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Peroxisome Proliferator-Activated Receptor-Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AAA, OOA and BOA managed the literature searches while author OOA wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Peroxisomes are subcellular organelles found in most plant and animal cells that perform diverse metabolic functions including hydrogen peroxide (H_2O_2)-based respiration, Î²-oxidation of fatty acids (FAs), and cholesterol metabolism. Peroxisomes are found in most eukaryotic cells, and their essential role has been emphasized by the discoveries of several human disorders caused by the lack of peroxisomes. Peroxisomes are unique for their ability to proliferate in response to several structurally different chemicals, which are designated "peroxisome proliferators (PPs)," in rodent liver cells. Peroxisome proliferator-activated receptors (PPARs) proteins belong to the superfamily of a phylogenetically related protein termed nuclear hormone factor. Activation of PPAR-α reduces triglyceride level and is involved in regulation of energy homeostasis. Activation of PPAR-γ causes insulin sensitization and enhances glucose metabolism, whereas activation of PPAR-β/δ enhances fatty acids metabolism. Thus, PPAR family of nuclear receptors plays a major regulatory role in energy homeostasis and metabolic function. Since intervention of PPAR agonist can provide therapeutic targets for a range of diseases such as dyslipidemia, diabetes, obesity, inflammation, a neurodegenerative disorder, and cancer, this review was carried out to update existing knowledge on these nuclear receptors.

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1. INTRODUCTION

Peroxisomes are subcellular organelles found in most plant and animal cells that perform diverse metabolic functions including H_2O_2-based respiration, β-oxidation of fatty acids (FAs), and cholesterol metabolism [1,2]. Peroxisomes are found in most eukaryotic cells, and their essential role has been emphasized by the discoveries of several human disorders caused by the lack of peroxisomes [2]. Peroxisomes are unique for their ability to proliferate in response to several structurally different chemicals, which are designated "peroxisome proliferators (PPs)," in rodent liver cells [3]. Peroxisome proliferator-activated receptors (PPARs) proteins belong to the superfamily of a phylogenetically related protein termed nuclear hormone factor [4]. PPARs were identified in rodents in 1990; it mainly exists in three subtypes comprising of: α, β/δ and γ, each of which mediates the physiological actions of a large variety of Fatty acid and Fatty acid-derived molecules [5]. Activation of PPAR-α reduces triglyceride level and is involved in regulation of energy homeostasis. Activation of PPAR-γ causes insulin sensitization and enhances glucose metabolism, whereas activation of PPAR-β/δ enhances fatty acids metabolism. Thus, PPAR family of nuclear receptors plays a major regulatory role in energy homeostasis and metabolic function [6].

2. STRUCTURE

Structurally, PPARs are similar to steroid or thyroid hormone receptor and are stimulated in response to small lipophilic ligands [6]. The PPARs possess the canonical domain structure common to other nuclear receptor family members, including the amino-terminal AF-1 transactivation domain, followed by a DNA-binding domain, and dimerization and ligand-binding domain with a ligand-dependent trans activation function AF-2 located at the carboxy-terminal region [7]. PPARs, which consist of PPAR-α (NR1C1), PPAR-β/δ (NR1C2, hereafter referred to as PPAR-δ), and PPAR-γ (NR1C3), are encoded by three different genes (PPARA, PPARD, and PPARG) located at chromosomes 22, 6, and three respectively [8].

3. MECHANISM OF ACTION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS

To be transcriptionally active, All PPAR form heterodimers with retinoid X receptor (RXR) thereby forming a complex that then binds to a specific DNA response element [9]. These DNA sequences are termed PPREs (peroxisome proliferator hormone response elements) present in promoter areas of target genes [4]. In this way, PPARs can transactivate specific target genes in a ligand-dependent manner [10]. Their natural

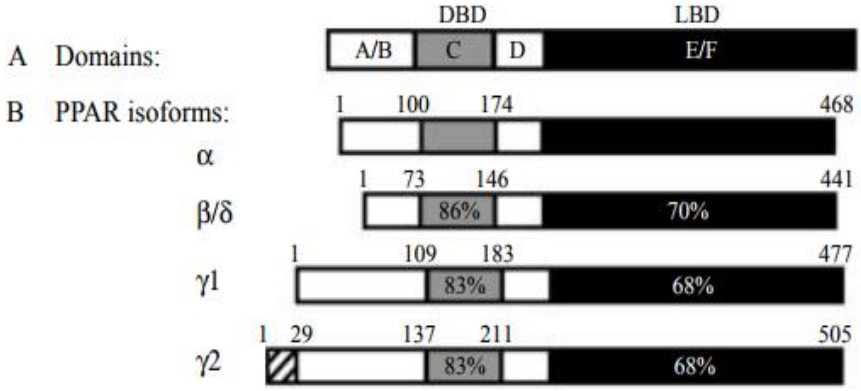

Fig. 1. Schematic representation of the structures of PPARs [8]

(A) Modular domain structures of nuclear receptors in general. Two most conserved domains, DBD (C domain) and LBD (E/F domain), are colored in gray and black respectively. (B) The human PPAR homologs. Compared with the DBD of PPAR-α (NR1C1), sequence homology is 86 and 83% in PPAR-β/δ (NR1C2) and PPAR-γ 1/2 (NR1C3) respectively. In LBD, sequences are less conserved with only 70 and 68% of homology for PPAR-β/δ and PPAR-γ 1/2 respectively using the sequence of PPAR-α as a reference

activating ligands are lipid-derived substrates [6]. In the absence of the ligands, these heterodimers are associated with co- repressor complex, which block gene transcription. Moreover, PPARs can negatively regulate the expression of genes without binding to DNA [11] or inhibit the activities of other transcription factors by direct interaction via a mechanism known as ligand-dependent trans-repression [12]. Trans-repression may occur either through physical interaction of PPARs with other transcription factors or co-activators or through modulation of kinase activity preventing activation of downstream transcription factors [13]. It is established that posttranslational modifications by phosphorylation, ubiquitination, or SUMOylation are involved in the regulation of PPAR activity and functions [14]. In this context, different kinase signaling pathways, including the Mitogen-activated protein kinase (MAPKs), 5' AMP-activated protein kinase (AMPK), Glycogen synthase kinase 3- beta (GSK3β), protein kinase (PKA), and protein kinase (PKC), phosphorylate PPARs at several residues to either increase or decrease their transcriptional activity, in a ligand-dependent or ligand-independent manner. Like PPARs, RXR exists as three distinct isoforms: RXR-α, β, and γ, all of which are activated by the endogenous agonist 9-cis retinoic acid [15].

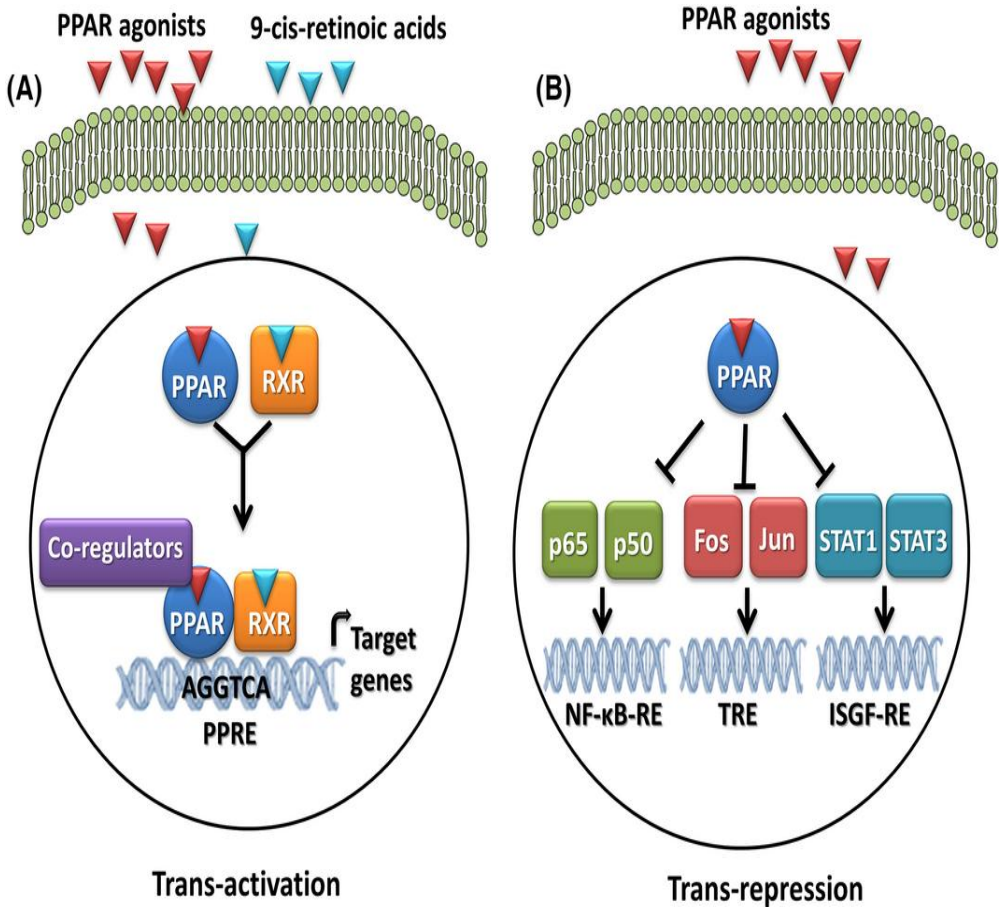

Fig. 2. Molecular mechanisms of PPAR actions [15]

