} ; pterostilbene, tetradecylglycidic acid, orthylthiopropionic acid ^{39,40}
Antagonists	MK886 (4.6) [pIC ₅₀] ⁴¹
Coactivators	PPARBP, NCOA6, BFE, CREBBP, CITED2, NCOA1, NCOA3, SWI2/SNF2, PGC-1 α , PPARGC1B ⁴²⁻⁵²
Corepressors	NRIP1, NCOR1 ^{39,53-57}
Biologically important isoforms	PPAR α (Hs, Mm, Rn): encoded by eight exons ^{1-3,58} ; PPAR α tr (truncated) (Hs): lacks exon 6, truncated protein lacking part of hinge region and LBD, dominant-negative, 20–50% of total PPAR α mRNA, not detected in rodents ⁵⁹
Tissue distribution	Very active peroxisomal β -oxidation tissues; liver, brown fat, kidney, heart, skeletal muscle, large intestine (Hs, Mm, Rn) [Northern blot, Q-PCR, in situ hybridization, immunohistology] ³⁹
Main target genes	Activated: liver fatty acid binding protein ^{39,60} , Acyl-CoA oxidase (Rn) ^{61,62} , bifunctional enzyme (Rn) ⁶¹ , CPTI (Hs) ⁶³⁻⁶⁵ , MCAD (Rn) ⁶⁶ , FIAF (Mm) ⁶⁷ , FATP (Mm) ⁶⁸ , apolipoprotein A-II (Mm) ⁶⁹ , G0/G1 switch gene 2 (G0S2) (Mm) ⁷⁰
Mutant phenotype	Hypothermia and hypoglycemia upon fasting, reduced insulin resistance, prolonged inflammatory reaction, transient delay in skin healing, resistance to fibrate-induced cancer (Mm) [knockout] ^{7,71-76} ; overexpression in the heart leads to cardiac insulin resistance associated with defects in insulin signaling and STAT3 activity, reduced heart function (Mm) [transgenesis] ^{77,78} ; overexpression in muscle leads to the development of glucose intolerance, increased fatty acid oxidation rates, reduced AMP-activated protein kinase activity, reduced insulin-stimulated glucose uptake, repression of GLUT4 gene (Mm) [transgenesis] ⁷⁹ ; PPAR α Δ 13: dominant-negative mutant results in transient-impaired wound-healing and impaired inflammatory phase (Mm) [transgenesis] ⁸⁰
Human disease	Arteriosclerosis ^{81,82}

aa, amino acids; chr., chromosome; HRE, hormone response element; HETE, hydroxyeicosatetraenoic acid; Q-PCR, quantitative polymerase chain reaction; FIAF, fasting-induced adipose factor; BFE, bifunctional enzyme; CREBBP, cAMP response element binding protein binding protein; CPTII, carnitine palmitoyl transferase; MCAD, medium-chain acyl-CoA dehydrogenase; FATP, fatty acid transport protein.

* Radioligand.

- Sher T, Yi HF, McBride OW, and Gonzalez FJ (1993) cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor. *Biochemistry* **32**:5598–5604.
- Gottlicher M, Widmark E, Li Q, and Gustafsson JA (1992) Fatty acids activate a chimera of the clofibrate acid-activated receptor and the glucocorticoid receptor. *Proc Natl Acad Sci USA* **89**:4653–4657.
- Issemann I and Green S (1990) Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature (Lond)* **347**:645–650.
- Kliwer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
- Brooks DA, Etgen GJ, Rito CJ, Shuker AJ, Dominianni SJ, Warshawsky AM, Ardecky R, Paterniti JR, Tyhonas J, Karanewsky DS, et al. (2001) Design and synthesis of 2-methyl-2-[4-(2-[5-methyl-2-aryloxazol-4-yl]ethoxy)phenoxy]propionic acids: a new class of dual PPAR α /gamma agonists. *J Med Chem* **44**:2061–2064.
- Brown PJ, Stuart LW, Hurley KP, Lewis MC, Winegar DA, Wilson JG, Wilkison WO, Ittoop OR, and Wilson TM (2001) Identification of a subtype selective human PPAR α agonist through parallel-array synthesis. *Bioorg Med Chem Lett* **11**:1225–1227.
- Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, and Wahli W (1996) The PPAR α -leukotriene B4 pathway to inflammation control. *Nature (Lond)* **384**:39–43.
- Ebdrup S, Pettersson I, Rasmussen HB, Deussen HJ, Frost Jensen A, Mortensen SB, Fleckner J, Pridal L, Nygaard L, and Sauerberg P (2003) Synthesis and biological and structural characterization of the dual-acting peroxisome proliferator-activated receptor alpha/gamma agonist ragaglitazar. *J Med Chem* **46**:1306–1317.
- Forman BM, Chen J, and Evans RM (1997) Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. *Proc Natl Acad Sci USA* **94**:4312–4317.
- Fu J, Gaetani S, Oveisi F, Lo Verme J, Serrano A, Rodriguez De Fonseca F, Rosengarth A, Luecke H, Di Giacomo B, et al. (2003) Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. *Nature (Lond)* **42**:90–93.
- Fu J, Oveisi F, Gaetani S, Lin E, and Piomelli D (2005) Oleylethanolamide, an endogenous PPAR-alpha agonist, lowers body weight and hyperlipidemia in obese rats. *Neuropharmacology* **48**:1147–1153.
- Guo Q, Sahoo SP, Wang PR, Milot DP, Ippolito MC, Wu MS, Baffic J, Biswas C, Hernandez M, Lam MH, et al. (2004) A novel peroxisome proliferator-activated receptor alpha/gamma dual agonist demonstrates favorable effects on lipid homeostasis. *Endocrinology* **145**:1640–1648.
- Henke BR (2004) Peroxisome proliferator-activated receptor alpha/gamma dual agonists for the treatment of type 2 diabetes. *J Med Chem* **47**:4118–4127.
- Inoue I, Itoh F, Aoyagi S, Tazawa S, Kusama H, Akahane M, Mastunaga T, Hayashi K, Awata T, Komoda T, et al. (2002) Fibrate and statin synergistically increase the transcriptional activities of PPAR α /RXR α and decrease the transactivation of NF κ B. *Biochem Biophys Res Commun* **290**:131–139.
- Krey G, Braissant O, L'Horsset F, Kalkhoven E, Perroud M, Parker MG, and Wahli W (1997) Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Mol Endocrinol* **11**:779–791.
- Liu K, Xu L, Berger JP, Macnaul KL, Zhou G, Doeberer TW, Forrest MJ, Moller DE, and Jones AB (2005) Discovery of a novel series of peroxisome proliferator-activated receptor alpha/gamma dual agonists for the treatment of type 2 diabetes and dyslipidemia. *J Med Chem* **48**:2262–2265.
- Sakamoto J, Kimura H, Moriyama S, Odaka H, Momose Y, Sugiyama Y, and Sawada H (2000) Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun* **278**:704–711. subtypes by pioglitazone. *Biochem Biophys Res Commun* **278**:704–711.

