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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 (PPARs¹) 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-

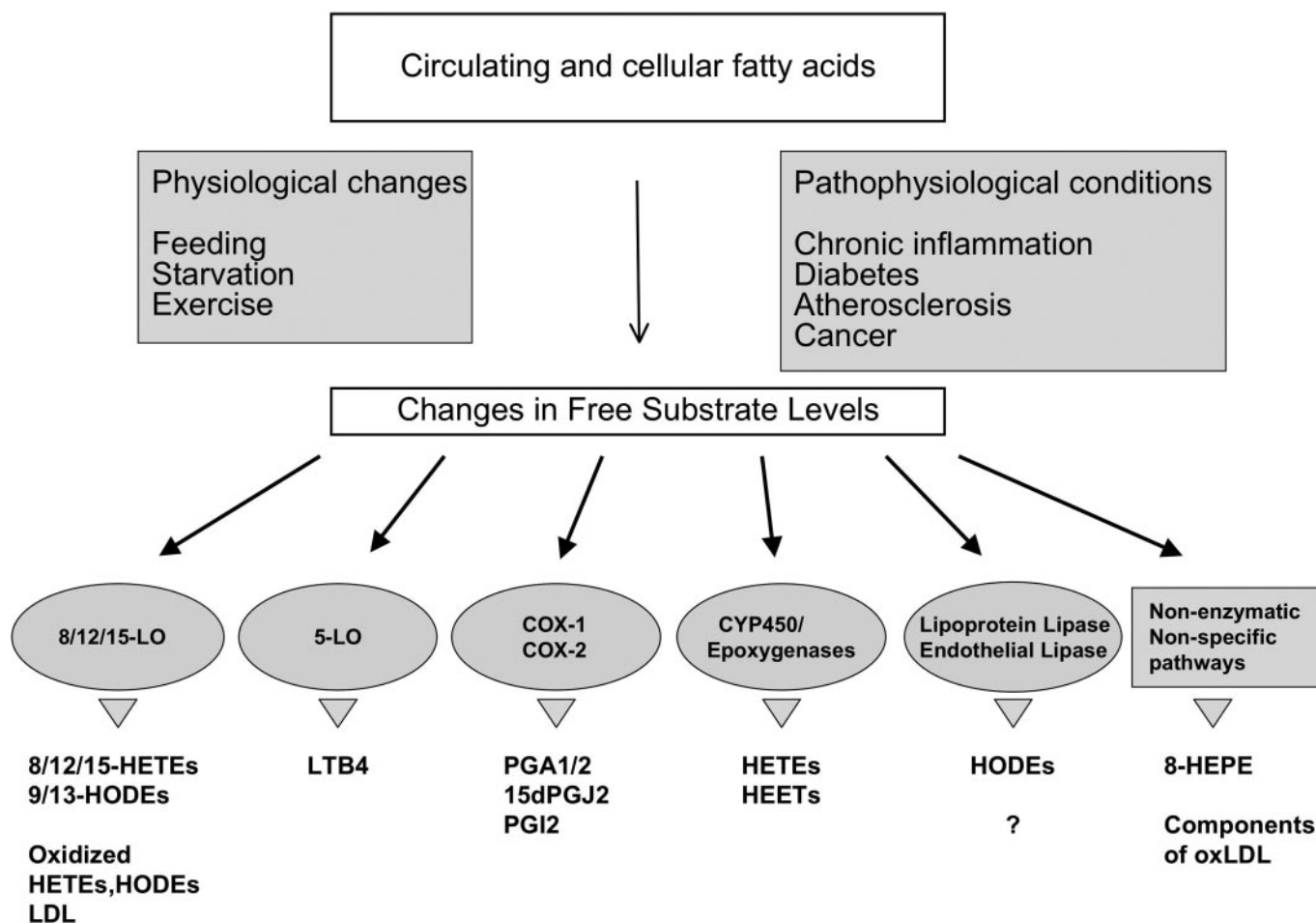


FIG. 1. Endogenous pathways for PPAR ligand production. Unsaturated fatty acids can act both as ligands and as substrates for ligand-generating enzymes, such as the 8/12/15- and 5-lipoxygenases (LOs), the cyclooxygenases (COX-1 and COX-2), the cytochrome (CYP)/epoxygenases, or the lipoprotein and endothelial 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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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.

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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.

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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 insuline 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-dioxoleana-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.

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