Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors. PPARs play an important role in the general transcriptional control of numerous cellular processes, including lipid metabolism, glucose homeostasis, cell cycle progression, cell differentiation, inflammation and extracellular matrix remodeling. Three PPAR isoforms, designated PPARα, PPARβ and PPARγ, have been cloned and are differentially expressed in several issues including the kidney. PPARα primary regulates lipid metabolism and modulates inflammation. PPARα is the molecular target of the hypolipidemic fibrates including bezafibrate and clofibrate. PPARβ participates in embryonic development, implantation and bone formation. PPARγ is a key factor in adipogenesis and also plays an important role in insulin sensitivity, cell cycle regulation and cell differentiation.

Antidiabetic thiazolidinediones (TZDs) such as troglitazone and rosiglitazone are specific ligands of PPARγ, and this interaction is responsible for the insulin-sensitizing and hypoglycemic effect of these drugs. The kidney has been shown to differentially express all PPAR isoforms. PPARα is predominantly expressed in proximal tubules and medullary thick ascending limbs, while PPARγ is expressed in medullary collecting ducts, pelvic urothelium and glomerular mesangial cells. PPARβ is ubiquitously expressed at low levels in all segments of nephron. Accumulating data has begun to emerge suggesting physiological and pathophysiological roles of PPARs in several tissues including the kidney. The availability of PPAR-selective agonists and antagonists may provide a new approach to modulate the renal response to diseases including glomerulonephritis, glomerulosclerosis and diabetic nephropathy.

PPARs are a group of structurally diverse compounds including industrial chemicals and pharmaceutical agents that were originally identified as inducers of hepatic peroxisomal proliferation. In rodents, chronic exposure to peroxisome proliferators results in nongenotoxic liver tumors [1] and alters gene expression involved in lipid β-oxidation, cell differentiation and inflammation [2]. These effects are now known to be mediated through binding of peroxisome proliferators to a specific subset of nuclear receptor and transcription factor superfamily, designated peroxisome proliferator-activated receptors (PPARs). Since the identification of the first PPAR receptor in mouse [3], three isoforms—designated PPARα, PPARβ/δ and PPARγ—have been cloned and characterized by their distinct expression patterns, different ligand binding specificity and metabolic functions. In the past decade, tremendous progress has been made towards understanding the role of PPARs in whole body physiology and in many human diseases including diabetes, obesity, atherosclerosis, hypertension and cancer. PPARα plays an important role in lipid metabolism and its activation by fibrates mediates their potent hypolipidemic effects [4]. Recently, PPARβ/δ has been suggested as having an important role in cell survival and colon tumorigenesis. It has been suggested as a molecular target mediating the beneficial effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on colorectal cancer [5]. Finally, activation of PPARγ by synthetic thiazolidinedione (TZD) ligands has been successfully used for treatment of patients with type II diabetes [6]. This review examines the current knowledge relating to PPARs’ action, ligand binding and tissue distribution. Recent developments regarding the role of PPARs in diabetes, insulin resistance, atherosclerosis, inflammatory disease, hypertension, and cancer, with particular relevance to the kidney will also be discussed.

PPAR RECEPTORS: CLONING, STRUCTURE AND LIGAND BINDING

Cloning and structure of PPARs

In 1990, Isseman and Green identified the first nuclear receptor to which peroxisome proliferators bound by
Fig. 1. (A) Structural and functional domains of the human peroxisome proliferator-activated receptors (PPARs). Domains are: A/B, N-terminal A/B domain containing a ligand-independent activation function (AF-1); C, DNA-binding domain (DBD); D, hinge region; and E/F, C-terminal ligand-binding domain (LBD) containing the ligand-dependent activation function (AF-2). Numbers inside the boxes represent the percentage (%) identity between the human PPAR isofoms. (B) The genomic organization of the human PPARγ gene. Alternative promoter usage and splicing of the three 5′ exons A1, A2, and B results in three different transcripts and two PPARγ protein products (PPARγ1 and PPARγ2). Note that transcription from the promoter γ1 and γ3 results in same protein of 477 amino acids (PPARγ1 protein) and transcript using the promoter γ2 encoded a protein of 505 amino acids (PPARγ2 protein), which has additional 28 amino acids at the N-terminus compared with PPARγ1 protein.

screening of cDNA library with a probe encoding the highly conserved C domain of nuclear hormone receptors [3]. This receptor is now designated PPARα. Shortly thereafter, two additional isoforms of PPAR were identified: PPARβ/δ and PPARγ [7]. To date, no mRNA splice variant for PPARα and PPARβ/δ has been identified. In contrast, multiple splicing forms of PPARγ mRNA have been reported in many species including mouse and human [8–10]. In humans three PPARγ transcripts have been reported [9]. These three isoforms of PPARγ are derived from a single gene as a result of differential splicing and alternate promoter usage (Fig. 1). Each PPARγ transcript shares the six 3′ coding exons, differing only in the 5′ exons. The 5′ untranslated region of PPARγ1 contains exons A1 and A2, while PPARγ3 only contains exon A2. Since none of the 5′ exons distinguishing PPARγ1 and PPARγ3 possess a translation initiation site, PPARγ1 and PPARγ3 mRNAs give rise to identical protein products: PPARγ1. In contrast, PPARγ2 has a γ2-specific coding exon located between exon A2 and exon 1, yielding 30 additional N-terminal amino acids in the PPARγ2 protein [6, 11]. Due to different promoter usage, each PPARγ isoform has a distinct expression pattern [9, 10].

All three PPAR isoforms share similar structural and functional organization with other nuclear receptors (Fig. 1). Four major domains have been identified: A/B, C, D and E/F domain [reviewed in 2, 11]. The N-terminal A/B domain differs in both length and predicted amino acid sequence and contains a ligand-independent transactivation domain, termed activation function 1 (AF1). This domain plays an important role in regulating PPAR expression through both phosphorylation and interdomain communication [12, 13]. The C domain is comprised of about 70 amino acids and encodes the DNA binding domain (DBD). This domain is responsible for the binding of PPAR receptor to peroxisome proliferator response element (PPRE) in the promoter region of target genes. The D hinge region is a docking domain for cofactors. The E/F C-terminal region contains two important domains. One is the ligand-binding domain (LBD), or E domain, responsible for ligand specificity and activation of PPAR binding to the peroxisomal proliferator response element (PPRE) with resultant modulation of gene expression. This region also has been found to play an important role in dimerization and nuclear localization. The other is the ligand-dependent activation domain AF-2, or F domain. AF-2 domain located in the
C-terminal α-helix 12 is critical for both ligand-binding and recruitment of PPAR cofactors.