18. Sakamoto J, Kimura H, Moriyama S, Imoto H, Momose Y, Odaka H, and Sawada H (2004) A novel oxyiminoalkanoic acid derivative, TAK-559, activates human peroxisome proliferator-activated receptor subtypes. *Eur J Pharmacol* **495**:17–26.
19. Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, et al. (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell* **3**:397–403.
20. Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Klierer SA, Gampe RT Jr, McKee DD, et al. (2001) Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA* **98**:13919–13924.
21. Xu Y, Mayhugh D, Saeed A, Wang X, Thompson RC, Dominianni SJ, Kauffman RF, Singh J, Bean JS, Bensch WR, et al. (2003) Design and synthesis of a potent and selective triazolone-based peroxisome proliferator-activated receptor alpha agonist. *J Med Chem* **46**:5121–5124.
22. Xu Y, Rito CJ, Etgen GJ, Ardecky RJ, Bean JS, Bensch WR, Bosley JR, Broderick CL, Brooks DA, Dominianni SJ, et al. (2004) Design and synthesis of alpha-aryloxy-alpha-methylhydrocinnamic acids: a novel class of dual peroxisome proliferator-activated receptor alpha/gamma agonists. *J Med Chem* **47**:2422–2425.
23. Brown KK, Henke BR, Blanchard SG, Cobb JE, Mook R, Kaldor I, Klierer SA, Lehmann JM, Lenhard JM, Harrington WW, et al. (1999) A novel N-aryl tyrosine activator of peroxisome proliferator-activated receptor-gamma reverses the diabetic phenotype of the Zucker diabetic fatty rat. *Diabetes* **48**:1415–1424.
24. Brown PJ, Winegar DA, Plunket KD, Moore LB, Lewis MC, Wilson JG, Sundseth SS, Koble CS, Wu Z, Chapman JM, et al. (1999) A ureido-thioisobutyric acid (GW9578) is a subtype-selective PPARalpha agonist with potent lipid-lowering activity. *J Med Chem* **42**:3785–3788.
25. Chakrabarti R, Misra P, Vikramadithyan RK, Premkumar M, Hiriyan J, Datla SR, Damarla RK, Suresh J, and Rajagopalan R (2004) Antidiabetic and hypolipidemic potential of DRF 2519—a dual activator of PPAR-alpha and PPAR-gamma. *Eur J Pharmacol* **491**:195–206.
26. Doebber TW, Kelly LJ, Zhou G, Meurer R, Biswas C, Li Y, Wu MS, Ippolito MC, Chao YS, Wang PR, et al. (2004) MK-0767, a novel dual PPARalpha/gamma agonist, displays robust antihyperglycemic and hypolipidemic activities. *Biochem Biophys Res Commun* **318**:323–328.
27. Henke BR, Blanchard SG, Brackeen MF, Brown KK, Cobb JE, Collins JL, Harrington WW Jr, Hashim MA, Hull-Ryde EA, Kaldor I, et al. (1998) N-(2-Benzoylphenyl)-L-tyrosine PPARgamma agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents. *J Med Chem* **41**:5020–5036.
28. Heppner TJ, Bonev AD, Eckman DM, Gomez MF, Petkov GV, and Nelson MT (2005) Novel PPARgamma agonists GI 262570, GW 7845, GW 1929, and pioglitazone decrease calcium channel function and myogenic tone in rat mesenteric arteries. *Pharmacology* **73**:15–22.
29. Keller H, Dreyer C, Medin J, Mahfoudi A, Ozato K, and Wahli W (1993) Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. *Proc Natl Acad Sci USA* **90**:2160–2164.
30. Keller H, Devchand PR, Perroud M, and Wahli W (1997) PPAR alpha structure-function relationships derived from species-specific differences in responsiveness to hypolipidemic agents. *Biol Chem* **378**:651–655.
31. Shibata T, Matsui K, Nagao K, Shinkai H, Yonemori F, and Wakitani K (1999) Pharmacological profiles of a novel oral antidiabetic agent, JTT-501, an isoxazolinedione derivative. *Eur J Pharmacol* **364**:211–219.
32. Willson TM, Brown PJ, Sternbach DD, and Henke BR (2000) The PPARs: from orphan receptors to drug discovery. *J Med Chem* **43**:527–550.
33. Zomer AW, van Der Burg B, Jansen GA, Wanders RJ, Poll-The BT, and van Der Saag PT (2000) Pristanic acid and phytanic acid: naturally occurring ligands for the nuclear receptor peroxisome proliferator-activated receptor alpha. *J Lipid Res* **41**:1801–1807.
34. Klierer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, et al. (1997) Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. *Proc Natl Acad Sci USA* **94**:4318–4323.
35. Kuwabara K, Murakami K, Todo M, Aoki T, Asaki T, Murai M, and Yano J (2004) A novel selective peroxisome proliferator-activated receptor alpha agonist, 2-methyl-c-5-[4-[5-methyl-2-(4-methylphenyl)-4-oxazolyl]butyl]-1,3-dioxane-r-2-carboxylic acid (NS-220), potently decreases plasma triglyceride and glucose levels and modifies lipoprotein profiles in KK-Ay mice. *J Pharmacol Exp Ther* **30**:970–977.
36. Murakami K, Tobe K, Ide T, Mochizuki T, Ohashi M, Akanuma Y, Yazaki Y, and Kadowaki T (1998) A novel insulin sensitizer acts as a coligand for peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and PPAR-gamma: effect of PPAR-alpha activation on abnormal lipid metabolism in liver of Zucker fatty rats. *Diabetes* **47**:1841–1847.
37. Murakami K, Ide T, Suzuki M, Mochizuki T, and Kadowaki T (1999) Evidence for direct binding of fatty acids and eicosanoids to human peroxisome proliferator-activated receptor alpha. *Biochem Biophys Res Commun* **260**:609–613.
38. Yu K, Bayona W, Kallen CB, Harding HP, Ravera CP, McMahon G, Brown M, and Lazar MA (1995) Differential activation of peroxisome proliferator-activated receptors by eicosanoids. *J Biol Chem* **270**:23975–23983.
39. Desvergne B and Wahli W (1999) Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* **20**:649–688.
40. Rimando AM, Nagmani R, Feller DR, and Yokoyama W (2005) Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. *J Agric Food Chem* **53**:3403–3407.
41. Kehrer JP, Biswal SS, La E, Thuillier P, Datta K, Fischer SM, and Vanden Heuvel JP (2001) Inhibition of peroxisome-proliferator-activated receptor (PPAR)alpha by MK886. *Biochem J* **356**:899–906.
42. Caira F, Antonson P, Peltto-Huikko M, Treuter E, and Gustafsson JA (2000) Cloning and characterization of RAP250, a novel nuclear receptor coactivator. *J Biol Chem* **275**:5308–5317.
43. Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevriy DJ, and Leid M (1997) p300 functions as a coactivator for the peroxisome proliferator-activated receptor alpha. *J Biol Chem* **272**:33435–33443.
44. Juge-Aubry CE, Kuenzli S, Sanchez JC, Hochstrasser D, and Meier CA (2001) Peroxisomal bifunctional enzyme binds and activates the activation function-1 region of the peroxisome proliferator-activated receptor alpha. *Biochem J* **353**:253–258.
45. Molnar F, Matilainen M, and Carlberg C (2005) Structural determinants of the agonist-independent association of human peroxisome proliferator-activated receptors with coactivators. *J Biol Chem* **280**:26543–26556.
46. Surapureddi S, Yu S, Bu H, Hashimoto T, Yeldandi AV, Kashireddy P, Cherkaoui-Malki M, Qi C, Zhu YJ, Rao MS, et al. (2002) Identification of a transcriptionally active peroxisome proliferator-activated receptor alpha-interacting cofactor complex in rat liver and characterization of PRIC285 as a coactivator. *Proc Natl Acad Sci USA* **99**:11836–11841.
47. Tien ES, Davis JW, and Vanden Heuvel JP (2004) Identification of the CREB-binding protein/p300-interacting protein CITED2 as a peroxisome proliferator-activated receptor alpha coregulator. *J Biol Chem* **279**:24053–24063.
48. Vega RB, Huss JM, and Kelly DP (2000) The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. *Mol Cell Biol* **20**:1868–1876.
49. Zhou G, Cummings R, Li Y, Mitra S, Wilkinson HA, Elbrecht A, Hermes JD, Schaeffer JM, Smith RG, and Moller DE (1998) Nuclear receptors have distinct affinities for coactivators: characterization by fluorescence resonance energy transfer. *Mol Endocrinol* **12**:1594–1604.
50. Zhu Y, Qi C, Calandra C, Rao MS, and Reddy JK (1996) Cloning and identification of mouse steroid receptor coactivator-1 (mSRC-1), as a coactivator of peroxisome proliferator-activated receptor gamma. *Gene Expr* **6**:185–195.
51. Zhu Y, Qi C, Jain S, Rao MS, and Reddy JK (1997) Isolation and characterization of PBP, a protein that interacts with peroxisome proliferator-activated receptor. *J Biol Chem* **272**:25500–25506.
52. Zhu Y, Kan L, Qi C, Kanwar YS, Yeldandi AV, Rao MS, and Reddy JK (2000) Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR. *J Biol Chem* **275**:13510–13516.
53. DiRenzo J, Soderstrom M, Kurokawa R, Ogliastrro MH, Ricote M, Ingrey S, Horlein A, Rosenfeld MG, and Glass CK (1997) Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors. *Mol Cell Biol* **17**:2166–2176.
54. Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevriy DJ, and Leid M (1999) Identification of nuclear receptor corepressor as a peroxisome proliferator-activated receptor alpha interacting protein. *J Biol Chem* **274**:15901–15907.
55. Joyeux A, Cavaillès V, Balaguer P, and Nicolas JC (1997) RIP 140 enhances nuclear receptor-dependent transcription in vivo in yeast. *Mol Endocrinol* **11**:193–202.
56. Miyata KS, McCaw SE, Meertens LM, Patel HV, Rachubinski RA, and Capone JP (1998) Receptor-interacting protein 140 interacts with and inhibits transactivation by peroxisome proliferator-activated receptor alpha and liver-X-receptor alpha. *Mol Cell Endocrinol* **146**:69–76.
57. Yan ZH, Karam WG, Staudinger JL, Medvedev A, Ghanayem BI, and Jetten AM (1998) Regulation of peroxisome proliferator-activated receptor alpha-induced transactivation by the nuclear orphan receptor TAK1/TR4. *J Biol Chem* **273**:10948–10957.
58. Gearing KL, Crickmore A, and Gustafsson JA (1994) Structure of the mouse peroxisome proliferator activated receptor alpha gene. *Biochem Biophys Res Commun* **199**:255–263.
59. Gervois P, Torra IP, Chinetti G, Grotzinger T, Dubois G, Fruchart JC, Fruchart-Najib J, Leitersdorf E, and Staels B (1999) A truncated human peroxisome proliferator-activated receptor alpha splice variant with dominant negative activity. *Mol Endocrinol* **13**:1535–1549.
60. Issemann I, Prince R, Tugwood J, and Green S (1992) A role for fatty acids and liver fatty acid binding protein in peroxisome proliferation? *Biochem Soc Trans* **20**:824–827.
61. Marcus SL, Miyata KS, Zhang B, Subramani S, Rachubinski RA, and Capone JP (1993) Diverse peroxisome proliferator-activated receptors bind to the peroxisome proliferator-responsive elements of the rat hydratase/dehydrogenase and fatty acyl-CoA oxidase genes but differentially induce expression. *Proc Natl Acad Sci USA* **90**:5723–5727.