(A) PPARs are ligand-activated transcription factors that regulate gene expression by heterodimerizing with RXR and binding to specific DNA sequence elements (PPREs) located in the promoter region of target genes using coactivators binding (trans-activation). (B) PPARs can also negatively regulate the expression of genes without binding to DNA (transrepression). Through this mechanism, PPARs inhibit the activity of several transcription factors such as NF-κB, STATs, cJun, and c-Fos in a DNA-binding-independent manner. PPAR, peroxisome proliferator-activated receptors; NF-κB-RE, nuclear factor-κB response element; PPRE, PPAR response element; RXR, retinoid X receptor; STATs, signal transducer and activator of transcription; TRE, TPA (12-O-tetradecanoyl phorbol-13-acetate) response element; ISGF-RE, interferon-stimulated gene factor response element

4. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS ISOFORMS AND TISSUE DISTRIBUTION

PPARs are transcription factors that belong to the Superfamily of nuclear receptors. Other members of this family include retinoic acid, estrogen, thyroid, vitamin D, and glucocorticoid receptors, and several other proteins involved in xenobiotic metabolism [6]. The family of PPARs is represented by the following three members: PPAR-α, PPAR-δ, and PPAR-γ. They play an essential role in energy metabolism; however, they differ in the spectrum of their activity–PPAR-γ regulates energy storage, whereas PPAR-α is expressed predominantly in the liver, and to a lesser extent, in muscle, in the heart, and in bone and PPAR-δ present ubiquitously expressed in the whole body regulate energy expenditure; expression of PPAR-γ in endothelial cells, vascular smooth muscle cells [16].

4.1 Peroxisome Proliferator-Activated Receptor-Alpha (PPAR-α)

The upper-α expression is relatively high in hepatocytes, enterocytes, vascular and immune cell types such as monocytes/macrophages, endothelial cells, smooth muscle cells, lymphocytes, non-neuronal cells like microglia and astroglia [17,18]. In the liver, PPAR-α plays a crucial role in fatty acid oxidation,

Fig. 3. Schematic representation of PPAR-α target gene transcription dependent on ligand binding and recruitment of coactivators [21]

PPAR-α can be activated by certain ligands, such as PUFAs, 16:00/18:1-GPC, and fibrates, which modulate transcription of PPAR-α target genes. However, DNA binding requires the formation of a heterodimer containing PPAR-α and retinoic X receptor (RXR) α, that can interact with peroxisome proliferator responsive elements (PPRE). The assembly of this heterodimer with coactivator proteins facilitates the recruitment of the basal transcription machinery with RNA polymerase II for transcription of specific target genes.

APO, apolipoprotein; BAF60, Brahma-related gene 1/Brahma -associated factor 60; CD36, Cluster of Differentiation 36; CPT-1, Carnitine palmitoyltransferase I; CYP, cytochrome P-450; FGF21, fibroblast growth factor 21; HMGCAS2, hydroxymethylglutaryl CoA synthase 2; p300, histone acetyltransferase p300; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-α PPRE, peroxisome proliferator responsive element; RNA POLII, RNA polymerase II; SRC, steroid receptor coactivator; SREBP1-c, sterol regulatory element binding protein 1c; SW1/SNF, switch/sucrose are said to be nonfermentable chromatin-modifying complex

which provides energy for peripheral tissues, elevated mitochondrial and peroxisomal fatty acid β-oxidation rates, such as liver, heart muscle, kidney, skeletal muscle, retina, and brown adipose tissues, and have a potential role in oxidant/antioxidant pathway [19,20]. PPAR-α ligands can be either synthetic or endogenous fatty acids, and fatty acid-derived compounds are natural ligands for PPAR-α [21].

In vivo and *In vitro* studies demonstrate that PPAR-α plays a central role in lipid and lipoprotein metabolism, and thereby decreases dyslipidemia associated with metabolic syndrome [22,23,24]. In the fasting state, PPAR-α is activated by adipose-derived fatty acid, thereby enhancing the generation of ketone bodies through fatty acid oxidation in liver and peripheral blood mononuclear cells [25].

4.2 Peroxisome Proliferator-Activated Receptor–γ (PPAR-γ)

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. PPARγ is predominantly expressed in adipose tissue and also in vasculature including vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) [26]. PPARγ forms a heterodimer with RXR and binds to the PPAR response elements (PPREs) in the promoter region of target genes [27]. PPAR-γ acts as sensors of hormones, vitamins, endogenous metabolites, and xenobiotic compounds; the nuclear receptors thus control the expression of a very large number of genes [28]. When activated by various natural and synthetic ligands such as prostaglandin metabolite 15d-PGJ2 [29] and the insulin sensitizer rosiglitazone [28], PPARγ transactivates the gene expression and regulates adipogenesis [30] and insulin response [31]. PPAR-γ has been known for some time to regulate adipocyte differentiation, fatty acid storage, and glucose metabolism, and is a target of antidiabetic drugs [28]. PPAR-γ agonist improves insulin resistance by opposing the effect of Tumor necrosis factor-α (TNF-α) in adipocytes [32]. PPAR-γ enhances the expression of some genes encoding proteins involved in glucose and lipid metabolism [33]. Also, PPARγ possesses antiatherogenic and anti-inflammatory actions in ECs [34]. Expression of the inducible nitric oxide synthase (iNOS) in the brain may contribute to neurotoxicity in Alzheimer's disease. PPAR-γ agonists such as antidiabetic thiazolidinedione troglitazone, the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen and 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a naturally occurring agonist can modulate inflammatory responses in brain by reducing iNOS expression and neuronal cell death whereas the anti-inflammatory actions of PPARγ are not attributable to inhibition of cyclooxygenase because injection of selective cyclooxygenase inhibitor NS-398 had no effect [35].

4.3 Peroxisome Proliferator-Activated Receptor-β/δ

PPAR-δ/β is expressed in skeletal muscle, adipocytes, macrophages, lungs, brain, and skin. It promotes fatty acid metabolism and suppresses macrophage-derived inflammation [36]. Newly synthesized compounds such as GW501516, GW610742, and GW0742X are shown to have high selectivity to PPARδ [37]. PPAR-δ has been noted to reduce

Table 1. Tissue distribution and main functions of PPAR isoforms

PPARα	PPARβ/δ	PPARγ
Tissue distribution		
Abundantly and ubiquitously expressed in: Heart, Liver, Kidney, Skeletal muscle, and Pancreas.	Abundantly and ubiquitously expressed in: Heart, Liver, Kidney, Skeletal muscle, Pancreas.	Abundantly expressed in: Adipose tissue, Immune system (macrophages), Lower levels in: Liver, Heart, Skeletal muscle and Bone marrow
Function		
↑ FA uptake ↑ FA storage ↑ FA β-oxidation ↓ Glucose oxidation ↓ Inflammation	↑ FA β-oxidation ↑ Glucose oxidation ↑ Glycolysis ↓ Inflammation	↑ FA storage ↑ FA uptake ↑ FA β-oxidation ↑ Insulin sensitization ↓ Inflammation

(↑ Increase, ↓ decrease); FA-Fatty acids

the expression of inflammatory mediators and adhesion molecules, suggesting their potential role in attenuating atherogenesis [38]. Few studies have shown that PPAR-δ ligands have the potential to inhibit cardiac hypertrophy due to their inhibitory activity on nuclear factor-κB (NF-κB), a transcription factor that produces inflammatory cytokines [6].