**PPAR ligands**

Similar to other members of the nuclear receptor family, PPARs are ligand-activated transcriptional factors, that is, modulation of target gene transcription depends on the binding of the ligands to the receptor. PPARs form heterodimers with the 9-cis retinoic acid receptor, RXRα. Activation of PPAR:RXRα by PPAR ligands and/or RXRα ligands results in a conformational change of these receptors, allowing the heterodimers to bind PPREs in target genes and modulate the gene transcription (Fig. 2). The divergent amino acid sequence in the LBD of the three PPAR isoforms provides the molecular basis for ligand specificity. Since PPARs have a large ligand-binding pocket (1300 Å) [14], these receptors are capable of binding several structurally diverse compounds, including industrial chemicals such as herbicides and plasticizers as well as pharmaceutical compounds including hypolipidemic fibrates (such as clofibrate) and antidiabetic thiazolidinediones (TZDs; for example, troglitazone and rosiglitazone). When assessed by transactivation assays, a variety of exogenous compounds have been shown to selectively activate PPAR isoforms (Table 1). Among them, several agents have been identified as PPARα activators, including hypolipidemic compounds WY-14,643 and clofibrate. Importantly, these compounds exhibit a good correlation between ability to activate PPARα and the potency to induce hepatocarcinoma in rodents, suggesting that PPARα is the major molecular target of hepatocarcinogenic peroxisome proliferators in the liver [15].

PPARγ is highly expressed in adipose tissue where it plays a critical role in adipocyte differentiation. Antidiabetic TZD including troglitazone and rosiglitazone promote adipocyte differentiation through activation of PPARγ [16–20]. In vitro, these TZDs have been shown to bind PPARγ with a kD of 30 to 10,000 nmol/L [21, 22]. A synthetic compound, L-165041, selectively activates PPARβ/δ at high affinity (kD = 6 nmol/L) with very poor affinity for PPARγ and no affinity to PPARα [23]. A search for naturally occurring ligands reveals that PPAR receptors are also activated by numerous fatty acid at physiologic concentrations [24]. PPARα is activated by a variety of long-chain polyunsaturated fatty acids including linoleic acid, branched, conjugated and oxidized fatty acids such as phytanic acid, conjugated linoleic acid and eicosanoids such as 8S-HETE and leukotriene B4 [25–28]. The endogenous prostaglandin D₂ (PGD₂) metabolite, 15-deoxy-Δ12,14-prostaglandin J₂ (15dPGJ₂) is the most potent natural ligand of PPARγ and might

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**Fig. 2. Model for gene activation and repression by PPARγ.**
play a role in adipogenesis in vivo [21]. Interestingly, 
two pathophysiological oxidized metabolites of linoleic 
acid, 9-hydroxy and 13-hydroxy octadecadienoic acids 
(9-HODE and 13-HODE) present in oxidized low-den-
sity lipoprotein have also been suggested as PPARγ 
ligands and could play a role in atherogenesis [29, 30]. 
Linoleic acid, arachidonic acid, eicosapentenoic acid 
(EPA) and PGA1 have been shown to bind PPARβ/δ 
receptor in the μmol/L range [31, 32].

### PPAR Isoforms: Tissue Distribution, Intrarenal Localization and Function

#### Tissue distribution and regulation of PPAR isoforms

Expression of the three PPAR isoforms has been exa-
mained in many species including *Xenopus*, rat, mouse, 
rabbit and human. In humans, PPARα is predominantly 
expressed in tissues exhibiting high catabolic rates of 
fatty acids (adipose tissue, liver, heart, muscle, and renal 
cortex) and it is also detected in lung, placenta, intestine, 
pancreas and skeletal muscle. PPARβ/δ is the most widely 
expressed isoform and low levels are found in almost all 
tissues examined. In general, PPARγ is highly expressed 
in adipose tissue and at lower levels in renal medulla, 
urinary bladder, skeletal muscle, liver, and heart [33–35]. 
Although all three PPARγ splice variants are expressed 
in adipose tissues at high levels, PPARγ2 and γ3 appear 
to be more restrictively expressed in fat than the γ1 
isoform [9, 33, 34]. Recently, low but significant levels 
of PPARγ expression has also been detected in vascular 
smooth muscle cells, endothelial cells, hepatic Stellate 
cells, bone marrow stromal cells, monocytes/macroph-
ages, and malignant epithelial cells including breast, 
colon, prostate and bladder cancer cells [36–46], sug-
uggesting that PPARγ may participate in many physiologi-
and pathophysiological events in these tissues as well.

The expression of PPARα in liver is decreased by 
insulin and increased by glucocorticoids, respectively 
[47, 48]. PPARα expression cycles in parallel with the 
circadian rhythm of circulating glucocorticoids [49]. In 
hepatic cells and pancreatic islets, expression of PPARα 
is down-regulated with treatment of growth hormone 
[50], but up-regulated by fibrates or free fatty acid (FFA) 
[51, 52]. In humans, alternative splicing of mRNA may 
play a role in regulating PPARα expression. Human liver 
has a splice variant of PPARα transcript lacking exon 6. 
The resulting reading frame shift results in a premature 
stop codon shortly after the DNA binding domain, re-
sulting in a truncated PPARα protein [53]. This process 
might diminish the hepatic expression of PPARα. In 
addition, a mutation at codon 162 (L162 V) of PPARα 
has been shown to be associated with hyperapobetalipo-
proteinemia in humans [54].

Regulation of PPARγ has been extensively investi-
gated. Insulin and corticosteroids synergistically induce 
PPARγ expression, while tumor necrosis factor-α (TNF-α) 
suppresses the PPARγ level in adipocytes [55, 56]. In 
rodents, in vivo studies revealed that PPARγ expression 
in adipose tissue is significantly up-regulated by high-
fat feeding and down-regulated by fasting [57–59]. In 
humans, increased expression of the PPARγ receptor has 
been observed in adipose tissue of obese humans [55] 
and skeletal muscle of patients with obesity or type II 
diabetes [55, 60, 61]. Genetic polymorphisms and muta-
tions have been also found to play a role in PPARγ 
function in humans [61–63]. Pro12Ala substitution of 
PPARγ2 is associated with decreased receptor activity, 
low body mass index (BMI), and increased insulin sensi-
tivity in nonobese subjects [62, 64]. In contrast, Pro115Gln 
mutation destroys the mitogen-activated protein (MAP) 
kine target site in Ser112, resulting in increased activity 
of PPARγ and severe obesity [63]. Thus far, very little 
is known about the regulation of PPARβ/δ receptor.

However a recent report suggests its expression may be 
repressed by the adenomatous polyposis coli (APC) gene 
through β-catenin/Tcf-4 transcription factor [65]. These 
data suggest a role for PPARβ/δ in the pathogenesis of 
colon cancer.