62. Tugwood JD, Issemann I, Anderson RG, Bundell KR, McPheat WL, and Green S (1992) The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene. *EMBO (Eur Mol Biol Organ) J* **11**:433–439.
63. Brandt JM, Djouadi F, and Kelly DP (1998) Fatty acids activate transcription of the muscle carnitine palmitoyltransferase I gene in cardiac myocytes via the peroxisome proliferator-activated receptor alpha. *J Biol Chem* **273**:23786–23792.
64. Mascaro C, Acosta E, Ortiz JA, Marrero PF, Hegardt FG, and Haro D (1998) Control of human muscle-type carnitine palmitoyltransferase I gene transcription by peroxisome proliferator-activated receptor. *J Biol Chem* **273**:8560–8563.
65. Yu GS, Lu YC, and Gulick T (1998) Co-regulation of tissue-specific alternative human carnitine palmitoyltransferase Ibeta gene promoters by fatty acid enzyme substrate. *J Biol Chem* **273**:32901–32909.
66. Gulick T, Cresci S, Caira T, Moore DD, and Kelly DP (1994) The peroxisome proliferator-activated receptor regulates mitochondrial fatty acid oxidative enzyme gene expression. *Proc Natl Acad Sci USA* **91**:11012–11016.
67. Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, Gonzalez FJ, Desvergne B, and Wahli W (2000) Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene. *J Biol Chem* **275**:28488–28493.
68. Frohnert BI, Hui TY, and Bernlohr DA (1999) Identification of a functional peroxisome proliferator-responsive element in the murine fatty acid transport protein gene. *J Biol Chem* **274**:3970–3977.
69. Vu-Dac N, Schoonjans K, Kosykh V, Dallongeville J, Fruchart JC, Staels B, and Auwerx J (1995) Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. *J Clin Invest* **96**:741–750.
70. Zandbergen F, Mandard S, Escher P, Tan NS, Patsouris D, Jatkoa T, Rojas-Caro S, Madore S, Wahli W, Tafuri S, et al. (2005) The G0/G1 switch gene 2 is a novel PPAR target gene. *Biochem J* **392**:313–324.
71. Guerre-Millo M, Rouault C, Poulain P, Andre J, Poitout V, Peters JM, Gonzalez FJ, Fruchart JC, Reach G, and Staels B (2001) PPAR-alpha-null mice are protected from high-fat diet-induced insulin resistance. *Diabetes* **50**:2809–2814.
72. Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, and Wahli W (1999) Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. *J Clin Invest* **103**:1489–1498.
73. Lee SS, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H, and Gonzalez FJ (1995) Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. *Mol Cell Biol* **15**:3012–3022.
74. Leone TC, Weinheimer CJ, and Kelly DP (1999) A critical role for the peroxisome proliferator-activated receptor alpha (PPARalpha) in the cellular fasting response: the PPARalpha-null mouse as a model of fatty acid oxidation disorders. *Proc Natl Acad Sci USA* **96**:7473–7478.
75. Michalik L, Desvergne B, Tan NS, Basu-Modak S, Escher P, Rieusset J, Peters JM, Kaya G, Gonzalez FJ, Zakany J, et al. (2001) Impaired skin wound healing in peroxisome proliferator-activated receptor (PPAR)alpha and PPARbeta mutant mice. *J Cell Biol* **154**:799–814.
76. Patel DD, Knight BL, Wiggins D, Humphreys SM, and Gibbons GF (2001) Disturbances in the normal regulation of SREBP-sensitive genes in PPAR alpha-deficient mice. *J Lipid Res* **42**:328–337.
77. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak R, Lopaschuk GD, et al. (2002) The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest* **109**:121–130.
78. Park SY, Cho YR, Finck BN, Kim HJ, Higashimori T, Hong EG, Lee MK, Danton C, Deshmukh S, Cline GW, et al. (2005) Cardiac-specific overexpression of peroxisome proliferator-activated receptor-alpha causes insulin resistance in heart and liver. *Diabetes* **54**:2514–2524.
79. Finck BN, Bernal-Mizrachi C, Han DH, Coleman T, Sambandam N, LaRiviere LL, Holloszy JO, Semenkovich CF, and Kelly DP (2005) A potential link between muscle peroxisome proliferator-activated receptor-alpha signaling and obesity-related diabetes. *Cell Metab* **1**:133–144.
80. Michalik L, Feige JN, Gelman L, Pedrazzini T, Keller H, Desvergne B, and Wahli W (2005) Selective expression of a dominant negative form of PPAR in keratinocytes leads to impaired epidermal healing. *Mol Endocrinol* **19**:2335–2348.
81. Kersten S, Desvergne B, and Wahli W (2000) Roles of PPARs in health and disease. *Nature (Lond)* **405**:421–424.
82. Kockx M, Gervois PP, Poulain P, Derudas B, Peters JM, Gonzalez FJ, Princen HM, Kooistra T, and Staels B (1999) Fibrates suppress fibrinogen gene expression in rodents via activation of the peroxisome proliferator-activated receptor-alpha. *Blood* **93**:2991–2998.

TABLE 2
PPAR β

Receptor nomenclature	NR1C2
Receptor code	4.10.1.FA:1:C2
Other names	PPAR β , PPAR δ , NUC1, FAAR
Molecular information	Hs: 441aa, Q03181, chr. 6p21.2–p21.1 ¹ Rn: 440aa, Q62879, chr. 20p12 ² Mm: 440aa, P35396, chr. 17 A3.3 ³
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AACTAGGNCA A AGGTCA (DR-1)
Partners	RXR (physical, functional) DNA binding ⁴
Agonists	GW0742X (7.52), GW2433 (6.57), GW9578 (5.9) [pEC ₅₀] ^{5–8} ; GW0742 (9), fatty acids (5.2) [pIC ₅₀] ^{9,10} ; L-783483* (9), GW501516 (8.96), retinoic acid (7.77) [pK _d] ^{9,11–13} ; L-796449 (8.7), L-165461 (8.52), L-165041 (8.22) [pK _i] ^{8,11,14}
Coactivators	NCOA1, NCOA3, NCOA6, PGC-1 α ^{15–18}
Corepressors	NCOR1, NCOR2 ^{19–22}
Biologically important isoforms	PPAR β (Hs, Mm, Rn): partial organization of the gene with six exons in <i>Xenopus</i> related so far ^{1–3,23}
Tissue distribution	Ubiquitous {Hs} [Northern blot, Q-PCR] ²⁴
Functional assays	Adipogenesis assay using 3T3-C2 fibroblasts {Mm} ²⁵
Main target genes	Activated: ILK {Mm} ²⁶ , PDK1 {Mm} ²⁶ , DFF45 {Mm} ²⁷ , FIAF {Hs} ²⁸ ; repressed: PTEN {Mm} ²⁶
Mutant phenotype	Overexpression in C2C12 myoblasts participates in their transdifferentiation into adipocytes {Mm} [retroviral infection] ²⁹ ; overexpression of constitutively active PPAR β -VP16 fusion protein in white adipose tissue triggers fatty acid mobilization and oxidation leading to mass reduction {Mm} [transgenesis] ¹⁸ ; overexpression in skeletal muscle provokes a shift toward more oxidative fibers and general decrease of body fat content {Mm} [transgenesis] ³⁰ ; knockout mice exhibit decreased amount of brown and white adipose tissues, enhanced sensitivity to skin carcinogenesis, exacerbated epithelial proliferation, delayed wound repair, enhanced colon carcinogenesis, and LDL hypertriglyceridemia {Mm} [knockout] ^{31–36} ; heterozygous knockout mice exhibit delayed wound closure {Mm}[knockout] ^{35,37,38}
Human disease	Atherosclerosis (controversial): deletion of PPAR β/δ from foam cells increases the availability of inflammatory suppressors, which in turn reduces atherosclerotic lesion formation ^{7,39–41}

aa, amino acids; chr., chromosome; HRE, hormone response element; Q-PCR, quantitative polymerase chain reaction; FIAF, fasting-induced adipose factor; FAAR, fatty acid-activated receptor; PTEN, phosphatase and tensing homolog deleted on chromosome 10; LDL, low-density lipoprotein.

* Radioligand.

- Schmidt A, Endo N, Rutledge SJ, Vogel R, Shinar D, and Rodan GA (1992) Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids. *Mol Endocrinol* **6**:1634–1641.
- Xing G, Zhang L, Heynen T, Yoshikawa T, Smith M, Weiss S, and Detera-Wadleigh S (1995) Rat PPAR delta contains a CGG triplet repeat and is prominently expressed in the thalamic nuclei. *Biochem Biophys Res Commun* **217**:1015–1025.
- Kliwer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umehono K, and Evans RM (1994) Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA* **91**:7355–7359.
- Kliwer SA, Umehono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
- Brown PJ, Smith-Oliver TA, Charifson PS, Tomkinson NC, Fivush AM, Sternbach DD, Wade LE, Orband-Miller L, Parks DJ, Blanchard SG, et al. (1997) Identification of peroxisome proliferator-activated receptor ligands from a biased chemical library. *Chem Biol* **4**:909–918.
- Brown PJ, Stuart LW, Hurley KP, Lewis MC, Winegar DA, Wilson JG, Wilkison WO, Ittoop OR, and Willson TM (2001) Identification of a subtype selective human PPAR α agonist through parallel-array synthesis. *Bioorg Med Chem Lett* **11**:1225–1227.
- Graham TL, Mookherjee C, Suckling KE, Palmer CN, and Patel L (2005) The PPARdelta agonist GW0742X reduces atherosclerosis in LDLR(–/–) mice. *Atherosclerosis* **181**:29–37.
- Willson TM, Brown PJ, Sternbach DD, and Henke BR (2000) The PPARs: from orphan receptors to drug discovery. *J Med Chem* **43**:527–550.
- Sznajdman ML, Haffner CD, Maloney PR, Fivush A, Chao E, Goreham D, Sierra ML, LeGrumec C, Xu HE, Montana VG, et al. (2003) Novel selective small molecule agonists for peroxisome proliferator-activated receptor delta (PPARdelta)–synthesis and biological activity. *Bioorg Med Chem Lett* **13**:1517–1521.
- Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, et al. (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell* **3**:397–403.
- Berger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Cullinan CA, Hayes NS, Li Y, et al. (1999) Novel peroxisome proliferator-activated receptor (PPAR) gamma and PPARdelta ligands produce distinct biological effects. *J Biol Chem* **274**:6718–6725.
- Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznajdman ML, Lambert MH, et al. (2001) A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci USA* **98**:5306–5311.
- Shaw N, Elholm M, and Noy N (2003) Retinoic acid is a high affinity selective ligand for the peroxisome proliferator-activated receptor beta/delta. *J Biol Chem* **278**:41589–41592.
- Henke BR (2004) Peroxisome proliferator-activated receptor alpha/gamma dual agonists for the treatment of type 2 diabetes. *J Med Chem* **47**:4118–4127.
- Caira F, Antonson P, Peltto-Huikko M, Treuter E, and Gustafsson JA (2000) Cloning and characterization of RAP250, a novel nuclear receptor coactivator. *J Biol Chem* **275**:5308–5317.
- Molnar F, Matilainen M, and Carlberg C (2005) Structural determinants of the agonist-independent association of human peroxisome proliferator-activated receptors with coactivators. *J Biol Chem* **280**:26543–26556.
- Qi C, Zhu Y, and Reddy JK (2000) Peroxisome proliferator-activated receptors, coactivators, and downstream targets. *Cell Biochem Biophys* **32**:187–204.
- Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, and Evans RM (2003) Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell* **113**:159–170.
- Jackson TA, Richer JK, Bain DL, Takimoto GS, Tung L, and Horwitz KB (1997) The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge domain-binding coactivator L7/SPA and the corepressors N-CoR or SMRT. *Mol Endocrinol* **11**:693–705.
- Krogsdam AM, Nielsen CA, Neve S, Holst D, Helledie T, Thomsen B, Bendixen C, Mandrup S, and Kristiansen K (2002) Nuclear receptor corepressor-dependent repression of peroxisome-proliferator-activated receptor delta-mediated transactivation. *Biochem J* **363**:157–165.
- Yu C, Markan K, Temple KA, Deplewski D, Brady MJ, and Cohen RN (2005) The nuclear receptor corepressors NCoR and SMRT decrease peroxisome proliferator-activated receptor gamma transcriptional activity and repress 3T3-L1 adipogenesis. *J Biol Chem* **280**:13600–13605.
- Zamir I, Harding HP, Atkins GB, Horlein A, Glass CK, Rosenfeld MG, and Lazar MA (1996) A nuclear hormone receptor corepressor mediates transcriptional silencing by receptors with distinct repression domains. *Mol Cell Biol* **16**:5458–5465.
- Krey G, Keller H, Mahfoudi A, Medin J, Ozato K, Dreyer C, and Wahli W (1993) *Xenopus* peroxisome proliferator activated receptors: genomic organization, response element recognition, heterodimer formation with retinoid X receptor and activation by fatty acids. *J Steroid Biochem Mol Biol* **47**:65–73.
- Desvergne B and Wahli W (1999) Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* **20**:649–688.