5. INTERACTION BETWEEN FATTY ACID BINDING PROTEINS WITH PPAR

Intracellular long-chain fatty acids (FAs) are key components in the synthesis of cellular membranes as well as being utilized as signaling molecules and for energy delivery [39]. The preservation of a proper balance between absorption, secretion, and storage of FA is, therefore, integral for cellular physiology [40]. Increasingly prominent diseases such as obesity, cardiovascular diseases, type II diabetes, and atherosclerosis, to a large extent, all evolve from disorders of lipid metabolism. In vivo, due to their poor aqueous solubility, FAs are bound and transported by a class of intracellular lipid binding proteins (iLBPs) termed fatty acid binding proteins (FABPs) [41]. Fatty acid binding proteins (FABPs) act as intracellular shuttles for fatty acids as well as lipophilic xenobiotics to the nucleus, where these ligands are released to a group of nuclear receptors called the peroxisome proliferator activated receptors (PPARs). PPAR mediated gene activation is ultimately involved in the maintenance of cellular homeostasis through the transcriptional regulation of metabolic enzymes and transporters that target the activating ligand [42]. The expression of genes involved in FA metabolism and glucose homeostasis is controlled by nuclear hormone receptors (NHRs); in particular, a class of NHRs known as peroxisome proliferator activated receptors (PPARs) [43]. PPARs are ligand-activated transcription factors that respond to FA and eicosanoids [44]. The most prevalent iLBPs in the enterocyte, the innate intestinal- (I-) FABP and L-FABP together constitute 3%–6% of the total cytosolic protein [45]. While L-FABP is known to bind FA with high affinity, in recent reports it's shown that both L- and I-FABP can specifically bind a structurally diverse set of non-FA lipophilic drugs [46]. In enterocytes, all three PPAR sub-types are present, the PPARα and PPARδ subtypes are predominantly expressed, and to a lesser extent PPARγ [47]. Whereas in hepatocytes, L-FABP is highly expressed together with PPARα, PPARδ and PPARγ are also expressed to a lesser extent [48]. Given the high abundance of these FABPs in the intestinal epithelia, it is tenable that L- and I-FABP potentially facilitate the intestinal absorption and trafficking of lipophilic drugs to their PPAR targets [42].

6. AGONISTS OF VARIOUS PPARS RECEPTORS

In light of the central regulatory role of PPARs in lipid homeostasis, it follows that the development of novel therapeutic ligands with improved pharmacological profiles to target these NHRs has become an important research priority in the pharmaceutical industry [49]. Dysfunction of these regulatory functions of PPARs leads to the manifestation of prominent human diseases such as obesity, cardiovascular diseases, type II diabetes, and atherosclerosis. Accordingly, PPARs are important targets for antidyslipidemic drugs [50].

Table 2. Natural and synthetic agonists of PPARs

	Natural agonists	Synthetic agonists
PPARα	Unsaturated and saturated fatty acids 8-hydroxy-eicosapentaenoic acid Leukotriene B4 8-hydroxy-eicosatetraenoic acid	WY-14643 Fibrates (clofibrate, fenofibrate)
PPARβ/δ	Unsaturated and saturated fatty acids Carbaprostacyclin Prostaglandin A1 15- hydroxy-eicosatetraenoic acid	GW0742 GW501516 LCI765
PPARγ	Unsaturated fatty acids 15-deoxy-D12,14-prostaglandin J2 Prostaglandin PGJ2 9- and 13-hydroxy-octadecadienoic acid	Thiazolidinediones (rosiglitazone, pioglitizone, troglitazone, ciglitazone)

Natural and synthetic ligands have been reported for the three PPAR isotypes [51,52]. For PPARα, ligands include natural unsaturated fatty acids (FAs), leukotriene, hydroxyeicosatetraenoic acids (HETEs), and synthetic hypolipemia-inducing drugs such as fibrates [53]. The fibrate hypolipidemic drug classes preferentially bind PPARα [54]. For PPARδ, ligands are less well known, but FAs have been suggested to be natural ligands for this subtype of PPAR [53]. Recent studies identified a few more PPARδ agonists, namely tetradecylthioacetic acid (TTA), L-165041, and GW501516 [55,56,57]. For PPARγ, endogenous ligands include polyunsaturated FAs, prostanoids, and oxidized FAs found in low-density lipoproteins [58,59]. Synthetic ligands for PPARγ include anti-diabetic drugs, such as rosiglitazone and pioglitazone of the thiazolidinedione class [60] and NSAIDs [61].

7. PHARMACOLOGICAL POTENTIALS OF PPARS RECEPTORS

7.1 Obesity

PPAR-α ligands such as fibrates have been used for the treatment of dyslipidemia due to their ability to lower plasma triglyceride levels and elevate HDL cholesterol levels. PPAR-α activators have been shown to regulate obesity in rodents by both increasing hepatic fatty acid oxidation and decreasing the levels of circulating triglycerides responsible for adipose cell hypertrophy and hyperplasia. However, these effects of PPAR-α on obesity and lipid metabolism may be exerted with sexual dimorphism and seem to be influenced by estrogen. Estrogen inhibits the actions of PPARα on obesity and lipid metabolism through its effects on PPARα-dependent regulation of target genes [62]. There is evidence that suggest that PPARs may be interesting therapeutic targets to modulate obesity-induced inflammation [63].

7.2 Inflammation

Inflammatory conditions are mainly characterized by activation of macrophages and monocytes at the injury site which subsequently increases the release of proinflammatory mediators like Tumor necrosis factor-α (TNF-α), Interleukin 6 (IL-6), and Interleukin 1 beta (IL-1β) which in turn stimulates the production of cyclooxygenase (COX) products. PPAR-α and fenofibrate reduce pain and inflammation and further inhibits the release of several pro-inflammatory and pro-angiogenic enzymes (e.g., inducible nitric oxide synthase (iNOS), chymase, and metalloproteinase MMP-9), and mediators (e.g., NO and TNF-α) [64,65]. PPAR-γ has been recognized as playing a fundamentally important role in the immune response through its ability to inhibit the expression of inflammatory cytokines and to direct the differentiation of immune cells toward anti-inflammatory phenotypes. In intestinal epithelium, PPARγ has been suggested to play an important role as an endogenous inhibitor of NF-κB–mediated inflammation [66]. A feature of PPAR-γ is the structural diversity of its ligands, which encompass endogenous metabolites, dietary compounds, and synthetic drugs. The high and increasing incidence of inflammatory and allergic disease, coupled with encouraging results from recent clinical trials, suggest that natural PPAR-γ agonists found in foods may be beneficial to human health by acting as anti-inflammatory molecules. PPAR-γ is therefore not only a target of the pharmaceutical industry but also of great potential interest to the food industry since it is activated by several natural dietary constituents [67].

7.3 Adipocyte Differentiation

Adipogenesis refers to the process of differentiation of the pre-adipocyte precursor cells into adipocytes that are capable of lipid filling, as well as the expression of hormones and cytokines. PPAR-γ regulates the expression of numerous genes involved in lipid metabolism, including aP2, PPCK, acyl-CoA synthase, and lipoprotein lipase (LPL) [27]. PPAR-γ has also been shown to control the expression of Fatty Acid Transport Protein 1 (FATP-1) and a cluster of differentiation 36/ platelet glycoprotein 4 (CD36), both involved in lipid uptake into adipocytes. These genes have all been shown to possess PPREs within their regulatory regions. PPAR-γ is mainly involved in the process of cell growth arrest, followed by progression into the fully differentiated adipocyte phenotype [68]. PPAR-γ and PPAR-β have both been implicated in molecular signaling that mediates adipocyte differentiation, whereas the role of PPAR-γ is well established in this process. The specific role of PPAR-γ is less certain. It has been reported that in the presence of standard differentiation medium, PPAR-γ is required for maximal adipocyte differentiation as PPAR-γ null adipocytes exhibit significantly impaired lipid accumulation and expression of adipose differentiate marker mRNAs [69].