#### Intrarenal localization of PPARs

Renal expression of PPARs have been investigated in 
many species including mouse, rat, rabbit and humans 
[34, 35, 66–68]. Northern hybridization and RNase pro-
tection assay show that all three PPAR isoforms are expressed in the kidney. In situ hybridization analysis and reverse transcription-polymerase chain reaction (RT-PCR) provide concordant results for nephron expression [35, 67, 69]. PPARα is predominantly expressed in proximal tubules and medullary thick ascending limbs, while PPARγ is selectively expressed in medullary collecting ducts and pelvic urothelium. PPARβ/δ, like in other tissues, is equally expressed in renal cortex and medulla and is expressed ubiquitously in all segments of nephron tested. Recently, functional expression of PPARγ has also been reported in freshly isolated glomeruli and cultured mesangial cells in both rabbit and rat (abstract; Guan et al, J Am Soc Nephrol 11:A3381, 2000) [70, 71]. Renal expression of PPAR isoforms is also developmentally regulated. All three PPAR isoforms are expressed in early embryonic kidneys. PPARα and PPARγ expression is enhanced with development and remains at high level 2 weeks after birth, while PPARβ/δ expression peaks in late gestation and declines after birth [69, 72].

**PHYSIOLOGICAL ROLES OF PPAR ISOFORMS**

Distinct expression patterns and differential ligand-binding profiles indicate unique roles for each of the three PPAR isoforms. The target genes of PPARα participate in lipid oxidation [73], suggesting that PPARα is mainly involved in lipid catabolism. Conversely, PPARγ target genes are generally implicated in the lipogenic pathway and the storage of fatty acids in adipose tissue, consistent with a critical role of PPARγ in adipogenesis [20, 74]. Although PPARβ/δ target genes are poorly characterized, the fact that PPARβ/δ regulates acyl coenzyme A (CoA) synthase 2 expression suggests a role for this receptor in lipid metabolism [75]. In addition, gene targeting and human genetic studies provide important clues regarding the functional roles of PPAR receptors in mammalian metabolism.

**PPARα in lipid catabolism**

PPARα is predominantly expressed in tissues with high mitochondrial and peroxisomal β-oxidation activities, exemplified by its high levels in liver, heart and renal cortex and intestine. Its known target genes comprise a relatively homogenous group of genes involved in almost all aspects of lipid metabolism, including uptake, binding and oxidation of fatty acids, lipoprotein assembly and lipid transport [11]. PPARα activated genes include fatty acid transport protein (FATP), fatty acid translocase (FAT/CD36) and hepatic cytosolic fatty acid binding protein (L-FABP), and it may play critical roles in uptake of fatty acids in the digestive tract [76, 77]. Other genes involved in the transformation of long-chain fatty acids into triglycerides and their incorporation into chylomicrons and VLDL particles, such as acyl CoA synthase (ACS) [78] and apolipoproteins (apo) are also PPARα target genes [79, 80]. In liver, PPARα is a pivotal factor involved in every aspect of fatty acid oxidation. Triglycerides in chylomicrons are extracellularly hydrolyzed into glycerol and fatty acids by the lipoprotein lipase (LPL), another well-characterized PPARα target gene [76, 81, 82]. The resultant nonesterified fatty acids are then subsequently taken up by hepatocytes through the PPARα target gene, fatty acid transport protein (FATP) [83]. Once imported into hepatocytes, fatty acids are activated into acyl CoA thioesters by ACS. Acyl CoA may then either be esterified or, alternatively, enter the pathway of β-oxidation. Metabolizing long-chain fatty acyl CoA (>C20) via β-oxidation takes place in peroxisomes. All three enzymes involved in this process have been shown to be directly regulated by PPARα via binding to the PPRE sites in the promoter region of these genes. These genes include acyl CoA oxidase (ACO), a rate-limiting enzyme, enoyl CoA hydratase/dehydrogenase multifunctional enzyme (HD), and keto-acyl CoA thiolase [7, 84–86]. Long- (C14 to C20) and medium-chain (C8 to C12) fatty acids can be oxidized either in peroxisome or mitochondria. Mitochondrial β-oxidation is approximately twice as efficient as peroxisomal β-oxidation. The rate-limiting step in mitochondrial oxidation is entry flux of fatty acids into the mitochondria, which is controlled by a carnitine-dependent facilitated transport system. One of its critical components, carnitine palmitoyl transferase I (CPT I), is a direct target gene of PPARα [87, 88]. In addition, PPARα further regulates the mitochondrial β-oxidation spiral by modulating the expression of the medium-chain acyl CoA dehydrogenase (MCAD) gene [89]. The acetyl CoA produced in mitochondria is converted to ketone bodies, mainly acetoacetate and 3-hydroxybutyrate, and serves as an important energy source for extrahepatic tissues such as brain, renal cortex, heart, and skeletal muscle. The main enzyme responsible for generation of ketone bodies is mitochondrial hydroxymethylglutaryl-CoA synthase (mHMG-CoAS), which is directly activated by PPARα [90]. The critical role of PPARα in fatty acid β-oxidation is confirmed by the studies in PPARα-null mice [91]. These animals are unresponsive to PPARα ligand stimulation in both peroxisomes and mitochondria, and exhibit fatty liver. Basal expression of mitochondrial enzymes are lower in PPARα knockout mice versus wild-type mice.

PPARα also plays an important role in regulating microsomal ω-oxidation of fatty acids and eicosanoids. The cytochrome P450 4 A (CYP4A) enzymes are central enzymes participating in this process. For example, ω-oxidation is the first step in the degradation of leukotriene B₄ (LTB₄), a PPARα ligand [92, 93]. To date, at least two CYP4A enzymes have been shown to be direct target genes of PPARα: 4A1 in rat and 4A6 in rabbit. Putative PPRE sites have been reported in the promoter
region of these genes and PPAR\(\alpha\) agonists are able to enhance their expression both in vivo and in vitro [94–97]. Since 4A1 and 4A6 are active arachidonic \(\omega\)-hydroxylase [98], these data suggest that PPAR\(\alpha\) may actively participate in the oxidation of a variety of endogenous lipids as well as exogenous compounds in microsomes.

Additional PPAR\(\alpha\) target genes include apolipoprotein (apo) I, apo-II and apo C-III. PPAR\(\alpha\) ligand fibrates decrease apo C-III by activation of PPAR\(\alpha\), leading to enhanced LPL-mediated catabolism of very low-density lipoprotein (VLDL) particles [99–101]. In contrast, PPAR\(\alpha\) activation increases plasma levels of HDL and its major constituents, apo A-I and A-II through PPAR/RXR heterodimers [79, 102]. These effects, together with negative regulation of apo C-III, contribute to the hypolipidemic effects of fibrates. Based on these observations, PPAR\(\alpha\) is a critical player in lipid catabolism, including peroxisomal and mitochondrial oxidation, microsomal \(\omega\)-oxidation, ketogenesis, and lipid transport.