25. Bastie C, Holst D, Gaillard D, Jehl-Pietri C, and Grimaldi PA (1999) Expression of peroxisome proliferator-activated receptor PPARdelta promotes induction of PPARgamma and adipocyte differentiation in 3T3C2 fibroblasts. *J Biol Chem* **274**:21920–21925.
26. Di-Poi N, Tan NS, Michalik L, Wahli W, and Desvergne B (2002) Antiapoptotic role of PPARbeta in keratinocytes via transcriptional control of the Akt1 signaling pathway. *Mol Cell* **10**:721–733.
27. Di-Poi N, Michalik L, Tan NS, Desvergne B, and Wahli W (2003) The anti-apoptotic role of PPARbeta contributes to efficient skin wound healing. *J Steroid Biochem Mol Biol* **82**:257–265.
28. Mandard S, Zandbergen F, Tan NS, Escher P, Patsouris D, Koenig W, Kleemann R, Bakker A, Veenman F, Wahli W, et al. (2004) The direct peroxisome proliferator-activated receptor target fasting-induced adipose factor (FIAF/PGAR/ANGPTL4) is present in blood plasma as a truncated protein that is increased by fenofibrate treatment. *J Biol Chem* **279**:34411–34420.
29. Holst D, Luquet S, Kristiansen K, and Grimaldi PA (2003) Roles of peroxisome proliferator-activated receptors delta and gamma in myoblast transdifferentiation. *Exp Cell Res* **288**:168–176.
30. Luquet S, Lopez-Soriano J, Holst D, Fredenrich A, Melki J, Rassoulzadegan M, and Grimaldi PA (2003) Peroxisome proliferator-activated receptor delta controls muscle development and oxidative capability. *FASEB J* **17**:2299–2301.
31. Akiyama TE, Lambert G, Nicol CJ, Matsusue K, Peters JM, Brewer HB Jr, and Gonzalez FJ (2004) Peroxisome proliferator-activated receptor beta/delta regulates very low density lipoprotein production and catabolism in mice on a Western diet. *J Biol Chem* **279**:20874–20881.
32. Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, Boland R, and Evans RM (2002) Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. *Proc Natl Acad Sci USA* **99**:303–308.
33. Harman FS, Nicol CJ, Marin HE, Ward JM, Gonzalez FJ, and Peters JM (2004) Peroxisome proliferator-activated receptor-delta attenuates colon carcinogenesis. *Nat Med* **10**:481–483.
34. Kim DJ, Bility MT, Billin AN, Willson TM, Gonzalez FJ, and Peters JM (2006) PPARbeta/delta selectively induces differentiation and inhibits cell proliferation. *Cell Death Diff* **13**:53–60.
35. Michalik L, Desvergne B, Tan NS, Basu-Modak S, Escher P, Rieusset J, Peters JM, Kaya G, Gonzalez FJ, Zakany J, et al. (2001) Impaired skin wound healing in peroxisome proliferator-activated receptor (PPAR)alpha and PPARbeta mutant mice. *J Cell Biol* **154**:799–814.
36. Peters JM, Lee SS, Li W, Ward JM, Gavrilova O, Everett C, Reitman ML, Hudson LD, and Gonzalez FJ (2000) Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor beta(delta). *Mol Cell Biol* **20**:5119–5128.
37. Michalik L, Desvergne B, Basu-Modak S, Tan NS, and Wahli W (2000) Nuclear hormone receptors and mouse skin homeostasis: implication of PPARbeta. *Horm Res* **54**:263–268.
38. Tan NS, Michalik L, Desvergne B, and Wahli W (2003) Peroxisome proliferator-activated receptor (PPAR)-beta as a target for wound healing drugs: what is possible? *Am J Clin Dermatol* **4**:523–530.
39. Desvergne B, Michalik L, and Wahli W (2004) Be fit or be sick: peroxisome proliferator-activated receptors are down the road. *Mol Endocrinol* **18**:1321–1332.
40. Lee CH, Chawla A, Urbiztondo N, Liao D, Boisvert WA, Evans RM, and Curtiss LK (2003) Transcriptional repression of atherogenic inflammation: modulation by PPARdelta. *Science* **302**:453–457.
41. Li AC, Binder CJ, Gutierrez A, Brown KK, Plotkin CR, Pattison JW, Villedor AF, Davis RA, Willson TM, Witztum JL, et al. (2004) Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPARalpha, beta/delta, and gamma. *J Clin Invest* **114**:1564–1576.

TABLE 3
PPAR γ

Receptor nomenclature	NR1C3
Receptor code	4.10.1:FA:1:C3
Molecular information	Hs: 478aa, P37231, chr. 3p25 ¹⁻³ Rn: 505aa, O88275, chr. 4q42 ⁴ Mm: 475aa, P37238, chr. 6 E3-F1 ⁵
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AACTAGGNCA A AGGTCA (DR-1)
Partners	RXR (physical, functional) DNA binding ⁶
Agonists	SB-219994 (8.68), LY-510929 (8), AD-5061 (7.7), TZD18 (7.24), L-764406 (7.15), ragaglitazar (7.03), GW0072 (6.96), nTzDpa (6.5), troglitazone (6.27), LY-465608 (6.26), pioglitazone (6.23), fatty acids (6), SB-219993 (5.5), 5-ASA (1.82) [pIC ₅₀] ⁷⁻²⁶ ; GW1929 (8.84), L-796449 (8.7), GW7845 (8.43), CDDO (8), L-783483 (7.85), L-165461 (7.8), AD5075 (7.66), [³ H]AD5075* (7.66), FMOC-L-leucine (~6), CS-045 (5.8) [pK _i] ²⁷⁻³² ; [³ H]AD-5061* (8), farglitazar (7.47), indomethacin (7.38), rosiglitazone* (7.37), [¹²⁵ I]SB-236636* (7.1), [³ H]GW2331* (6.52), GW2331 (6.52), KRP-297/MK-0767 (6.49), PAT5A (6.35), MCC555 (~6.3), linoleic acid (5.3), BADGE (4) [pK _d] ^{13,15,34,21,22,26,33-43} ; GW409544 (9.55), GW9578 (6) BVT0.13 (7.52), TAK-559 (7.5), reglitazar (7.08), GW9578 (6), ciglitazone (4.64), KRP-297/MK-0767 (7) [pEC ₅₀] ^{13,22,44-49} ; DRF2519, LG10074, ibuprofen, diclofenac, COOH ⁵⁰⁻⁵⁶
Antagonists	GW9662 (8.48), PD068235 (6.1), BADGE (5), SR-202 (3.85) [pIC ₅₀] ^{57-59,42} ; CDDO-Me (8), LG100641 (6.36) [pK _i] ^{32,60} ; diclofenac ⁵⁵
Coactivators	PGC-2, ARA-70, PGC-1 α , PPARGC1B, CREBBP, p300, CITED2, ERAP140, PPARBP, PRMT-2, PIMT, NCOA1, NCOA2, NCOA3, NCOA6, SWI/SNF, PDIP ^{61-76,80-88,137}
Corepressors	NRIP1, SAF-B, TAZ, NCOR1, NCOR2 ^{68,89-94}
Biologically important isoforms	PPAR γ 1 {Hs, Mm}: encoded by eight exons (two of them PPAR γ 1-specific) ^{2,95,96} ; PPAR γ 2 {Hs, Mm, Rn}: N terminus carries 30 additional amino acids encoded by exon B PPAR γ 2-specific, encoded by seven exons ^{2,95} ; PPAR γ 3 {Hs}: gives rise to a protein indistinguishable from PPAR γ 1 from a distinct promoter—expression restricted to the colon and adipose tissue ⁹⁷ ; γ ORF4 {Hs}: read-through in intron 4, encoded protein lacks the LBD, dominant-negative vs. PPAR γ , expressed in tumor cell lines and tissues ³
Tissue distribution	Adipose tissues, lymphoid tissues, colon, liver, and heart {Hs, Mm, Rn} [Northern blot, Western blot, immunohistology] ⁹⁰
Functional assays	BADGE adipogenesis assay using 3T3-L1 and 3T3-F442A cells {Mm} ⁴² ; induction of apoptotic cell death by measuring lipogenesis in C6 glioma cells {Rn} ⁹⁸ ; measurement of lipogenesis in C3H10T1/2 cells to determine adipocyte differentiation {Hs} ^{29,35}
Main target genes	Activated: FATP {Mm} ⁹⁹ , acyl CoA-synthetase {Mm} ^{100,101} , aP2 adipocyte lipid-binding protein {Mm} ¹⁰² , Lpl {Mm} ¹⁰³ , UCP-1 {Mm} ^{104,105} , PEPCK {Mm} ¹⁰⁶ , ApoA2 {Mm} ¹⁰⁷
Mutant phenotype	Forced expression in hepatocytes induced the classic pattern of PPAR γ -mediated gene activation and resulted in steatosis {Mm} [retroviral infection] ¹⁰⁸ ; disrupted expression in macrophages {Mm} [transgenesis] ¹⁰⁹ ; knockout not viable due to defects in placenta formation {Mm} [knockout] ¹¹⁰ ; conditional knockout in adipocytes causes white and brown adipocytes to be replaced with newly formed PPAR γ -positive adipocytes {Mm} [conditional knockout] ¹¹¹ ; conditional knockout in adipocytes results in lipodystrophy (hypocellularity and hypertrophy), elevated plasma FFAs and TGs, decreased plasma leptin and adiponectin, and insulin resistance in fat and liver {Mm} [conditional knockout] ¹¹² ; conditional knockout in white adipocytes results in retarded growth, severe lipodystrophy (hypocellularity and hypertrophy) and hyperlipidemia {Mm} [conditional knockout] ¹¹³ ; conditional knockout in muscle causes progressive insulin resistance combined with increased adipose tissue mass {Mm} [conditional knockout] ^{114,115} ; conditional knockout in pancreatic β -cells results in significant islet hyperplasia on chow diet, blunted expansion of β -cell mass {Mm} [conditional knockout] ¹¹⁶ ; L466A dominant-negative knockin mutant {Mm} [knockin] ¹¹⁷ ; heterozygous mice have reduced body size and weight, reduced insulin resistance, smaller adipocytes and fat depots {Mm} [knockout] ^{54,118,119}
Human disease	Obesity and insulin resistance: associated with a mutation in the ligand-independent activation domain of PPAR γ 2—increased PPAR γ 2 mRNA found in obese subjects ¹²⁰⁻¹²⁴ ; insulin resistance, type II diabetes mellitus and hypertension: associated with a mutation of the LBD—improved insulin sensitivity associated with polymorphism (Pro12Ala) in PPAR γ 2 ^{46,121,123,125,126} ; syndrome X or metabolic syndrome: associated with dominant-negative PPAR γ mutations ¹²⁵⁻¹²⁷ ; atherosclerosis: increased receptor expression in atherosclerotic lesions, macrophages, and monocytic cell lines ^{123,128} ; colon cancer: associated with loss-of-function mutations in PPAR γ LBD—potential antitumor efficacy of combining RXR and PPAR γ agonist ¹²⁹⁻¹³² ; prostate cancer: PPAR γ expressed in human prostate adenocarcinomas and cell lines derived from human prostate tumors ¹³³ ; thyroid tumors: the PAX8-PPAR γ fusion protein promotes differentiated follicular thyroid neoplasia ¹³⁴⁻¹³⁶