7.4 Anti-cancer Effect

Peroxisome proliferator-activated receptor (PPAR) is a Double-Edged Sword in Cancer Therapy. PPAR-α stimulation appears to inhibit proliferation of human colon cancer cell lines and to reduce poly formation in the mouse model of familial adenomatous. PPAR-β (also referred to as PPARδ) in epithelial homeostasis have been described including the regulation of keratinocyte differentiation, apoptosis and cell proliferation, inflammation, and wound healing [70]. PPAR-γ not only controls the expression of genes involved in differentiations but also negatively regulates the cell cycle [71]. TZDs induce the tumor suppressor gene PTEN (Phosphatase and tensin homolog), which also contributes to their antiproliferative activity. PPAR-γ activation inhibits the proliferation of malignant cells, including those derived from liposarcoma, breast adenocarcinoma [72], prostate carcinoma, colorectal carcinoma, non-small-cell lung carcinoma, pancreatic carcinoma, bladder cancer, gastric carcinoma, and glial tumors of the brain [73]. Sarraf et al. [74] also demonstrated that troglitazone and rosiglitazone suppress the growth of human colonic cancer cells.

7.5 Neurodegenerative Disorder

PPAR-γ agonists have also shown efficacy in Parkinson disease, Alzheimer disease, brain injury, and ALS. They act on microglial cells and inhibit the microglial cells activation. The role of PPARs in modulating lipid and glucose metabolism is well established. More recently, PPARs have been demonstrated to modulate inflammation. For example, PPAR agonists inhibit the production of proinflammatory molecules by peripheral immune cells as well as resident glial cells. Furthermore, PPAR receptor agonists have proven effective in suppressing the development of animal models of CNS inflammatory and neurodegenerative disorders [75]. *In vivo* oral administration of the PPAR-γ agonist, pioglitazone reduced glial activation and the accumulation of Aβ-positive plaques in the hippocampus and cortex. Various neurodegenerative diseases are associated with electron transport chain enzyme activity reductions and increased mitochondrial-generated oxidative stress [76].

7.6 Lung Pathophysiology and Disease

PPARs plays a pivotal role in the regulation of multiple cellular events in lung pathogenesis. Such events include lung morphogenesis, the inhibition of the release of inflammatory mediators from lung immune and stromal/parenchymal cells *In vitro*, and reduction of both inflammation and damage in animal models of acute lung injury (ALI), ischemia-reperfusion injury, and allergic airways inflammation. PPAR-γ plays a central role in the regulation of critical aspects of lung tumor initiation, progression, and metastasis [62].

7.7 Anti-diabetes Effects

The three PPAR subtypes, α, β/δ and γ, have distinct expression patterns and regulate glucose homeostasis based on the need of a specific tissue. Although PPAR α potentiates fatty acid catabolism in the liver and is the molecular target of the lipid-lowering fibrates, PPAR-γ is essential for adipocyte differentiation and hypertrophy and mediates the activity of the insulin-sensitizing TZDs. PPAR- δ may be important in regulating body weight and lipid metabolism in fat tissues [77].

7.8 Pain Reduction

Synthetic PPAR-α receptor agonists produce broad-spectrum analgesia in a dose-dependent manner [78]. It was recently reported that supraspinal (intracerebroventricular) administration of PPAR-α ligands (perfluorooctanoic acid) reduced peripheral edema and inflammatory hyperalgesia [64] and that intrathecal administration of PPARγ ligands, rosiglitazone, and 15d-PGJ2, reduced behavioral signs of neuropathic pain [79]. It was recently reported that systemic administration of pioglitazone reduced behavioral signs of neuropathic pain, raising the possibility that this FDA-approved drug can be effective as an analgesic agent [80].

7.9 Neuroprotective Properties

Synthetic PPARα and PPARγ ligands have neuroprotective properties. Recently, PPARβ/δ activation emerged as the focus of a novel approach for the treatment of a wide range of neurodegenerative diseases [81].

8. REGULATION OF ANTIOXIDANT GENES BY PPARS IN RESPONSE TO OXIDATIVE STRESS

Numerous studies elucidated the main functional role of PPAR as key transcriptional regulators of lipid metabolism, mitochondrial biogenesis, and

anti-oxidant defense. Since redox activity is an integral part of oxidative metabolism, changes in PPAR signaling in a specific cell or tissue will lead to alterations of redox state. PPAR's regulation of cellular redox states appears to be a highly diversified function that is mostly dependent on the specific subtype at a particular tissue under different metabolic and stress conditions [82].

Mitochondria are the powerhouse for cells and are vulnerable targets of oxidative damage. The maintenance of redox homeostasis is critical for normal cellular function. The utilization of oxygen for ATP generation in the mitochondria accompanies the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) from electron transport chain complex I, II and III [83] Mitochondrial ROS further triggers ROS production from other sources, such as Ang II, hyperglycemia, hypoxia, oxidized low-density lipoprotein, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) [84]. NOXs are membrane-bound enzyme complexes that generate superoxide by transferring electrons from intracellular NADPH across the membrane and coupling these to molecular oxygen [85]. In general, the balance between ROS formation and endogenous antioxidant defenses enable redox homeostasis in cells. Under normal conditions, ROS and RNS also serve as signaling molecules [86]. Oxidative stress occurs when there is an imbalance between ROS/RNS production and the endogenous antioxidant defense. Oxidative stress is associated with the major pathological development of cardiovascular disease [86]. Macrophage-derived ROS contribute to the initiation and development of atherosclerosis. Vascular dysfunction in response to reactive ROS plays an important role in the pathological development and progression of atherosclerotic lesions and heart failure. Oxidative damages are also the main features during the pathological development of cardiac hypertrophy, ischemia/reperfusion and heart failure [87].

Antioxidant: Several key endogenous antioxidants play crucial roles in maintaining cellular homeostasis, especially in those cells with actively oxidative metabolism. Superoxide dismutase (SOD) is a major superoxide-scavenging enzyme converting superoxide ($O_2^{\cdot-}$) to O_2 and hydrogen peroxide (H_2O_2), which is further converted into H_2O by catalase [88], thioredoxin (Trx) [89], or glutathione peroxidizes [90]. In mammals, three isoforms of SOD have been reported: the cytosolic Cu/Zn SOD (SOD1) [91], the mitochondrial manganese SOD (SOD2 or MnSOD) [88,90], and the extracellular form of Cu/Zn-SOD (SOD3 or ecSOD) [92]. Trx reduces the oxidized form of Trx peroxidase, and this reduced form of Trx peroxidase scavenges ROS in both cytosol and nucleus, where it modifies the activity of transcription factors [89]. Also, heme oxygenase (HO) is an antioxidant enzyme family, consisting three isoforms: the oxidative stress-inducible HO-1 (HSP32), constitutive HO-2, and less active HO-3. HO protects cells against oxidative stress by degrading the prooxidant heme to carbon monoxide (CO), biliverdin, and ferrous iron [93]. These multiple endogenous antioxidants are crucial in maintaining cellular redox balance. If this balance is interrupted, oxidative stress increases, resulting in damage to essential cellular components.

8.1 Effects of Oxidative Stress on PPAR Signaling

PPAR expression, PPAR activities and PPAR interactions with their coregulators are the factors that directly determine the effects of PPAR signaling. Oxidative stress is a common cellular stress condition that can trigger a series of responses leading to altered PPAR expression and activity by different mechanisms. Increased oxidative stress regulates a variety of signaling pathways that subsequently affect gene expression by modulating a large number of transcription factors, including PPARs. Additionally, redox states may also regulate PPAR signaling *via* transcriptional regulation and post-translational modification [82]. Oxidative stress-induced signaling pathways affect peroxisome-proliferator-activated receptor transcript and protein activity. Oxidative stress triggers activation of ERK1/2 - one of the common consequences of oxidative stress [94]; platelet-derived growth factor (PDGF), and phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway resulting in increased transcription of peroxisome-proliferator-activated receptors (PPARs) expression as a defense mechanism [95]. Increased lipid oxidation not only causes oxidative stress, but it also activates transcription and activation of PPARs causing increases expression of PPARγ in the skeleton (osteoblasts) [96]. The transcriptional activity of PPARs can be regulated by post-translational modifications such as phosphorylation, SUMOylation, and ubiquitination [50]. Increase in ROS levels during oxidative stress is accompanied by increases p38