**PPAR\(\beta/\delta\) in development, fertility, bone formation and lipid metabolism**

While it has been widely accepted that PPAR\(\alpha\) and PPAR\(\gamma\) are two key players in lipid metabolism, it now appears likely that PPAR\(\beta/\delta\) is also involved in lipid homeostasis. A recent study by Leibowitz et al showed that PPAR\(\beta/\delta\) specific agonist L-165041 significantly increased high-density lipoprotein (HDL)-cholesterol levels without effects on blood glucose or triglycerides concentration in \(db/db\) obese mice. These results suggest that PPAR\(\beta/\delta\) agonists could be a novel therapeutic agents in dyslipidemia [103].

Ubiquitous expression, poor availability of specific ligands and lack of a connection to clinical disorders have impeded progress in elucidating the specific function of PPAR\(\beta/\delta\). PPAR\(\beta/\delta\) expression is particularly high in certain developing and adult tissues, such as central nervous system, kidney and placenta [34, 35, 66]. This expression pattern indicates a potential function of PPAR\(\beta/\delta\) in these tissues. For example, PPAR\(\beta/\delta\) has been found to be predominant isotype expressed in the uterus during the pre-implantation period in mice [104]. Its expression was induced in the stroma surrounding the implanting blastocyst and localized in the decidual zone postimplantation. Its obligate partner RX\(\alpha\) was also highly expressed in endometrial cells and decidua. In addition, PGI\(_3\), an endogenous PPAR\(\beta/\delta\) ligand, is generated in stromal cells at the site of implantation. More importantly, the PPAR\(\beta/\delta\) agonists such as carbaprostacyclin or L-165041 in combination of 9-cis retinoic acid were able to restore implantation in the COX-2 gene knockout mice, in whom defects in implantation and decidualization were previously reported [104, 105]. These data suggest that PPAR\(\beta/\delta\) plays an essential role in fertility. Recently, PPAR\(\beta/\delta\) has been reported to be the predominant PPAR isoform expressed in bone osteoclasts, implicating it in regulating resorption of mineralized bone surface [106]. Activation of PPAR\(\beta/\delta\) by carbox prostacyclin significantly induced both bone-resorbing activity and mRNA expression of the osteoclastic genes including carbonic anhydrase type II (CA II) and cathepsin K. Moreover, these effects were completely blocked by an antisense oligonucleotide of PPAR\(\beta/\delta\), suggesting a critical role for PPAR\(\beta/\delta\) in modulating osteoclastic bone resorption.

**PPAR\(\gamma\) and adipogenesis**

PPAR\(\gamma\) has been the most extensively investigated PPAR isoform. The receptor has been cloned from many species and identified as the isoform most highly expressed in adipose tissues. The expression of adipocyte fatty acid binding protein (ap2), as well as many other adipose target genes including lipoprotein lipase (LPL), fatty acid translocase (FAT), fatty acid transport protein (FATP), ACS, malic enzyme (ME), insulin-dependent glucose transporter (GLUT4) and c-Blk-associated protein (CAP), are activated by PPAR\(\gamma\) ligands [49, 86]. This array of PPAR\(\gamma\) target genes is consistent with the role of PPAR\(\gamma\) in lipid accumulation. Moreover, a gain-of-function study showed that forced ectopic expression of PPAR\(\gamma\) in fibroblasts produced a marked stimulation adipogenesis in the presence of PPAR\(\gamma\) activators [107, 108]. This observation was confirmed further in vivo. Mutation of Pro115Gln in PPAR\(\gamma\) destroys a MAP kinase target site in Ser112, resulting in increased activity of PPAR\(\gamma\) receptor and severe obesity in humans [63]. Conversely, in vitro introduction of a dominant negative PPAR\(\gamma\) mutant with a defective transactivation domain blocked TZD-induced terminal differentiation of human pre-adipocytes [109]. Unfortunately, loss-of-function (gene knockout) studies of adipogenesis using gene targeting have been hampered by an unexpected requirement of PPAR\(\gamma\) for placental development and embryonic lethality [110]. Recently, several lines of evidence supported the critical role of PPAR\(\gamma\) in adipogenesis in vivo. Study on mice chimeric for wild-type and PPAR\(\gamma\)-null cells showed that PPAR\(\gamma\) (\(-/-\)) embryonic stem (ES) cells fail to contribute to adipose tissues, whereas most other organs examined did not require PPAR\(\gamma\) for proper development [18]. These data support an essential role for PPAR\(\gamma\) in fat formation. Similar conclusions were supported in another study using PPAR\(\gamma\) mutant mice generated by supplementing PPAR\(\gamma\) null embryos with wild-type placenta, via aggregation with tetraploid embryos [110]. The live-born PPAR\(\gamma\) null mice were notable for total absence of white and brown adipose tissue (lipodystrophy). Taken together, these data demonstrate that PPAR\(\gamma\) is required for adipogenesis both in vitro and in vivo. Thus, together with a number of other transcription factor including CAAT/enhancer binding
proteins (C/EBPs), sterol regulatory element binding proteins (SREBPs) and PPARβ/δ, PPARγ promotes and maintains adipocyte function [19, 86, 111, 112].

**PPARs and Renal Disease**

Beyond a role in adipogenesis, PPARs have been linked to many human diseases including obesity, insulin resistance, type II diabetes, atherosclerosis, hypertension, inflammation and cancer. Ligands for these receptors have been suggested to have therapeutic potential for selected human diseases.

**PPARγ, insulin resistance, and type II diabetes**

Numerous studies have supported a therapeutic role for PPARγ in the treatment of type II diabetes. TZD PPARγ ligands including troglitazone (Rezulin®), pioglitazone (ACTOS®) and rosiglitazone (Avandia®) are a relatively new class of oral antidiabetic agents that improve all three primary defects in patients with type II diabetes, that is, insulin resistance, hyperinsulinemia and hyperglycemia [113]. Troglitazone significantly reduces plasma glucose, % glycosylated hemoglobin, insulin and C-peptide level in type II diabetes [113–116]. Moreover, this agent also shows beneficial effects of lipid metabolism, blood pressure and cardiac output [113, 117]. These effects are generally thought to be mediated by activation of PPARγ and enhanced insulin sensitivity in peripheral tissues [118]. In support of this, ligands of RXRα, the obligate partner of PPARγ, also exhibit a glucose- and lipid-lowering activity [119] that is additive to a PPARγ agonist [120]. Although TZDs have been successfully used in the treatment of type II diabetes, the relevant tissue targets remains undefined. Since PPARγ is abundantly expressed in adipose tissues, fat cells have been implicated as a primary target tissue for TZDs [121]. Arguing against this hypothesis is the observation that mice genetically manipulated to delete adipose tissue develop severe insulin resistance, and that troglitazone ameliorates hyperinsulinemia and hyperglycemia in this model as well [122]. This suggests that the insulin-sensitizing effects of TZD are independent of effects on adipose tissues. Another proposed target tissue for TZDs is skeletal muscle, the major site of impaired insulin action in type II diabetes. PPARγ has been found to be expressed in skeletal muscle tissue [123] and its expression is enhanced in type II diabetic patients [60, 124–126]. The activation of PPARγ increases expression of adipocyte lipid binding protein (ALBP) and muscle fatty acid binding protein (mFABP) in this tissue [125], potentially modulating lipid and fatty acid uptake. Fatty acids are key regulators of insulin sensitivity. It is well-established that fatty acids decrease glucose usage in skeletal muscle. PPARγ-induced increase in fatty acids uptake by ALBP and mFABP may be responsible, at least in part, for enhanced insulin sensitivity. TZD PPARγ ligands have been also shown to ameliorate TNF-α-induced insulin resistance, suggesting that suppression of TNF-α activation also might be involved in favorable effect of TZDs in diabetes and insulin resistance [127, 128].