aa, amino acids; chr., chromosome; HRE, hormone response element; CDDO, 2-cyano-3,12-dioxoleano-1,9-dien-28-oic acid; BADGE, bisphenol A diglycidyl ether; ASA, aminosalicic acid; FMOC, fluorenylmethoxycarbonyl; CREBB, cAMP response element binding protein binding protein; PIMT, peroxisome proliferator-activated receptor-interacting protein with methyltransferase domain; SWI/SNF, mating-type switching/sucrose nonfermenting; PDIP, PPAR γ -DNA-binding domain-interacting protein; SAF-B, scaffold attachment factor B; TAZ, transcriptional coactivator with postsynaptic density 95/disc-large/zona occludens-binding motif; FATP, fatty acid transport protein; PEPCK, phosphoenolpyruvate carboxykinase; FFA, free fatty acid; TG, triglyceride.

* Radioligand.

1. Beamer BA, Negri C, Yen CJ, Gavrilo O, Rumberger JM, Durcan MJ, Yarnall DP, Hawkins AL, Griffin CA, Burns DK, et al. (1997) Chromosomal localization and partial genomic structure of the human peroxisome proliferator activated receptor-gamma (hPPAR gamma) gene. *Biochem Biophys Res Commun* 233:756-759.

2. Greene ME, Blumberg B, McBride OW, Yi HF, Kronquist K, Kwan K, Hsieh L, Greene G, and Nimer SD (1995) Isolation of the human peroxisome proliferator activated receptor gamma cDNA: expression in hematopoietic cells and chromosomal mapping. *Gene Expr* **4**:281–299.
3. Sabatino L, Casamassimi A, Peluso G, Barone MV, Capaccio D, Migliore C, Bonelli P, Pedicini A, Febraro A, Ciccodicola A, et al. (2005) A novel peroxisome proliferator-activated receptor gamma isoform with dominant negative activity generated by alternative splicing. *J Biol Chem* **280**:26517–26525.
4. Guardiola-Diaz HM, Rehmark S, Usuda N, Albrektsen T, Feltkamp D, Gustafsson JA, and Alexson SE (1999) Rat peroxisome proliferator-activated receptors and brown adipose tissue function during cold acclimatization. *J Biol Chem* **274**:23368–23377.
5. Zhu Y, Alvares K, Huang Q, Rao MS, and Reddy JK (1993) Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver. *J Biol Chem* **268**:26817–26820.
6. Klierer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
7. Berger JP, Petro AE, Macnaul KL, Kelly LJ, Zhang BB, Richards K, Elbrecht A, Johnson BA, Zhou G, Doebber TW, et al. (2003) Distinct properties and advantages of a novel peroxisome proliferator-activated protein [gamma] selective modulator. *Mol Endocrinol* **17**:662–676.
8. Brooks DA, Etgen GJ, Rito CJ, Shuker AJ, Dominianni SJ, Warshawsky AM, Ardecky R, Paterniti JR, Tyhonas J, Karanewsky DS, et al. (2001) Design and synthesis of 2-methyl-2-[4-(2-[5-methyl-2-aryloxazol-4-yl]ethoxy)phenoxy]propionic acids: a new class of dual PPARalpha/gamma agonists. *J Med Chem* **44**:2061–2064.
9. Chakrabarti R, Vikramadithyan RK, Misra P, Hiriyani J, Raichur S, Damarla RK, Gershon C, Suresh J, and Rajagopalan R (2003) Ragaglitazar: a novel PPAR alpha PPAR gamma agonist with potent lipid-lowering and insulin-sensitizing efficacy in animal models. *Br J Pharmacol* **140**:527–537.
10. Ebdrup S, Petterson I, Rasmussen HB, Deussen HJ, Frost Jensen A, Mortensen SB, Fleckner J, Pridal L, Nygaard L, and Sauerberg P (2003) Synthesis and biological and structural characterization of the dual-acting peroxisome proliferator-activated receptor alpha/gamma agonist ragaglitazar. *J Med Chem* **46**:1306–1317.
11. Elbrecht A, Chen Y, Adams A, Berger J, Griffin P, Klatt T, Zhang B, Menke J, Zhou G, Smith RG, et al. (1999) L-764406 is a partial agonist of human peroxisome proliferator-activated receptor gamma. The role of Cys313 in ligand binding. *J Biol Chem* **274**:7913–7922.
12. Guo Q, Sahoo SP, Wang PR, Milot DP, Ippolito MC, Wu MS, Baffie J, Biswas C, Hernandez M, Lam MH, et al. (2004) A novel peroxisome proliferator-activated receptor alpha/gamma dual agonist demonstrates favorable effects on lipid homeostasis. *Endocrinology* **145**:1640–1648.
13. Henke BR, Blanchard SG, Brackeen MF, Brown KK, Cobb JE, Collins JL, Harrington WW Jr, Hashim MA, Hull-Ryde EA, Kaldor I, et al. (1998) N-(2-benzoylphenyl)-L-tyrosine PPARgamma agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents. *J Med Chem* **41**:5020–5036.
14. Klierer SA, Lenhard JM, Willson TM, Patel I, Morris DC, and Lehmann JM (1995) A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. *Cell* **83**:813–819.
15. Klierer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, et al. (1997) Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. *Proc Natl Acad Sci USA* **94**:4318–4323.
16. Nichols JS, Parks DJ, Conslor TG, and Blanchard SG (1998) Development of a scintillation proximity assay for peroxisome proliferator-activated receptor gamma ligand binding domain. *Anal Biochem* **257**:112–119.
17. Nosjean O and Boutin JA (2002) Natural ligands of PPARgamma: are prostaglandin J(2) derivatives really playing the part? *Cell Signal* **14**:573–583.
18. Oberfield JL, Collins JL, Holmes CP, Goreham DM, Cooper JP, Cobb JE, Lenhard JM, Hull-Ryde EA, Mohr CP, Blanchard SG, et al. (1999) A peroxisome proliferator-activated receptor gamma ligand inhibits adipocyte differentiation. *Proc Natl Acad Sci USA* **96**:6102–6106.
19. Pickavance LC, Brand CL, Wassermann K, and Wilding JP (2005) The dual PPARalpha/gamma agonist, ragaglitazar, improves insulin sensitivity and metabolic profile equally with pioglitazone in diabetic and dietary obese ZDF rats. *Br J Pharmacol* **144**:308–316.
20. Rousseaux C, Lefebvre B, Dubuquoy L, Lefebvre P, Romano O, Auwerx J, Metzger D, Wahli W, Desvergne B, Naccari GC, et al. (2005) Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. *J Exp Med* **201**:1205–1215.
21. Sakamoto J, Kimura H, Moriyama S, Odaka H, Momose Y, Sugiyama Y, and Sawada H (2000) Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun* **278**:704–711.
22. Sakamoto J, Kimura H, Moriyama S, Imoto H, Momose Y, Odaka H, and Sawada H (2004) A novel oxyminoalkanoic acid derivative, TAK-559, activates human peroxisome proliferator-activated receptor subtypes. *Eur J Pharmacol* **495**:17–26.