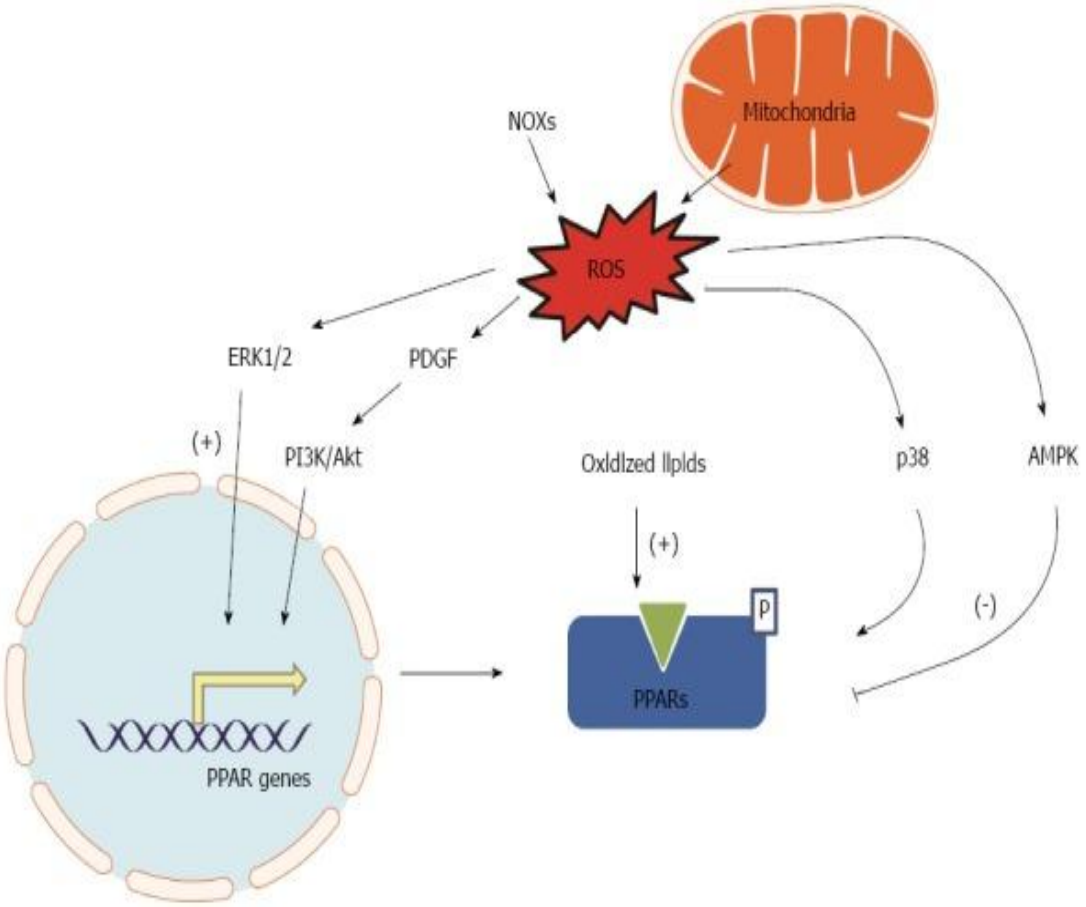

Fig. 4. Effect of oxidative stress-induced signaling pathways on peroxisome-proliferator-activated receptor transcript and protein activity [82]

mitogen-activated protein kinase (p38 MAPK) and 5'AMP-activated protein kinase (AMPK) activation, resulting in the phosphorylation of PPAR proteins resulting in suppressed transcription of PPARs. The PPARα phosphorylation by the p38 MAPK decreases the transcriptional activity of PPARα [97].

As shown below in Fig. 4 PPAR expression and activity may be altered by the status of cellular energy metabolism (redox), and oxidative stress is attributed to altered PPAR expression and activity as adaptive feedback or maladaptive feedback that leads to a vicious cycle [82].

9. SUBTYPE SPECIFIC ROLE OF PPARS ON THE REGULATION OF REDOX PATHWAY

The three subtypes of PPARs regulate cellular lipid and energy metabolism in most tissues in the body with overlapping and preferential effects on different metabolic steps depending on the specific tissue. Adding to the complexity, specific ligands of each PPAR subtype may also display different potencies and specificities of their role in regulating the redox pathways. Each PPAR subtype regulates redox status with various intensity and extension in a tissue and cell type-specific manner [82].

9.1 PPARα and Oxidative Stress

Activation of PPARα protects the heart from ischemia/reperfusion injury [98]. It has been shown that clofibrate a PPARα ligand protects rat hearts from coronary artery occlusion-induced myocardial ischemia by reducing ROS production and lipid peroxidation. These protective effects of PPARα ligand are mainly attributed to significantly increased expression and activity of SOD1, SOD2, and catalase in the

heart tissue [98]. Another synthetic ligand of PPARα, Wy14643, also protects rabbit hearts from ischemia/reperfusion injury by increasing HO-1 expression and decreasing caspase-3 activation [99]. In human macrophage, PPARα activation by another selective subtype ligand, GW647, can upregulate the transcript and protein expression of Trx-1 [100]. Moreover, PPARα activation could also enhance the Trx-1 activity by indirect down-regulation of the natural Trx-1 inhibitor; vitamin D3 up-regulated protein 1 [100]. Therefore, stimulation of PPARα could exert a beneficial effect against the development oxidative damage [82]. PPARα agonists induce ROS production by increasing NOXs expression and stimulating its activity, which will generate more endogenous PPARα ligands. This vicious cycle will lead to augmented oxidative stress in macrophages. It has become obvious that the activation of PPARα in macrophage could have opposite effects on regulating redox state in other tissues showing an increase in the expression and activity of either Trx-1 or NOXs.

9.2 PPARγ and Oxidative Stress

PPARγ is a primary regulator of lipid storage and adipogenesis mainly in adipose tissue. However, it also plays an important role in other tissues and cells in the body [100]. The PPARγ has been suggested in signaling the transcriptional transrepression of nuclear factor kappa-B (NF-κB), and it also serves as a transcriptional regulator of endogenous antioxidants [82]. PPARγ is an essential regulator of redox signaling and can protect against oxidative damages *via* transcriptional activation of antioxidant genes. Both PPARα and PPARγ are involved in the regulation of mitochondrial SOD2 under specific conditions, playing a crucial role in cardiac redox balance [82]. Sekulic-Jablanovic et al. [101] show that the PPARα and γ are expressed in the cochlea and play distinct roles in the cochlear response to oxidative stress, which has become appreciated as a common mechanism for hearing the loss of all causes. Pioglitazone (PPARγ-specific), tesaglitazar (PPARγ/α-specific), and fenofibric acid (PPARα-specific) all provided >90% protection from gentamicin toxicity by regulation of overlapping subsets of genes controlling ROS detoxification. Treatment of PPARγ-specific ligands, rosiglitazone, and pioglitazone, can ameliorate H_2O_2-induced oxidative damages in the newborn rabbit heart. The protective effect of PPARγ ligands against oxidative damage seems to be mediated by catalase, since the effect is abolished by PPARγ blocker or catalase inhibitor, indicating that the PPARγ-regulated catalase is crucial for the cardioprotective effect of PPARγ ligands [102]. PPAR-γ ligands can directly alter vascular endothelial function by enhancing endothelial NO bioavailability, in part by altering endothelial superoxide metabolism through suppression of NOXs and induction of SOD1 [103]. Thiazolidinediones (TZDs) are full agonists of PPARγ, and they have strong insulin sensitizing actions hence they have been used effectively in restoring the metabolic control in the treatment of type 2 diabetes [104]. TZDs are known to oppose the effect of TNF-alpha, a pro-inflammatory cytokine in adipocytes probably through mechanisms involving the suppression of NF-KB, a transcription factor [105]. It should be noted that PPAR-c is best known for its abilities to regulate pathways linked to adipocyte differentiation and metabolism. However, it is now known that it is also important for podocyte function through the use of in vitro and cell-specific transgenic knockout (KO) models [105].

9.3 PPARδ and Oxidative Stress

PPARδ is ubiquitously expressed with differential expression abundances in various tissues depending on pathophysiological condition [106]. PPARδ is also expressed in VSMCs and up-regulated after vascular injury [107]. PPARδ activation facilitates VSMC proliferation causing matrix modulation and vascular remodeling. This is an opposite outcome to the activation of PPARα and PPARγ by which inflammation is decreased [107]. Ligand-activated PPARδ plays an important role in the cellular response to oxidative stress by decreasing Ang II-induced ROS production in vascular cells. A PPARδ-specific ligand GW501516 significantly reduced Ang II-induced ROS generation in VSMCs via inhibiting PTEN-mediated modulation of PI3K/Akt/Rac1 signaling. Activation of PPARδ suppresses the translocation of Rac1 to the plasma membrane, a key step in NOXs-induced ROS production, in VSMCs [108]. Also, PPARδ is essential for not only the constitutive function of fatty acid metabolism and mitochondrial biogenesis but also in maintaining the antioxidant defense of the heart. Cardiomyocytes-restricted PPARδ knockout from adult heart leads to oxidative damages with repressed expression of SOD1 and SOD2 [109].