Most recently, a new adipocyte-secreted hormone designated resistin (for “resistant to insulin”) has been proposed as a molecular link between obesity and type II diabetes. TZD rosiglitazone markedly reduced resistin’s expression in adipocytes as well as its circulating level. Resistin appears to play a role in pathogenesis of insulin resistance [129, 130], since administration of neutralizing antibody to resistin significantly improved blood glucose and insulin action in mice with diet-induced obesity, suggesting that TZD activation of PPARγ might increase insulin sensitivity by suppressing the production of resistin by adipocytes.

Despite the successful use of TZDs as antidiabetic drugs, the specific role of altered PPARγ function in the pathogenesis of insulin resistance and type II diabetes remains uncertain. It has long been known that obesity is a major risk factor in the development of type II diabetes. In contrast, with a gain-of-function mutation of PPARγ are obese, but have a relatively low level of insulin and increased sensitivity to insulin [63]. These data suggest that excess PPARγ activity contributes to obesity and reduced PPARγ activity elicits insulin resistance. However, studies on mice heterozygous for the PPARγ gene paint a more complex picture [134, 135]. PPARγ (+/−) mice develop normally, have a normal number and size of adipocytes and show no metabolic defect. However, the size of the adipocytes in PPARγ (+/−) mice on a high-fat diet is much smaller than those in wild-type mice, and PPARγ (+/−) mice unexpectedly exhibit enhanced insulin sensitivity and reduced weight gain as compared to wild-type mice. In this setting, PPARγ may promote small adipocyte formation, which is insulin sensitive. On the other hand, PPARγ activation can stimulate hypertrophy (large adipocytes) of pre-existing adipocytes, which leads to insulin resistance. Taken together, these data suggest a complex role for PPARγ in adiposity and insulin resistance.
PPARs and obesity

Both PPARα and PPARγ receptors have been implicated in the pathogenesis of obesity. PPARα agonist fibrate treatment has been reported to reduce weight gain in rodents [136, 137]. Moreover, PPARα null mice accumulate more body fat with aging [138, 139]. These data suggest that PPARα plays an important role in obesity. The mechanisms may involve both regulation of lipid catabolism and energy expenditure. PPARα has been shown to increase the expression of uncoupling proteins (UCP-1, UCP-2, and UCP-3), mitochondrial inner-membrane transporters responsible for heat generation through uncoupling proton entry from ATP synthesis [140, 141]. UCPs are important regulators of thermogenesis and body weight regulation. All three UCPs are abundantly expressed in brown adipose tissue (BAT), however, each UCP differs in its expression pattern in other tissues [142–147]. UCP-1 is relatively restricted to brown fat tissue [148]. In contrast, UCP-2 is expressed in most tissues at varying levels, while UCP-3 is expressed predominantly in skeletal muscle and brown adipose tissue. Given the wide tissue distribution pattern of UCP-2 and UCP-3, it was originally thought that they may contribute more to adaptive thermogenesis than UCP-1. However, increased rather than decreased expression of UCP-2 and UCP-3 has been observed after starvation, a state known to be associated with decreased energy expenditure [149, 150]. Furthermore, although transgenic mice with toxigen-mediated reduction of brown fat (UCP-DTA) develop obesity [151], UCP-1 targeted mice have a defect in adaptive thermogenesis but not obesity [142]. Thus, based on these undefined roles of UCPs in obesity, regulation of PPARα in this setting of disease requires more investigation.

The role of PPARγ in pathogenesis of obesity appears more clear. As discussed above, PPARγ plays a critical role in adipogenesis both in vitro and in vivo. Dysfunction of the PPARγ receptor has significant effects on body fat mass. This has been confirmed both by transgenic studies and human genetic studies [152]. Patients with an activating missense mutation of the PPARγ2 protein exhibit accelerated adipocyte differentiation and develop severe obesity [63]. In contrast, patients with a PPARγ2 mutation associated with decreased receptor activity exhibit lower body mass and improved insulin sensitivity [64]. Together with the previously discussed effects of PPARγ disruption on adiposity in knockout mice, these data clearly demonstrate that PPARγ plays a critical role in obesity. These effects on adipocytes may include modulation of leptin-stimulated lipolysis and glucose utilization. Thiazolidinediones inhibit leptin production [153] through PPARγ-dependent PPRE in promoter region of the leptin (ob) gene [154]. In addition, PPARγ has been also shown to regulate many other genes implicated in energy homeostasis, including TNF-α and UCPs [127, 155]. These data suggest that multiple mechanisms contribute to the pathogenic role of PPARγ in obesity.

PPARγ and hypertension

Hypertension in Western countries is commonly linked to obesity and insulin resistance [156, 157]. Recently thiazolidinediones (TZDs) have been found not only to sensitize tissue to insulin but also to lower blood pressure in both animals and humans [158–161]. Studies on hyperinsulinemic Watanabe heritable hyperlipidemic (WHHL) rabbits or obese Zucker rats show that the PPARγ ligand troglitazone increases insulin sensitivity and lowers blood pressure [159–161]. Similarly, troglitazone has been shown to be effective in ameliorating hypertension in patients with type II diabetes [158]. It has been suggested that the antihypertensive effect of TZDs is a result of improved insulin resistance, since enhanced insulin sensitivity has been found to be associated with lower blood pressure both in diabetic animals [162–165] and humans [166]. Direct vascular effects of PPARγ also may play a role, since recent studies have identified PPARγ in both endothelium and vascular smooth muscle cells [167–171]. Studies on one-kidney, one-clip hypertensive rats, a model not associated with insulin resistance, shows that pioglitazone significantly lowers the blood pressure [172]. It is conceivable that vascular expression of PPARγ could modulate the release of vasodilator autacoids [173]. Troglitazone has been reported to dilate peripheral blood vessels both in vitro and in vivo in animals [173, 174] and humans [117, 175]. These effects seem to depend on prostaglandin synthesis since troglitazone-induced vasorelaxation was abolished by the prostaglandin synthase inhibitor indomethacin [175], suggesting that these vasorelaxant effects are mediated by locally generated prostanooids, possibly endothelial derived prostacyclin [175]. Other studies suggest that antihypertensive effects of TZDs also involve decreased fatty acid levels, blockade of L-type calcium channels and modulation of vascular production of vasoactive peptides including type-C natriuretic peptide, endothelin, and plasminogen activator inhibitor-1 (PAI-1) [176, 177]. Alternatively, PPARγ may directly affect vascular smooth muscle cell (VSMC) tone. Troglitazone has been shown to inhibit VSMC proliferation and migration in vitro [40, 168], as well as following angioplasty [178]. Finally, PPARγ has been identified in collecting ducts and glomeruli (abstract; Guan et al, J Am Soc Nephrol 11:A3381, 2000) [35]. Constitutive expression of PPARγ in these segments might have important regulatory effects on salt and water absorption. These effects could contribute to the edema complicating treatment using TZDs in patients and animals [161, 179, 180]. Taken together, these data suggest that PPARγ expression con-
PPARs and kidney disease