23. Soares AF, Nosjean O, Cozzone D, D'Orazio D, Becchi M, Guichardant M, Ferry G, Boutin JA, Lagarde M, and Geloan A (2005) Covalent binding of 15-deoxy-delta(12,14)-prostaglandin J(2) to PPARgamma. *Biochem Biophys Res Commun* **337**:521–525.
24. Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, et al. (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell* **3**:397–403.
25. Xu Y, Rito CJ, Etgen GJ, Ardecky RJ, Bean JS, Bensch WR, Bosley JR, Broderick CL, Brooks DA, Dominianni SJ, et al. (2004) Design and synthesis of alpha-aryloxy-alpha-methylhydrocinnamic acids: a novel class of dual peroxisome proliferator-activated receptor alpha/gamma agonists. *J Med Chem* **47**:2422–2425.
26. Young PW, Buckle DR, Cantello BC, Chapman H, Clapham JC, Coyle PJ, Haigh D, Hindley RM, Holder JC, Kallender H, et al. (1998) Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor gamma. *J Pharmacol Exp Ther* **284**:751–759.
27. Berger J, Bailey P, Biswas C, Cullinan CA, Doebber TW, Hayes NS, Saperstein R, Smith RG, and Leibowitz MD (1996) Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-gamma: binding and activation correlate with antidiabetic actions in db/db mice. *Endocrinology* **137**:4189–4195.
28. Berger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Cullinan CA, Hayes NS, Li Y, et al. (1999) Novel peroxisome proliferator-activated receptor (PPAR) gamma and PPARdelta ligands produce distinct biological effects. *J Biol Chem* **274**:6718–6725.
29. Brown KK, Henke BR, Blanchard SG, Cobb JE, Mook R, Kaldor I, Klierer SA, Lehmann JM, Lenhard JM, Harrington WW, et al. (1999) A novel N-aryl tyrosine activator of peroxisome proliferator-activated receptor-gamma reverses the diabetic phenotype of the Zucker diabetic fatty rat. *Diabetes* **48**:1415–1424.
30. Cobb JE, Blanchard SG, Boswell EG, Brown KK, Charifson PS, Cooper JP, Collins JL, Dezube M, Henke BR, Hull-Ryde EA, et al. (1998) N-(2-benzoylphenyl)-L-tyrosine PPARgamma agonists. 3. Structure-activity relationship and optimization of the N-aryl substituent. *J Med Chem* **41**:5055–5069.
31. Rocchi S, Picard F, Vamecq J, Gelman L, Potier N, Zeyer D, Dubuquoy L, Bac P, Champy MF, Plunket KD, et al. (2001) A unique PPARgamma ligand with potent insulin-sensitizing yet weak adipogenic activity. *Mol Cell* **8**:737–747.
32. Wang Y, Porter WW, Suh N, Honda T, Gribble GW, Leesnitzer LM, Plunket KD, Mangelsdorf DJ, Blanchard SG, Willson TM, et al. (2000) A synthetic triterpenoid, 2-cyano-3,12-dioxoleano-1,9-dien-28-oic acid (CDDO), is a ligand for the peroxisome proliferator-activated receptor gamma. *Mol Endocrinol* **14**:1550–1556.
33. Bishop-Bailey D, Hla T and Warner TD (2000) Bisphenol A diglycidyl ether (BADGE) is a PPARgamma agonist in an EC304 cell line. *Br J Pharmacol* **131**:651–654.
34. Ferry G, Bruneau V, Beauverger P, Goussard M, Rodriguez M, Lamamy V, Dromaint S, Canet E, Galizzi JP, and Boutin JA (2001) Binding of prostaglandins to human PPARgamma: tool assessment and new natural ligands. *Eur J Pharmacol* **417**:77–89.
35. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, and Klierer SA (1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* **270**:12953–12956.
36. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, and Klierer SA (1997) Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J Biol Chem* **272**:3406–3410.
37. Misra P, Chakrabarti R, Vikramadithyan RK, Bolusu G, Juluri S, Hiriyani J, Gershon C, Rajjak A, Kashireddy P, Yu S, et al. (2003) PAT5A: a partial agonist of peroxisome proliferator-activated receptor gamma is a potent antidiabetic thiazolidinedione yet weakly adipogenic. *J Pharmacol Exp Ther* **306**:763–771.
38. Murakami K, Tobe K, Ide T, Mochizuki T, Ohashi M, Akanuma Y, Yazaki Y, and Kadowaki T (1998) A novel insulin sensitizer acts as a coligand for peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and PPAR-gamma: effect of PPAR-alpha activation on abnormal lipid metabolism in liver of Zucker fatty rats. *Diabetes* **47**:1841–1847.
39. Murakami K, Ide T, Suzuki M, Mochizuki T, and Kadowaki T (1999) Evidence for direct binding of fatty acids and eicosanoids to human peroxisome proliferator-activated receptor alpha. *Biochem Biophys Res Commun* **260**:609–613.
40. Reginato MJ, Bailey ST, Krakow SL, Minami C, Ishii S, Tanaka H, and Lazar MA (1998) A potent antidiabetic thiazolidinedione with unique peroxisome proliferator-activated receptor gamma-activating properties. *J Biol Chem* **273**:32679–32684.
41. Vikramadithyan RK, Chakrabarti R, Misra P, Premkumar M, Kumar SK, Rao CS, Ghosh A, Reddy KN, Uma C, and Rajagopalan R (2000) Euglycemic and hypolipidemic activity of PAT5A: a unique thiazolidinedione with weak peroxisome proliferator activated receptor gamma activity. *Metabolism* **49**:1417–1423.
42. Wright HM, Clish CB, Mikami T, Hauser S, Yanagi K, Hiramatsu R, Serhan CN, and Spiegelman BM (2000) A synthetic antagonist for the peroxisome proliferator-activated receptor gamma inhibits adipocyte differentiation. *J Biol Chem* **275**:1873–1877.
43. Yu C, Chen L, Luo H, Chen J, Cheng F, Gui C, Zhang R, Shen J, Chen K, Jiang H, et al. (2004) Binding analyses between Human PPARgamma-LBD and ligands. *Eur J Biochem* **271**:386–397.
44. Brown PJ, Stuart LW, Hurlley KP, Lewis MC, Winegar DA, Wilson JG, Wilkison WO, Ittoop OR, and Willson TM (2001) Identification of a subtype selective human PPARalpha agonist through parallel-array synthesis. *Bioorg Med Chem Lett* **11**:1225–1227.
45. Doebber TW, Kelly LJ, Zhou G, Meurer R, Biswas C, Li Y, Wu MS, Ippolito MC, Chao YS, Wang PR, et al. (2004) MK-0767, a novel dual PPARalpha/gamma agonist, displays robust antihyperglycemic and hypolipidemic activities. *Biochem Biophys Res Commun* **318**:323–328.
46. Henke BR (2004) Peroxisome proliferator-activated receptor alpha/gamma dual agonists for the treatment of type 2 diabetes. *J Med Chem* **47**:4118–4127.