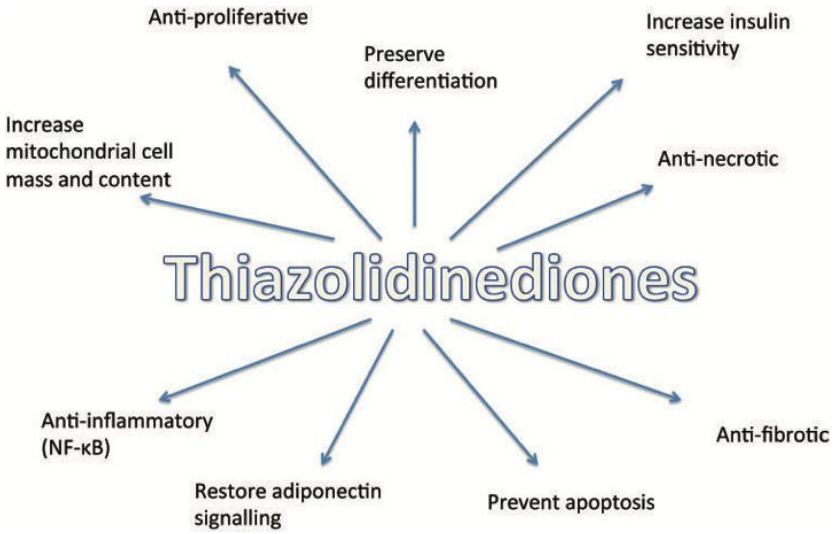

Fig. 5. Effects of TZDs at a cellular level [105]

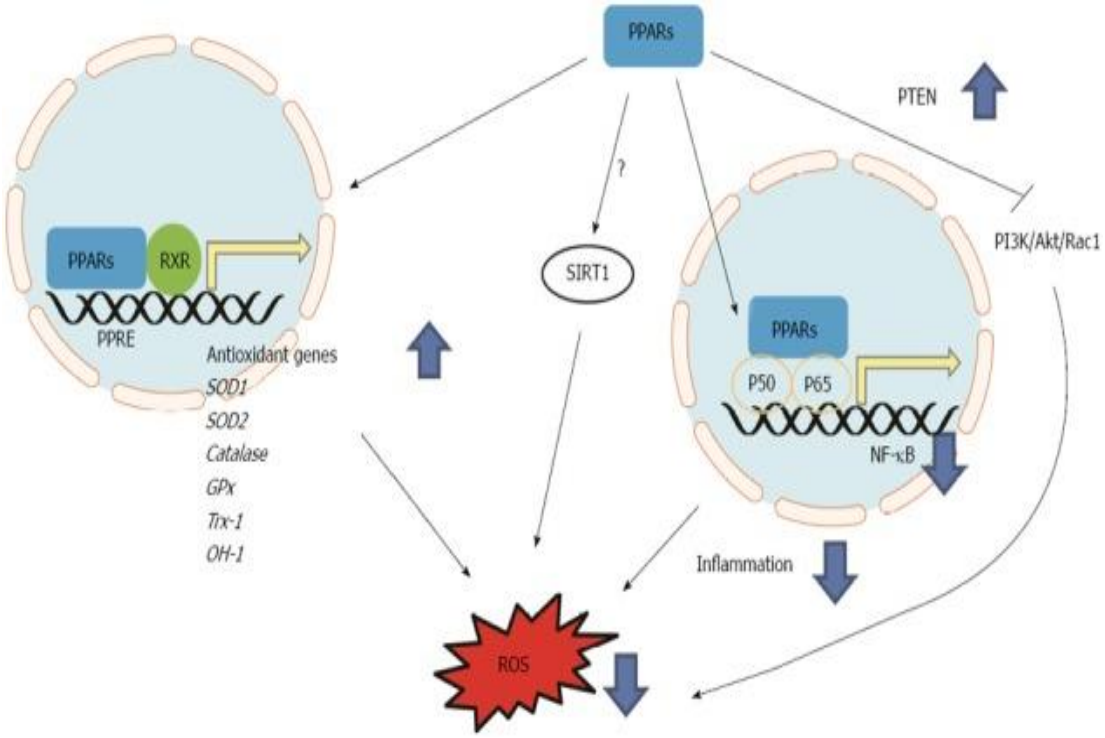

Fig. 6. Antioxidant mechanisms of peroxisome-proliferator-activated receptors [91]
ROS: Reactive oxygen species; RXR: Retinoid X receptor; SOD: Superoxide dismutase; TRX: Thioredoxin; GPX: Glutathione peroxidase; HO: Heme oxygenase

10. MECHANISMS OF ACTION OF PPAR IN REGULATING REDOX

PPARs may exert their antioxidant effects by direct transcriptional regulation of endogenous antioxidants and by directly or indirectly interfering/coordinating the related signaling transduction pathways to reduced ROS production [82]. PPAR activation exerts direct transcriptional regulation on the expression of several key endogenous antioxidants, including SOD1 [91], SOD2 [110], catalase [111], GPx,

OH-1 and Trx-1 [100]. PPARs activate antioxidant genes *via* transcriptional regulation by binding on PPAR response element (PPRE) of the promoter region of target genes. PPARs suppress nuclear factor kappa-B (NF-κB)-light-chain-enhancer of activated B cells *via* interaction with p50 and p65 resulting in decreased inflammatory response and oxidative stress [112]. PPARs suppress phosphatidylinositol 3-kinase (PI3K)/Akt/Rac1 signaling axis *via* activation of PTEN resulting in decreased reactive oxygen species (ROS) [82].

11. CONCLUSIONS

PPARs are involved in various independent and DNA-dependent molecular and enzymatic pathways in adipose tissue, liver, and skeletal muscles and these pathways are affected by disease condition thus causing metabolic energy imbalance. This way, PPAR agonist intervention can provide therapeutic targets for a range of diseases such as dyslipidemia, diabetes, obesity, inflammation, a neurodegenerative disorder, and cancer. As a matter of fact, existing literature strongly support a key role for PPARs as they serve as regulators of redox signaling in response to oxidative stress. This redox signaling regulatory property is carried out through their exerting antioxidative effects. There is, therefore, the need for a further study that will provide insights into the potential development of partial PPAR modulators that regulate specific cellular redox state without major unwanted effects. These will then help to truly explore possible therapeutic roles these nuclear receptor agonists can play in many diseased conditions.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lazarow PB, Fujiki Y. Biogenesis of peroxisomes, Ann Rev Cell Biol. 1985;1: 489-530.
2. Lock EA, Mitchell AM, Elcombe CR. Biochemical mechanisms of induction of hepatic peroxisome proliferation. Ann Rev Toxicol. 1989;29:145-163.
3. Lazarow PB, Moser HW. Disorders of peroxisome biogenesis, in The Metabolic Basis of Inherited Disease. 6 Ed. (Scrivr, C.R., Beaudet, A.I., Sly, W.S., and Valle, D. Eds.). McGraw-Hill, New York. 1989; 1479-1509.
4. Michalic L, Wahil W. Involvement of PPAR nuclear receptors in tissue injury and wound repair. Clin Investig J. 2006;116: 598–606.
5. Oliveira AC, Bertollo CM, Rocha LT, Nascimento EB, Costa KA, Coelho MM. Antinociceptive and antiedematogenic activities of fenofibrate, an agonist of PPAR alpha, and pioglitazone, an agonist of PPAR gamma. Eur J Pharmacol. 2007; 561:194–201.
6. Tyagi S, Sharma S, Gupta P, Saini A, Kaushal C. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res. 2011;2(4): 236.
7. Zoete V, Grosdidier A, Michielin O. Peroxisome proliferator activated receptor structures: Ligand specificity, molecular switch and interactions with regulators. Biochem Biophys Acta. 2007; 1771:915–925.
8. Lu C, Cheng S. Thyroid hormone receptors regulate adipogenesis and carcinogenesis via crosstalk signaling with peroxisome proliferator-activated receptors. J Mol Endocrinol. 2010;44:143–154.
9. Kliewer SA, Umesono K, Noonan DJ, Heyman RA, Evans RM. Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. Nature. 1992;358:771–774.
10. Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med. 2002; 53:409–435.
11. Daynes RA, Jones DC. Emerging roles of PPARs in inflammation and immunity. Nat Rev Immunol. 2002;2:748–759.
12. Abdelrahman M, Sivarajah A, Thiemermann C. Beneficial effects of PPAR-gamma ligands in ischemia-reperfusion injury, inflammation and shock. Cardiovasc Res. 2005;65:772–781.
13. Johnson TE, Holloway MK, Vogel R, Rutledge SJ, Perkins JJ, Rodan GA, Schmidt A. Structural requirements and cell-type specificity for ligand activation of peroxisome proliferator-activated receptors. J Steroid Biochem Mol Biol. 1997;63:1–8.