The role of PPAR isoform expression in the kidney is just now being elucidated. All three PPAR isoforms are expressed in the kidney of many species including humans [35, 69, 72]. PPARα expression predominates in the proximal tubule and thick limb, and could contribute to dietary lipid-induced gene expression of peroxisomal and mitochondrial β-oxidation in these segments [181]. The PPARα agonist clofibrate significantly induced expression of β-oxidation enzymes in renal cortex, including long-chain acyl CoA dehydrogenase (LCAD), medium-chain acyl CoA dehydrogenase (MCAD) and acyl CoA oxidase (ACO). These data suggest that renal PPARα plays a major role in triggering fatty acid utilization and the adaptive response to dietary lipids in the kidney. Notably, renal PPARα also colocalizes with P450 4 A enzymes, which are known PPARα target genes [93] that appear to be involved in blood pressure regulation [182]. Interestingly, clofibrate has been shown to reduce blood pressure in Dahl salt-sensitive rats [183]. These findings suggest that PPARα participates in blood pressure regulation through activation of P450 4 A enzymes in the proximal tubules. In addition, PPARα has also been shown to play an important role in maintaining a sustained balance of energy production/utilization in the kidney through regulating expression of genes involved in fatty acid β-oxidation [184]. This effect may contribute to the observation that PPARα ligands appear to protect kidney from ischemia/reperfusion injury in rats [184]. Mice lacking the PPARα gene exhibit more severe cortical necrosis and worse kidney function than wild-type control animals [184]. These findings help to explain the molecular mechanisms by which ischemia/reperfusion leads to suppression of fatty acid β-oxidation, and might provide a new therapeutic strategy for ischemic renal injury.

PPARγ mRNA is also highly expressed in the kidney, but in contrast to PPARα is predominantly expressed in collecting ducts, which suggests that this isoform might play a role in systemic water and sodium retention. In fact, in both rodents and humans, treatment with TZD PPARγ ligands may cause marked fluid retention, edema and hemodilution [161, 179, 180]. Although other mechanisms may be involved, the possibility that collecting duct PPARγ activation is responsible for water and sodium retention in TZD-treated diabetic patients has not been examined.

Cultured mesangial cells have also been found to express PPARγ [70]. Interestingly they also may produce a precursor of 15dPGJ2, a putative endogenous PPARγ ligand [185]. A preliminary report also demonstrates the presence of PPARγ in freshly isolated glomeruli, and suggest that a paracrine PPARγ system exists in glomerular mesangial cells (abstract: Guan et al, J Am Soc Nephrol 11:A3381, 2000). It is well established that mesangial cells play an important role in the progression of nephropathy. During inflammatory injury or high glucose stimulation, mesangial cells undergo a process of activation from a quiescent phenotype to a proliferative myofibroblast-like phenotype, characterized by increased α-smooth muscle actin and pro-inflammatory cytokines, as well as enhanced production of extracellular matrix proteins [186–188]. This phenotypic alteration has been considered a fundamental feature in the development of diabetic nephropathy and glomerulonephritis. Studies by Asano et al showed that the TZD PPARγ ligands, troglitazone, and endogenous PPARγ ligand, 15dPGJ2, can significantly suppress the production of α-smooth muscle actin, indicating that PPARγ activation may inhibit de-differentiation of mesangial cells [70]. In addition, in vitro studies have shown PPARγ ligands can significantly inhibit proliferation of mesangial cells in a dose-dependent manner [70]. These data suggest that PPARγ activation may reverse the phenotypic change of mesangial cells and induce cell growth arrest and reduction of extracellular matrix production. Therefore, glomerular PPARγ activation could be a therapeutic target for treating diabetic nephropathy. Indeed, troglitazone treatment has been shown to ameliorate microalbuminuria both in the streptozotocin-induced diabetic rat and type II diabetic patients [189, 190]. In the fa/fa rat, a genetic model of type II diabetes, intervention with troglitazone decreased proteinuria and halted the early onset and progression of mesangial expansion and glomerulosclerosis [191]. Similarly, pioglitazone and rosiglitazone markedly reduce proteinuria and slow the progression of diabetic nephropathy in genetically obese diabetic rats [161, 192].

Accumulating evidence suggests that TZDs have direct and beneficial glomerular effects. A recent study in streptozotocin-induced diabetic rat showed that troglitazone was not only able to prevent diabetic glomerular hyperfiltration and albuminuria, but also to reduce mRNA expression of extracellular matrix proteins (fibronectin and type IV collagen) and TGF-β1 in diabetic glomeruli. These beneficial effects in insulin-dependent diabetes mellitus suggest that PPARγ ligands can protect glomerular function independently of their capacity to increase glucose tolerance. Furthermore, in a nondiabetic glomerulosclerotic model, PPARγ ligands were effective in preventing the deterioration of renal function. In a 5/6 ablation model of renal failure, Ma et al recently noted that troglitazone treatment significantly reduced proteinuria, serum creatinine level and glomerulosclerosis possibly via inhibition of glomerular cell proliferation and reduction of TGF-β1 expression in glomeruli and renal tubules, suggesting a paracrine PPARγ system in glomerular mesangial cells (Note added in proof). This is consistent with
other studies showing a beneficial effect of troglitazone on glomeruli. Taken together, these studies suggest that TZDs may be used as possible therapeutic agents for diabetic nephropathy and glomerulosclerosis.

Finally, both PPARα and PPARγ have potent anti-inflammatory effects in macrophages [42, 193]. It is reasonable to anticipate that PPAR activation might also play a role in renal inflammation, including glomerulonephritis and interstitial nephritis; however, thus far few reports have addressed this important issue. A recent preliminary report suggested that the PPARγ ligand, troglitazone, significantly enhanced rather than repressed glomerular expression of MCP-1, a critical cytokine in recruiting monocytes in glomeruli, in a rat model of mesangiproliferative glomerulonephritis (abstract; Panzer et al., J Am Soc Nephrol 11:A2625, 2000). These results raise the possibility that certain PPARγ ligands might promote, rather than inhibit, the progression of glomerulonephritis. If so, PPARγ antagonists could provide a novel therapeutic approach to renal inflammatory diseases.