47. Ostberg T, Svensson S, Selen G, Uppenberg J, Thor M, Sundbom M, Sydow-Backman M, Gustavsson AL, and Jendeborg L (2004) A new class of peroxisome proliferator-activated receptor agonists with a novel binding epitope shows antidiabetic effects. *J Biol Chem* **279**:41124–41130.
48. Shibata T, Matsui K, Nagao K, Shinkai H, Yonemori F, and Wakitani K (1999) Pharmacological profiles of a novel oral antidiabetic agent, JTT-501, an isoxazolidinedione derivative. *Eur J Pharmacol* **364**:211–219.
49. Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Kliewer SA, Gampe RT Jr, McKee DD, et al. (2001) Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA* **98**:13919–13924.
50. Carley AN, Semeniuk LM, Shimoni Y, Aasum E, Larsen TS, Berger JP, and Severson DL (2004) Treatment of type 2 diabetic db/db mice with a novel PPARgamma agonist improves cardiac metabolism but not contractile function. *Am J Physiol Endocrinol Metab* **286**:E449–E455.
51. Cesario RM, Klausung K, Razzaghi H, Crombie D, Rungta D, Heyman RA, and Lala DS (2001) The retinoid LG100754 is a novel RXR:PPARgamma agonist and decreases glucose levels in vivo. *Mol Endocrinol* **15**:1360–1369.
52. Chakrabarti R, Misra P, Vikramadithyan RK, Premkumar M, Hiriyan J, Datla SR, Damarla RK, Suresh J, and Rajagopalan R (2004) Antidiabetic and hypolipidemic potential of DRF 2519—a dual activator of PPAR-alpha and PPAR-gamma. *Eur J Pharmacol* **491**:195–206.
53. Forman BM (2002) The antidiabetic agent LG100754 sensitizes cells to low concentrations of peroxisome proliferator-activated receptor gamma ligands. *J Biol Chem* **277**:12503–12506.
54. Jaradat MS, Wongsud B, Phornchirasilp S, Rangwala SM, Shams G, Sutton M, Romstedt KJ, Noonan DJ, and Feller DR (2001) Activation of peroxisome proliferator-activated receptor isoforms and inhibition of prostaglandin H(2) synthases by ibuprofen, naproxen, and indomethacin. *Biochem Pharmacol* **62**:1587–1595.
55. Kojo H, Fukagawa M, Tajima K, Suzuki A, Fujimura T, Aramori I, Hayashi K, and Nishimura S (2003) Evaluation of human peroxisome proliferator-activated receptor (PPAR) subtype selectivity of a variety of anti-inflammatory drugs based on a novel assay for PPAR delta(beta). *J Pharmacol Sci* **93**:347–355.
56. Laplante M, Sell H, MacNaul KL, Richard D, Berger JP, and Deshaies Y (2003) PPAR-gamma activation mediates adipose depot-specific effects on gene expression and lipoprotein lipase activity: mechanisms for modulation of postprandial lipemia and differential adipose accretion. *Diabetes* **52**:291–299.
57. Camp HS, Chaudhry A, and Leff T (2001) A novel potent antagonist of peroxisome proliferator-activated receptor gamma blocks adipocyte differentiation but does not revert the phenotype of terminally differentiated adipocytes. *Endocrinology* **142**:3207–3213.
58. Leesnitzer LM, Parks DJ, Bledsoe RK, Cobb JE, Collins JL, Conlser TG, Davis RG, Hull-Ryde EA, Lenhard JM, Patel L, et al. (2002) Functional consequences of cysteine modification in the ligand binding sites of peroxisome proliferator activated receptors by GW9662. *Biochemistry* **41**:6640–6650.
59. Rieusset J, Touri F, Michalik L, Escher P, Desvergne B, Niesor E, and Wahli W (2002) A new selective peroxisome proliferator-activated receptor gamma antagonist with antiobesity and antidiabetic activity. *Mol Endocrinol* **16**:2628–2644.
60. Mukherjee R, Hoener PA, Jow L, Bilakovics J, Klausung K, Mais DE, Faulkner A, Croston GE, and Paterniti JR Jr (2000) A selective peroxisome proliferator-activated receptor-gamma (PPARgamma) modulator blocks adipocyte differentiation but stimulates glucose uptake in 3T3-L1 adipocytes. *Mol Endocrinol* **14**:1425–1433.
61. Castillo G, Brun RP, Rosenfield JK, Hauser S, Park CW, Troy AE, Wright ME, and Spiegelman BM (1999) An adipogenic cofactor bound by the differentiation domain of PPARgamma. *EMBO Eur Mol Biol Organ J* **18**:3676–3687.
62. Debril MB, Dubuquoy L, Feige JN, Wahli W, Desvergne B, Auwerx J, and Gelman L (2005) Scaffold attachment factor B1 directly interacts with nuclear receptors in living cells and represses transcriptional activity. *J Mol Endocrinol* **35**:503–517.
63. Gelman L, Zhou G, Fajas L, Raspe E, Fruchart JC, and Auwerx J (1999) p300 interacts with the N- and C-terminal part of PPARgamma2 in a ligand-independent and -dependent manner, respectively. *J Biol Chem* **274**:7681–7688.
64. Guan HP, Ishizuka T, Chui PC, Lehrke M, and Lazar MA (2005) Corepressors selectively control the transcriptional activity of PPARgamma in adipocytes. *Genes Dev* **19**:453–461.
65. Heinlein CA, Ting HJ, Yeh S, and Chang C (1999) Identification of ARA70 as a ligand-enhanced coactivator for the peroxisome proliferator-activated receptor gamma. *J Biol Chem* **274**:16147–16152.
66. Huss JM, Kopp RP, and Kelly DP (2002) Peroxisome proliferator-activated receptor coactivator-1alpha (PGC-1alpha) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor-alpha and -gamma. Identification of novel leucine-rich interaction motif within PGC-1alpha. *J Biol Chem* **277**:40265–40274.
67. Huss JM, Torra IP, Staels B, Giguere V, and Kelly DP (2004) Estrogen-related receptor alpha directs peroxisome proliferator-activated receptor alpha signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle. *Mol Cell Biol* **24**:9079–9091.
68. Jackson TA, Richer JK, Bain DL, Takimoto GS, Tung L, and Horwitz KB (1997) The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge domain-binding coactivator L7/SPA and the corepressors N-CoR or SMRT. *Mol Endocrinol* **11**:693–705.
69. Kamei Y, Ohizumi H, Fujitani Y, Nemoto T, Tanaka T, Takahashi N, Kawada T, Miyoshi M, Ezaki O, and Kakizuka A (2003) PPARgamma coactivator 1beta/ERR ligand 1 is an ERR protein ligand, whose expression induces a high-energy expenditure and antagonizes obesity. *Proc Natl Acad Sci USA* **100**:12378–12383.
70. Knutti D and Kralli A (2001) PGC-1, a versatile coactivator. *Trends Endocrinol Metab* **12**:360–365.
71. Kodera Y, Takeyama K, Murayama A, Suzawa M, Masuhiro Y, and Kato S (2000) Ligand type-specific interactions of peroxisome proliferator-activated receptor gamma with transcriptional coactivators. *J Biol Chem* **275**:33201–33204.
72. Leers J, Treuter E, and Gustafsson JA (1998) Mechanistic principles in NR box-dependent interaction between nuclear hormone receptors and the coactivator TIF2. *Mol Cell Biol* **18**:6001–6013.
73. Lemon B, Inouye C, King DS, and Tjian R (2001) Selectivity of chromatin-remodelling cofactors for ligand-activated transcription. *Nature (Lond)* **414**:924–928.
74. Mizukami J and Taniguchi T (1997) The antidiabetic agent thiazolidinedione stimulates the interaction between PPAR gamma and CBP. *Biochem Biophys Res Commun* **240**:61–64.
75. Molnar F, Matilainen M, and Carlberg C (2005) Structural determinants of the agonist-independent association of human peroxisome proliferator-activated receptors with coactivators. *J Biol Chem* **280**:26543–26556.
76. Oberkofler H, Esterbauer H, Linnemayr V, Strosberg AD, Krempler F, and Patsch W (2002) Peroxisome proliferator-activated receptor (PPAR) gamma coactivator-1 recruitment regulates PPAR subtype specificity. *J Biol Chem* **277**:16750–16757.
77. Puigserver P, Wu Z, Park CW, Graves R, Wright M, and Spiegelman BM (1998) A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* **92**:829–839.
78. Qi C, Zhu Y, and Reddy JK (2000) Peroxisome proliferator-activated receptors, coactivators, and downstream targets. *Cell Biochem Biophys* **32**:187–204.
79. Qi C, Chang J, Zhu Y, Yeldandi AV, Rao SM, and Zhu YJ (2002) Identification of protein arginine methyltransferase 2 as a coactivator for estrogen receptor alpha. *J Biol Chem* **277**:28624–28630.
80. Qi C, Surapureddi S, Zhu YJ, Yu S, Kashireddy P, Rao MS, and Reddy JK (2003) Transcriptional coactivator PRIP, the peroxisome proliferator-activated receptor gamma (PPARgamma)-interacting protein, is required for PPARgamma-mediated adipogenesis. *J Biol Chem* **278**:25281–25284.
81. Shao W, Halachmi S, and Brown M (2002) ERAP140, a conserved tissue-specific nuclear receptor coactivator. *Mol Cell Biol* **22**:3358–3372.
82. Tien ES, Davis JW, and Vanden Heuvel JP (2004) Identification of the CREB-binding protein/p300-interacting protein CITED2 as a peroxisome proliferator-activated receptor alpha coregulator. *J Biol Chem* **279**:24053–24063.
83. Yang W, Rachez C, and Freedman LP (2000) Discrete roles for peroxisome proliferator-activated receptor gamma and retinoid X receptor in recruiting nuclear receptor coactivators. *Mol Cell Biol* **20**:8008–8017.
84. Zhou G, Cummings R, Li Y, Mitra S, Wilkinson HA, Elbrecht A, Hermes JD, Schaeffer JM, Smith RG, and Moller DE (1998) Nuclear receptors have distinct affinities for coactivators: characterization by fluorescence resonance energy transfer. *Mol Endocrinol* **12**:1594–1604.
85. Zhu Y, Qi C, Calandra C, Rao MS, and Reddy JK (1996) Cloning and identification of mouse steroid receptor coactivator-1 (mSRC-1), as a coactivator of peroxisome proliferator-activated receptor gamma. *Gene Expr* **6**:185–195.
86. Zhu Y, Qi C, Jain S, Rao MS, and Reddy JK (1997) Isolation and characterization of PBP, a protein that interacts with peroxisome proliferator-activated receptor. *J Biol Chem* **272**:25500–25506.
87. Zhu Y, Kan L, Qi C, Kanwar YS, Yeldandi AV, Rao MS, and Reddy JK (2000) Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR. *J Biol Chem* **275**:13510–13516.
88. Zhu Y, Qi C, Cao WQ, Yeldandi AV, Rao MS, and Reddy JK (2001) Cloning and characterization of PIMT, a protein with a methyltransferase domain, which interacts with and enhances nuclear receptor coactivator PRIP function. *Proc Natl Acad Sci USA* **98**:10380–10385.
89. Debril MB, Gelman L, Fayard E, Annicotte JS, Rocchi S, and Auwerx J (2004) Transcription factors and nuclear receptors interact with the SWI/SNF complex through the BAF60c subunit. *J Biol Chem* **279**:16677–16686.
90. Desvergne B and Wahli W (1999) Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* **20**:649–688.
91. Hong JH, Hwang ES, McManus MT, Amsterdam A, Tian Y, Kalmukova R, Mueller E, Benjamin T, Spiegelman BM, Sharp PA, et al. (2005) TAZ, a transcriptional modulator of mesenchymal stem cell differentiation. *Science* **309**:1074–1078.
92. Treuter E, Albrechtsen T, Johansson L, Leers J, and Gustafsson JA (1998) A regulatory role for RIP140 in nuclear receptor activation. *Mol Endocrinol* **12**:864–881.
93. Yu C, Markan K, Temple KA, Deplewski D, Brady MJ, and Cohen RN (2005) The nuclear receptor corepressors NCoR and SMRT decrease peroxisome proliferator-activated receptor gamma transcriptional activity and repress 3T3-L1 adipogenesis. *J Biol Chem* **280**:13600–13605.
94. Zamir I, Harding HP, Atkins GB, Horlein A, Glass CK, Rosenfeld MG, and Lazar MA (1996) A nuclear hormone receptor corepressor mediates transcriptional silencing by receptors with distinct repression domains. *Mol Cell Biol* **16**:5458–5465.