14. Wadosky KM, Willis MS. The story so far: Post-translational regulation of peroxisome proliferator-activated receptors by ubiquitination and SUMOylation. Am J Physiol Heart Circ Physiol. 2012;302: H515–H526.
15. Lemberger T, Braissant O, Aubry C, Keller H, Saladin R, Staels B, et al. PPAR tissue distribution and interactions with other hormone–signalling pathways. Ann NY Acad Sci. 1996;804:231–251.
16. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med. 2004;10:355–361.
17. Moreno S, Farioli-Vecchioli S, Cerù MP. Immuno localization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS. Neuroscience. 2004;123:131–145.
18. Heneka MT, Landreth GE. PPARs in the brain. Biochim Biophys Acta. 2007;1771: 1031–1045.
19. Lefebvre P, Chinetti G, Fruchart JC, Staels B. Sorting out the roles of PPAR alpha in energy metabolism and vascular homeostasis. J Clin Invest. 2006;116:571–580.
20. Rigamonti E, Chinetti-Gbaguidi G, Staels B. Regulation of macrophage functions by PPAR-alpha, PPAR-gamma, and LXRs in mice and men. Arterioscler Thromb Vasc Biol. 2008;28:1050–1059.
21. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs from orphan receptors to drug discovery. J Med Chem. 2000;43:527–550.
22. Berger JP, Akiyama TE, Meinke PT. PPARs: Therapeutic targets for metabolic disease. Trends Pharmacol Sci. 2005;26: 244–251.
23. Jay MA, Ren J. Peroxisome proliferator-activated receptor (PPAR) in metabolic syndrome and type 2 diabetes mellitus. Curr Diabetes Rev. 2007;3:33–39.
24. Barter PJ, Rye KA. Is there a role for fibrates in the management of dyslipidemia in the metabolic syndrome? Arterioscler Thromb Vasc Biol. 2008;28:39–46.
25. Mukherjee R, Davies PJ, Crombie DL, Bischoff ED, Cesario RM, Jow L et al. Sensitization of diabetic and obese mice to insulin by retinoid receptor agonists. Nature. 1997;386:407–410.
26. Braissant O, Foufelle F, Scotto C, Dauça M, Wahli W. Differential expression of peroxisome proliferator-activated receptors (PPARs): Tissue distribution of PPAR-α, -β, and -γ in the adult rat. Endocrinol. 1996; 137(1):354–366.
27. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S. PPARα and PPARγ activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J. 1996;15:5336–5348.
28. Lehman JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor (PPAR gamma). J Biol Chem. 1995;270(22):12953–12956.
29. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-deoxy-Δ12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPARγ. Cell. 1995;83(5):803–812.
30. Farmer SR. Regulation of PPARγ activity during adipogenesis. Intl J Obesity. 2005; 29(Supplement 1):S13–S16.
31. Nehlin JO, Mogensen JP, Petterson I. Selective PPAR agonists for the treatment of type 2 diabetes. Ann NY Acad Sci. 2006;1067(1):448–453.
32. Kubota N, Terauchi Y, Kubota K, Itoh S, Moroi M. Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and independent pathways. J Biol Chem. 2006;281:8748–8755.
33. Ferre P. The biology of peroxisome proliferator-activated receptor. Diabetes. 2004;53:S43–50.
34. Reiss AB, Vagell ME. PPARγ activity in the vessel wall: anti-atherogenic properties. Curr Medicinal Chem. 2006;13(26):3227–3238.
35. Heneka MT, Klockgether T, Feinstein DL. Peroxisome Proliferator-Activated Receptor-g Ligands Reduce Neuronal Inducible Nitric Oxide Synthase Expression and Cell Death *in vivo*. J Neurosci. 2000; 20(18):6862–6867.
36. Barish GD, Narkar VA, Evans RM. PPAR delta: A dagger in the heart of the metabolic syndrome. J Clin Invest. 2006; 116:590–597.

37. Nagasawa T, Inada Y, Nakano S, Tamura T, Takashashi T, Maruyama K. Effects of bezafibrate, PPAR pan agonist and GW501516, PPAR delta agonist, on development of steatohepatitis in mice fed a methionine and choline-deficient diet. Eur J Phamacol. 2006;536:182–191.

38. Graham TL, Mookherjee C, Suckling KE, Palmer CN, Patel L. The PPAR delta agonist GW0742X reduces atherosclerosis in LDLR(-/-) mice. Atherosclerosis. 2005; 181:29–37.

39. Yue TL, Nerurkar SS, Bao W, Jucker BM, Sarov-Blat L, Steplewski K, Ohlstein EH, Willette RN. *In vivo* activation of peroxisome proliferator-activated receptor-delta protects the heart from ischemia/reperfusion injury in Zucker fatty rats. J Pharmacol Exp Ther. 2008;325: 466-474.

40. Green S. PPAR: a mediator of peroxisome proliferator action. Mutat Res. 1995;333: 101–109.

41. Jucker BM, Doe CP, Schnackenberg CG, Olzinski AR, Manis-calco K, Williams C, Hu TC, Lenhard SC, Costell M, Bernard R, Sarov-Blat L, Steplewski K, Willette RN. PPARdelta acti-vation normalizes cardiac substrate metabolism and reduces right ventricular hypertrophy in congestive heart failure. J Cardiovasc Pharmacol. 2007;50: 25-34.

42. Velkov T. Interactions between human liver fatty acid binding protein and peroxisome proliferator activated receptor selective drugs. PPAR Res. 2013;2013:1-14.

43. Chung SS, Kim M, Youn BS, Lee NS, Park JW, Lee IK, Lee YS, Kim JB, Cho YM, Lee HK, Park KS. Glutathione per-oxidase 3 mediates the antioxidant effect of peroxisome proliferator-activated receptor gamma in human skeletal muscle cells. Mol Cell Biol. 2009;29:20-30.

44. Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, Rose DW, Willson TM, Rosenfeld MG, Glass CK. A SU-MOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. Nature. 2005; 437:759-763.

45. Kim HJ, Ham SA, Kim MY, Hwang JS, Lee H, Kang ES, Yoo T, Woo IS, Yabe-Nishimura C, Paek KS, Kim JH, Seo HG. PPARδ coordinates angiotensin II-induced senes-cence in vascular smooth muscle cells through PTEN-mediated inhibition of superoxide generation. J Biol Chem. 2011; 286:44585-44593.

46. Kim MY, Kang ES, Ham SA, Hwang JS, Yoo TS, Lee H, Paek KS, Park C, Lee HT, Kim JH, Han CW, Seo HG. The PPARδ-mediated inhibition of angiotensin II-induced premature senescence in human endothelial cells is SIRT1-dependent. Biochem Pharmacol. 2012;84:1627-1634.

47. Stockl KM, Le L, Zhang S, Harada AS. Risk of acute myo-cardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiol Drug Saf. 2009;18: 166-174.

48. Luo J, Wu S, Liu J, Li Y, Yang H, Kim T, Zhelyabovska O, Ding G, Zhou Y, Yang Y, Yang Q. Conditional PPARγ knock-out from cardiomyocytes of adult mice impairs myocardial fatty acid utilization and cardiac function. Am J Transl Res. 2010;3:61-72.

49. Oka S, Alcendor R, Zhai P, Park JY, Shao D, Cho J, Yama-moto T, Tian B, Sadoshima J. PPARα-Sirt1 complex mediates cardiac hypertrophy and failure through suppression of the ERR transcriptional pathway. Cell Metab. 2011; 14:598-611.

50. Burns KA, Vanden Heuvel JP. Modulation of PPAR activity via phosphorylation. Biochim Biophys Acta. 2007;1771:952–960.

51. Balakumar P, Rose M, Singh M. PPAR ligands: are they potential agents for cardiovascular disorders? Pharmacol. 2007;80:1–10.