**PPARs, inflammation and atherosclerosis**

Renovascular stenosis and arteriemboli represent increasingly common disorders contributing to renal dysfunction in elderly diabetic patients [194, 195]. PPAR activation also may modify the course of atherosclerosis via effects on inflammation, modulation of lipid accumulation in the arterial wall and altered endothelial function, proliferation of vascular smooth muscle, and foam cell formation. All three PPAR isoforms may modify the progression of atherosclerosis through multiple mechanisms including modulation of plasma lipoprotein concentration, foam cell formation, inflammatory response and pro-atherosclerotic protein level.

Hypolipidemic fibrates (clofibrate and bezafibrate) are potent PPARα agonists proven to be beneficial in the prevention of atherosclerosis [196]. Formation of atherosclerotic lesions require recruitment of monocytes into the arterial wall through expression of specific adhesion molecules by endothelial cells. Not only is PPARα expressed in human endothelial cells [197], but its activation decreases the expression of the adhesion molecule VCAM-1 in these cells [198]. Moreover, PPARα has been implicated in inflammatory processes of the atherosclerotic lesion, which is believed to be responsible for disruption of atherosclerotic plaque [199]. PPARα-deficient mice show a prolonged response to inflammatory stimuli, suggesting PPARα modulates inflammation [200]. In hyperlipidemic patients, the PPARα ligand fenofibrate, significantly decreased plasma concentrations of interleukin-6 (IL-6). Anti-inflammatory effects were also observed in cultured vascular smooth muscle cells (VSMCs), which participate in plaque formation and postangioplasty re-stenosis. PPARα is functionally active in VSMCs and another ligand, Wy14643, inhibited the IL-1-stimulated release of IL-6 and prostaglandin and expression of cyclooxygenase-2 (COX-2) [199]. Data suggest that these effects were mediated by inhibition of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), two ubiquitous transcription factors that transduce the effects of many pro-atherogenic and inflammatory factors [201–203]. PPARα has also been shown to lower the plasma concentration of fibrinogen, an important risk factor for cardiovascular disease, both in rat and in human [199, 204]. In addition, PPARα ligands effectively increased HDL cholesterol level and decreased the low-density lipoprotein (LDL) cholesterol level in hyperlipidemic patients, as a result of transcriptional induction of HDL apolipoproteins, apo A-I and apo A-II, and LPL, and inhibition of hepatic apo C-III production through the PPARα receptor (see above) [4].

Little is known about the role of PPARβ/δ in atherosclerosis. Recent evidence has emerged that PPARβ/δ might be a target for treatment of dyslipidemia since a PPARβ/δ ligand increases the HDL-cholesterol level [103]. Since hyperlipidemia is a key atherogenic factor, the effect of PPARβ/δ in increasing HDL-cholesterol may be beneficial in prevention of atherosclerosis.

PPARγ has also been implicated in at least three pathologic processes in atherosclerosis: foam cell differentiation, inflammatory reaction and cell proliferation. The infiltrating monocytes in the intima of the arterial wall take up oxidized LDL via scavenger receptors (SRα/II, SR-BI, CD36, etc.), promoting accumulation of intracellular lipids and generation of lipid-laden foam cells [205]. It has been shown that the oxidized LDL (OxLDL) scavenger receptor CD36 (fat) is under direct control of PPARγ. PPARγ ligand, in combination of RXRα agonist LG268, significantly up-regulates the expression of CD36 and the binding of OxLDL in a monocyte cell line [30]. Interestingly, OxLDL contains naturally occurring PPARγ ligands (9-HODE and 13-HODE). Furthermore, in the presence of OxLDL, PPARγ expression was markedly induced [206]. This positive feedback loop could promote atherosclerosis by stimulating the uptake of OxLDL in macrophage/foam cells. Cyto-kines produced by these activated macrophage/foam cells include M-CSF, IL-1, and TNF-α, and they initiate inflammation and induce proliferation of VSMCs. In contrast, other effects of PPARγ might be beneficial in the treatment of atherosclerosis. An anti-inflammatory effect of PPARγ in monocytes has been described. PPARγ has been shown to reduce cytokine (TNFα, IL-1, and IL-6) production [42], probably by inhibiting the activity of pro-inflammatory transcription factors such as NF-κB, AP-1 and STAT [207]. Other favorable effects of PPARγ include induction of apoptosis in monocytes [208], inhibition of proliferation of VSMCs [37, 178], suppression of metalloproteinase-9 expression [39], and reduction of plasma triglycerides [209]. On the basis of
these data, an important role for PPAR\(\gamma\) in atherosclerosis remains uncertain.

Most recently, two studies provide clear evidence that TZDs treatment reduced atherosclerosis in vivo [210, 211]. In the Watanabe heritable hyperlipidemic (WHHL) rabbits, troglitazone treatment potently developed atherosclerotic lesions [210]. Similarly, rosiglitazone improved atherosclerotic lesions in LDL receptor knockout mice [211]. These data suggest that the anti-atherogenic effect of TZDs outweighs its pro-atherogenic effects in vivo. Although it is uncertain whether the reduction in atherosclerosis following TZD treatment is a direct effect of PPAR\(\gamma\) activation in macrophages or an indirect effect secondary to improvements of insulin sensitivity, several lines of evidence demonstrated that PPAR\(\gamma\) is not required for differentiation of macrophage lineage and the formation of foam cells [212, 213]. More importantly, PPAR\(\gamma\) activation can promote cholesterol removal from human foam cells through stimulation of ABCA1, a protein involved in cholesterol export [212]. Additionally, PPAR\(\gamma\) activation also results in the down-regulation of the LDL receptor scavenger SR-A in mouse macrophage [213]. Thus, macrophage is a direct target for TZD and PPAR\(\gamma\) activation has multiple effects on the influx and efflux of cholesterol and oxidized lipid, countering their atherosclerotic effects of CD36 induction [214]. Data from a clinical trial of PPAR\(\gamma\) ligands in dyslipidemic patients without type II diabetic patients will be required to clarify the role of PPAR\(\gamma\) in this setting of disease.

PPARs, the cell cycle and cancer

Effects of PPARs on renal cell proliferation seem likely, but remain unexplored. All three isoforms of PPAR have been suggested to play a role in regulating the cell cycle and in carcinogenesis. PPAR\(\alpha\), the predominant form of PPAR in the liver, is involved in the growth promoting and hepatocarcinogenic effect of peroxisome proliferators in rodents [15]. However, these rodent data do not appear relevant to humans. No carcinogenic effect of peroxisome proliferators has been shown in humans, possibly because of the much lower level of PPAR\(\alpha\) expression in human hepatocytes as a result of exon 6 splicing of PPAR\(\alpha\) transcripts [53].