95. Fajas L, Fruchart JC, and Auwerx, J (1998) PPARgamma3 mRNA: a distinct PPARgamma mRNA subtype transcribed from an independent promoter. *FEBS Lett* **438**:55–60.
96. Zhu Y, Qi C, Korenberg JR, Chen XN, Noya D, Rao MS, and Reddy JK (1995) Structural organization of mouse peroxisome proliferator-activated receptor gamma (mPPAR gamma) gene: alternative promoter use and different splicing yield two mPPAR gamma isoforms. *Proc Natl Acad Sci USA* **92**:7921–7925.
97. Fajas L, Aubouef D, Raspe E, Schoonjans K, Lefebvre AM, Saladin R, Najib J, Laville M, Fruchart JC, Deeb S, et al. (1997) The organization, promoter analysis, and expression of the human PPARgamma gene. *J Biol Chem* **272**:18779–18789.
98. Grommes C, Landreth GE, Schlegel U, and Heneka MT (2005) The nonthiazolidinedione tyrosine-based peroxisome proliferator-activated receptor gamma ligand GW7845 induces apoptosis and limits migration and invasion of rat and human glioma cells. *J Pharmacol Exp Ther* **313**:806–813.
99. Frohnert BI, Hui TY, and Bernlohr DA (1999) Identification of a functional peroxisome proliferator-responsive element in the murine fatty acid transport protein gene. *J Biol Chem* **274**:3970–3977.
100. Martin G, Schoonjans K, Lefebvre AM, Staels B, and Auwerx J (1997) Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. *J Biol Chem* **272**:28210–28217.
101. Schoonjans K, Watanabe M, Suzuki H, Mahfoudi A, Krey G, Wahli W, Grimaldi P, Staels B, Yamamoto T, and Auwerx J (1995) Induction of the acyl-coenzyme A synthetase gene by fibrates and fatty acids is mediated by a peroxisome proliferator response element in the C promoter. *J Biol Chem* **270**:19269–19276.
102. Tontonoz P, Hu E, Graves RA, Budavari AI, and Spiegelman BM (1994) mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev* **8**:1224–1234.
103. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S, Staels B, and Auwerx J (1996) PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO (Eur Mol Biol Organ) J* **15**:5336–5348.
104. Sears IB, MacGinnitie MA, Kovacs LG, and Graves RA (1996) Differentiation-dependent expression of the brown adipocyte uncoupling protein gene: regulation by peroxisome proliferator-activated receptor gamma. *Mol Cell Biol* **16**:3410–3419.
105. Xue B, Coulter A, Rim JS, Koza RA, and Kozak LP (2005) Transcriptional synergy and the regulation of Ucp1 during brown adipocyte induction in white fat depots. *Mol Cell Biol* **25**:8311–8322.
106. Tontonoz P, Hu E, and Spiegelman BM (1995) Regulation of adipocyte gene expression and differentiation by peroxisome proliferator activated receptor gamma. *Curr Opin Genet Dev* **5**:571–576.
107. Vu-Dac N, Schoonjans K, Kosykh V, Dallongeville J, Fruchart JC, Staels B, and Auwerx J (1995) Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. *J Clin Invest* **96**:741–750.
108. Yu S, Matsusue K, Kashireddy P, Cao WQ, Yeldandi V, Yeldandi AV, Rao MS, Gonzalez FJ, and Reddy JK (2003) Adipocyte-specific gene expression and adipogenic steatosis in the mouse liver due to peroxisome proliferator-activated receptor gamma1 (PPARgamma1) overexpression. *J Biol Chem* **278**:498–505.
109. Welch JS, Ricote M, Akiyama TE, Gonzalez FJ, and Glass CK (2003) PPARgamma and PPARdelta negatively regulate specific subsets of lipopolysaccharide and IFN-gamma target genes in macrophages. *Proc Natl Acad Sci USA* **100**:6712–6717.
110. Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, and Evans RM (1999) PPAR gamma is required for placental, cardiac, and adipose tissue development. *Mol Cell* **4**:585–595.
111. Imai T, Takakawa R, Marchand S, Dentz E, Bornert JM, Messaddeq N, Wendling O, Mark M, Desvergne B, Wahli W, et al. (2004) Peroxisome proliferator-activated receptor gamma is required in mature white and brown adipocytes for their survival in the mouse. *Proc Natl Acad Sci USA* **101**:4543–4547.
112. He W, Barak Y, Hevener A, Olson P, Liao D, Le J, Nelson M, Ong E, Olefsky JM, and Evans RM (2003) Adipose-specific peroxisome proliferator-activated receptor gamma knock-out causes insulin resistance in fat and liver but not in muscle. *Proc Natl Acad Sci USA* **100**:15712–15717.
113. Koutnikova H, Cock TA, Watanabe M, Houten SM, Champy MF, Dierich A, and Auwerx J (2003) Compensation by the muscle limits the metabolic consequences of lipodystrophy in PPAR gamma hypomorphic mice. *Proc Natl Acad Sci USA* **100**:14457–14462.
114. Hevener AL, He W, Barak Y, Le J, Bandyopadhyay G, Olson P, Wilkes J, Evans RM, and Olefsky J (2003) Muscle-specific Pparg deletion causes insulin resistance. *Nat Med* **9**:1491–1497.
115. Norris AW, Chen L, Fisher SJ, Szanto I, Ristow M, Jozsi AC, Hirshman MF, Rosen ED, Goodyer LJ, Gonzalez FJ, et al. (2003) Muscle-specific PPARgamma-deficient mice develop increased adiposity and insulin resistance but respond to thiazolidinediones. *J Clin Invest* **112**:608–618.
116. Rosen ED, Kulkarni RN, Sarraf P, Ozcan U, Okada T, Hsu CH, Eisenman D, Magnuson MA, Gonzalez FJ, Kahn CR, et al. (2003) Targeted elimination of peroxisome proliferator-activated receptor gamma in beta cells leads to abnormalities in islet mass without compromising glucose homeostasis. *Mol Cell Biol* **23**:7222–7229.
117. Freedman BD, Lee EJ, Park Y, and Jameson JL (2005) A dominant negative peroxisome proliferator-activated receptor-gamma knock-in mouse exhibits features of the metabolic syndrome. *J Biol Chem* **280**:17118–17125.
118. Kubota N, Terauchi Y, Miki H, Tamemoto H, Yamauchi T, Komeda K, Satoh S, Nakano R, Ishii C, Sugiyama T, et al. (1999) PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. *Mol Cell* **4**:597–609.
119. Rieusset J, Seydoux J, Anghel SI, Escher P, Michalik L, Soon Tan N, Metzger D, Chambon P, Wahli W, and Desvergne B (2004) Altered growth in male peroxisome proliferator-activated receptor gamma (PPARgamma) heterozygous mice: involvement of PPARgamma in a negative feedback regulation of growth hormone action. *Mol Endocrinol* **18**:2363–2377.
120. Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J, and Shuldiner AR (1998) Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma2 gene with obesity in two Caucasian populations. *Diabetes* **47**:1806–1808.
121. Deeb SS, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, Laakso M, Fujimoto W, and Auwerx J (1998) A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* **20**:284–287.
122. Ek J, Urhammer SA, Sorensen TI, Andersen T, Auwerx J, and Pedersen O (1999) Homozygosity of the Pro12Ala variant of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2): divergent modulating effects on body mass index in obese and lean Caucasian men. *Diabetologia* **42**:892–895.
123. Kersten S, Desvergne B, and Wahli W (2000) Roles of PPARs in health and disease. *Nature (Lond)* **405**:421–424.
124. Valve R, Sivenius K, Miettinen R, Pihlajamaki J, Rissanen A, Deeb SS, Auwerx J, Uusitupa M, and Laakso M (1999) Two polymorphisms in the peroxisome proliferator-activated receptor-gamma gene are associated with severe overweight among obese women. *J Clin Endocrinol Metab* **84**:3708–3712.
125. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, et al. (1999) Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature (Lond)* **402**:880–883.
126. Desvergne B, Michalik L, and Wahli W (2004) Be fit or be sick: peroxisome proliferator-activated receptors are down the road. *Mol Endocrinol* **18**:1321–1333.
127. Lee CH, Olson P, and Evans RM (2003) Mini-review: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. *Endocrinology* **144**:2201–2207.
128. Ricote M, Huang J, Fajas L, Li A, Welch J, Najib J, Witztum JL, Auwerx J, Palinski W, and Glass CK (1998) Expression of the peroxisome proliferator-activated receptor gamma (PPARgamma) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. *Proc Natl Acad Sci USA* **95**:7614–7619.
129. Cesario RM, Stone J, Yen WC, Bissonnette RP, and Lamph WW (2006) Differentiation and growth inhibition mediated via the RXR:PPARgamma heterodimer in colon cancer. *Cancer Lett* **240**:225–233.
130. Kim E, Chen F, Wang CC, and Harrison LE (2006) CDK5 is a novel regulatory protein in PPARgamma ligand-induced antiproliferation. *Int J Oncol* **28**:191–194.
131. Sarraf P, Mueller E, Smith WM, Wright HM, Kum JB, Aaltonen LA, de la Chapelle A, Spiegelman BM, and Eng C (1999) Loss-of-function mutations in PPAR gamma associated with human colon cancer. *Mol Cell* **3**:799–804.
132. Sasaki T, Fujii K, Yoshida K, Shimura H, Sasahira T, Ohmori H, and Kuniyasu H (2005) Peritoneal metastasis inhibition by linoleic acid with activation of PPARgamma in human gastrointestinal cancer cells. *Virchows Arch* **448**:422–427.
133. Mueller E, Smith M, Sarraf P, Krull T, Aiyyer A, Kaufman DS, Oh W, Demetri G, Figg WD, Zhou XP, et al. (2000) Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. *Proc Natl Acad Sci USA* **97**:10990–10995.
134. Cheung L, Messina M, Gill A, Clarkson A, Learoyd D, Delbridge L, Wentworth J, Philips J, Clifton-Bligh R, and Robinson BG (2003) Detection of the PAX8-PPAR gamma fusion oncogene in both follicular thyroid carcinomas and adenomas. *J Clin Endocrinol Metab* **88**:354–357.
135. Marques AR, Espadinha C, Catarino AL, Moniz S, Pereira T, Sobrinho LG, and Leite V (2002) Expression of PAX8-PPAR gamma 1 rearrangements in both follicular thyroid carcinomas and adenomas. *J Clin Endocrinol Metab* **87**:3947–3952.
136. Nikiforova MN, Lynch RA, Biddinger PW, Alexander EK, Dorn GW, Tallini G 2nd, Krull TG, and Nikiforov YE (2003) RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. *J Clin Endocrinol Metab* **88**:2318–2326.
137. Tomaru T, Satoh T, Yoshino S, Ishizuka T, Hashimoto K, Monden T, Yamada M, and Mori M (2006) Isolation and characterization of a transcriptional cofactor and its novel isoform that bind the deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-gamma. *Endocrinology* **147**:377–388.