Potent effects of PPAR\(\gamma\) on cell proliferation and cell cycling have been described. PPAR\(\gamma\) ligands can trigger cell cycle arrest in NIH3T3 cells and HIB-1B cells [215]. PPAR\(\gamma\) ligands can also induce terminal differentiation and withdrawal of human liposarcoma cells from the cell cycle [216]. Importantly, TZD PPAR\(\gamma\) ligands have been found to slow the progression of advanced liposarcoma in humans [217]. Given the expression of PPAR\(\gamma\) in non-adipose tissues, the effect of PPAR\(\gamma\) on human breast cancer, gastric cancer, prostate cancer, colon cancer and transitional cell bladder cancer have been explored.

Treatment of cultured breast cancer cells with troglitazone results in cell growth arrest and promotes differentiation [44]. Troglitazone has also been shown to inhibit tumor growth and induce apoptosis in human breast cancer cells in vitro and in BNX mice [218]. Moreover, another PPAR\(\gamma\) ligand, GW7845, has been shown to decrease tumor incidence, tumor growth and tumor burden in the NMU induced mammary carcinoma [219]. These data suggest that PPAR\(\gamma\) ligands may be used as novel, nontoxic and selective chemotherapeutic agents for human breast cancer. A role for PPAR\(\gamma\) activation also has been suggested in human transitional bladder cancers [46]. PPAR\(\gamma\) is highly expressed in normal as well as malignant human transitional cell bladder cancer. Several PPAR\(\gamma\) ligands (including troglitazone, ciglitazone and 15dPGJ2) significantly inhibit growth in cultured human bladder cancer cells, and this action is associated with induction of cyclin-dependent kinase inhibitors (p21 and p16) and reduction of cyclin D expression. Importantly, RXR\(\alpha\) ligands 9-cis retinoic acid and LG100026 exhibited synergy with PPAR\(\gamma\) ligands in inducing cell death. Anti-tumor effects of PPAR\(\gamma\) ligands have been observed in human prostate cancer and gastric cancer as well [43, 220]. Conversely, the role of PPAR\(\gamma\) in human colon cancer remains controversial. While PPAR\(\gamma\) is expressed in human colon tumor and in cultured colon cell lines [221, 222], two groups recently reported that PPAR\(\gamma\) ligands promote polyp formation in APC\(^{min/+}\) mice, a murine model of the human genetic disease familial adenomatous polyposis coli (FAP) [223, 224]. These studies showed that when such mice are treated with troglitazone or with rosiglitazone, they develop an increased frequency of large but not small bowel polyps. In contrast, troglitazone reduces colon tumor xenograft volume in nude mice [222]. This corresponds to in vitro studies showing that activation of PPAR\(\gamma\) results in colon cancer cell cycle arrest (G\(\text{\text{1}}\) phase) and differentiation [221], supporting the idea that PPAR\(\gamma\) activation might be beneficial for human colon cancer as well. The different effects of troglitazone on polyp formation and cancer growth may reflect important biological differences in the two processes.

Recently, an important role for PPAR\(\beta/\delta\) in carcinogenesis has been proposed [65]. PPAR\(\beta/\delta\) expression appears to be increased in colorectal cancer and localized in dysplastic epithelial cells [225]. The NSAID sulindac, which suppress colorectal tumorigenesis, can antagonize PPAR\(\beta/\delta\)-activated gene transcription in an in vitro assay system. These findings suggest that NSAIDs may inhibit tumorigenesis through inhibition of PPAR\(\beta/\delta\) activity, thereby contributing to their chemopreventive effects [226], and raise the possibility that PPAR\(\beta/\delta\) antagonists might have chemopreventive effects in human colorectal cancer. Specific roles of PPARs in renal cancers and cystic disease remain unexplored.
SUMMARY

In summary, PPARs are widely expressed throughout the body and are potent regulators of cellular metabolism. Activation of PPARs can be selectively achieved with specific ligands resulting in distinct biologic effects. Activation of PPARα by fibrates activates expression of genes involved in lipid catabolism. PPARγ activation by thiazolidinediones and 15dPGJ2 exerts many diverse biological effects on adipogenesis, inflammation, insulin sensitivity and tumorigenesis. PPARβ/δ, possibly activated by prostacyclin and other lipids, may be involved in lipid metabolism and tumorigenesis. Given the high expression of all three isoforms in the kidney, PPARs may play an important role in renal physiology and pathophysiology. The availability of PPAR-selective agonists and antagonists provide a new approach to modulate renal function in disease states including diabetic nephropathy, glomerulonephritis, glomerulosclerosis, hypertensive nephropathy, and diseases of renal epithelial proliferation. The use of these compounds in treating renal disease awaits experimental testing.

APPENDIX

Abbreviations used in this article are: ACO, acyl CoA oxidase; ACS, acyl CoA synthase; AFl, activation function 1; ALBP, adipocyte lipid-binding protein; AP-1, activator protein-1; aP2, adipocyte fatty acid-binding protein; APC, adenosomatous polyposis coli; apo, apolipoprotein; ATP, adenosine 5'-triphosphate; BMM, body mass index; CAP, c-Myb-associated protein; C/EBPs, CAAT/enhancer binding proteins; COX, cyclooxygenase; CYP4a, cytochrome P450 4A; DBD, DNA binding domain; EPA, eicosapentaenoic acid; ES, embryonic stem; FAP, familial adenomatous polyposis; FAS, fat-specific hormone-sensitive lipase; FAT, fatty acid translocase; FATP, fatty acid transport protein; HD, enoyl-CoA hydratase/dehydrogenase multifunctional enzyme; IL, interleukin; LBD, ligand-binding domain; LCAD, long-chain acyl CoA dehydrogenase; LDL, low-density lipoprotein; L-FABP, hepatic cytosolic fatty acid binding protein; LPL, lipoprotein lipase; LTB4, leukotriene B4; MAP, mitogen-activated protein; MCAD, medium-chain acyl CoA dehydrogenase; MDA, malondialdehyde; mPPARγ, mRNA subtype transcribed from an independent promoter; MCP, monocyte chemotactic protein; MCN, Vanderbilt University Medical Center; MPP, mitochondria peroxisome proliferator-activated receptor; NBC, nuclear factor-κB; NSAID, nonsteroidal antiinflammatory drug; OxLDL, oxidized low-density lipoprotein; PGD2, prostaglandin D2; PPARs, peroxisome proliferator-activated receptors; PPRE, peroxisome proliferator response element; SREBPs, sterol regulatory element binding proteins; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; T2Ds, thiazolidinediones; UCP, uncoupling proteins; VACAM, vascular cell adhesion molecule; VSMC, vascular smooth muscle cell; WHHL, Watanabe heritable hyperlipidemia.

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