52. Bensinger SJ, Tontonoz P. Integration of metabolism and inflammation by lipid-activated nuclear receptors. Nature. 2008; 454:470–477.

53. Fyffe SA, Alphey MS, Buetow L, Smith TK, Ferguson MA, Sorensen MD, Bjorkling F, Hunter WN. Recombinant human PPARbeta/delta ligand-binding domain is locked in an activated conformation by endogenous fatty acids. J Mol Biol. 2006; 356:1005–1013.

54. Noy N. Ligand specificity of nuclear hormone receptors: Sifting through promiscuity. Biochem. 2007;46(47):13461–13467.

55. Berger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Cullinan CA, Hayes NS, Li Y. Novel

peroxisome proliferator-activated receptor (PPAR) g and PPARdelta ligands produce distinct biological effects. J Biol Chem. 1999;274:6718–6725.

56. Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznaidman ML, Lambert MH. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. PNAS. 2001; 98:5306–5311.
57. Westergaard M, Henningsen J, Svendsen ML, Johansen C, Jensen UB, Schroder HD, Kratchmarova I, Berge RK, Iversen L, Bolund L. Modulation of keratinocyte gene expression and differentiation by PPAR-selective ligands and tetradecylthioacetic acid. J Invest Dermatol. 2001;116:702–712.
58. Kliewer SA, Lenhard JM, Willson TM, Patel I, Morris DC, Lehmann JM. A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation. Cell. 1995;83:813–819.
59. Davies SS, Pontsler AV, Marathe GK, Harrison KA, Murphy RC, Hinshaw JC, Prestwich GD, Hilaire AS, Prescott SM, Zimmerman GA. Oxidized alkyl phospholipids are specific, high affinity peroxisome proliferator-activated receptor γ ligands and agonists. J Biol Chem. 2001; 276:16015–16023.
60. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, Milburn MV. Ligand binding and co-activator assembly of the peroxisome proliferator activated receptor-γ. Nature. 1998;395:137–143.
61. Xu D, Murakoshi N, Igarashi M, Hirayama A, Ito Y, Seo Y, Tada H, Aonuma K. PPAR-γ activator pioglitazone prevents age-related atrial fibrillation susceptibility by improving antioxidant capacity and reducing apoptosis in a rat model. J Cardiovasc Electrophysiol. 2012;23:209-217.
62. Badr MZ. PPAR research: Successful launching and promising future. PPAR Res. 2009;10:11–55.
63. Planavila A, Laguna JC, Vázquez-Carrera M. Nuclear factor kappa B activation leads to down-regulation of fatty acid oxidation during Cardiac hypertrophy. J Biol Chem. 2005;280:17464–17471.
64. D'Agostino G, LaRana G, Russo R, Sasso O, Iacono A, Esposito E. Acute intracerebroventricular administration of palmitoylethanolamide, an endogenous peroxisome proliferator-activated receptor-alpha agonist, modulates carrageenan-induced paw edema in mice. J Pharmacol Exp Ther. 2007;322:1137–1143.
65. DeFilippis D, D'Amico A, Cinelli MP, Esposito G, DiMarzo V, Iuvone T. Adelmidrol, a palmitoylethanolamide analog, reduces chronic inflammation in a carrageenin-granuloma model in rats. J Cell Mol Med. 2009;13:1086–1095.
66. Suzawa M, Takada I, Yanagisawa J, Ohtake F, Ogawa S, Yamauchi T. Cytokine suppresses adipogenesis and PPAR-gamma function through the TAK1/TAB1/NIK cascade. Nat Cell Biol. 2003;5:224–230.
67. Majdalawieh A, Ro HS. PPARγ1 and LXRα face a new regulator of macrophage cholesterol homeostasis and inflammatory responsiveness, AEBP1. Nucl Recept Signal. 2010;8:e004.
68. Wu Z, Rosen ED, Brun R, Hauser S, Adelmant G, Troy AE. Cross regulation of C/EBP alpha and PPAR gamma controls the transcriptional pathway of adipogenesis and insulin sensitivity. Mol Cell. 1999;3:151–158.
69. Matsusue K, Jefrey M, Peter FJ. PPAR β/δ potentiates PPARγ-stimulated adipocyte differentiation. FASEB. 2004;18:1477–1479.
70. Colin C, Salamone S, Grillier-Vuissoz I, Boisbrun M, Kuntz S, Lecomte J. New Troglitazone derivatives devoid of PPARα agonist activity display and Increased antiproliferative effect in both hormone dependent and hormone-independent breast cancer cell lines. Breast Cancer Res Treat. 2010;124:101–110.
71. Grommes C, Landreth GE, Heneka MT. Antineoplastic effects of Peroxisome proliferator-activated receptor gamma agonists. Lancer Oncol. 2004;5:419–429.
72. Rubin G, Zhao Y, Kalus A, Simpson E. Peroxisome proliferator-activated receptor gamma ligands estrogen biosynthesis in human breast adipose tissue; possible implication for the breast cancer therapy. Cancer Res. 2000;60:1604–1608.
73. Chattopadhyay N, Singh D, Heese O, Godbole MM, Sinohara T, Black PM.

Expression of peroxisome proliferator-activated receptors in human astrocytic cells: PPARgamma agonists as inducers of apoptosis. J Neurosci Res. 2000;61:67–74.

74. Sarraf P, Mueller E, Jones D, King FJ, DeAngelo DJ, Partridge JB. Differentiation and reversal of malignant changes in colon cancer through PPARgamma. Nat Med. 1998;4:1046– 1052.
75. Racke MK, Drew PD. PPARs in Neuroinflammation. PPAR Res. 2008; 638356.
76. Swerdlow R. Mitochondria in cybrids containing mtDNA from persons with mitochondriopathies. J Neurosci Res. 2007;85:3416–3428.
77. Terauchi Y, Kadowaki T. PPAR and diabetes. Nippon Rinsho. 2005;63:623–629.
78. LoVerme J, Russo R, La Rana G, Fu J, Farthing J, Mattace-Raso G. Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-alpha. J Pharmacol Exp Ther. 2006;319: 1051–1061.
79. Churi SB, Abdel-Aleem OS, Tumber KK, Scuderi-Porter H, Taylor BK. Intrathecal rosiglitazone acts at peroxisome proliferator-activated receptor gamma to rapidly inhibit neuropathic pain in rats. J Pain. 2008;9:639–649.
80. Maeda T, Kiguchi N, Kobayashi Y, Ozaki M, Kishioka S. Pioglitazone attenuates tactile allodynia and thermal hyperalgesia in mice subjected to peripheral nerve injury. J Pharmacol Sci. 2008;108:341–347.
81. Aleshin S, Strokin M, Sergeeva M, Reiser G. Peroxisome proliferator-activated receptor (PPAR)β/δ, a possible nexus of PPARα- and PPARγ-dependent molecular pathways in neurodegenerative diseases: Review and novel hypotheses. Neurochem. Int. 2013;63(4):322-330.
82. Kim T, Yang Q. Peroxisome-proliferator-activated receptors regulate redox signaling in the cardiovascular system. Worl d J Cardiol. 2013;5(6):164–174.
83. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009; 417:1–13.
84. Hamanaka RB, Chandel NS. Mitochondrial reactive oxygen species regulate hypoxic signaling. Curr Opin Cell Biol. 2009;21: 894–899.
85. Lassègue B, San Martín A, Griendling KK. Biochemistry, physiology, and pathophysiology of NADPH oxidases in the cardiovascular system. Circ Res. 2012; 110:1364–1390.
86. Sawyer DB, Siwik DA, Xiao L, Pimentel DR, Singh K, Colucci WS. Role of oxidative stress in myocardial hypertrophy and failure. J Mol Cell Cardiol. 2002;34: 379–388.
87. Takimoto E, Kass DA. Role of oxidative stress in cardiac hypertrophy and remodeling. Hypertension. 2007;49:241–248.
88. Kunau WH, Dommes V, Schulz H. Beta-oxidation of fatty acids in mitochondria, peroxisomes, and bacteria: A century of continued progress. Prog Lipid Res. 1995; 34:267–342.
89. Tanaka T, Nakamura H, Nishiyama A, Hosoi F, Masutani H, Wada H, Yodoi J. Redox regulation by thioredoxin superfamily; protection against oxidative stress and aging. Free Radic Res. 2000; 33:851–855
90. Wallace DC. Animal models for mitochondrial disease. Methods Mol Biol. 2002;197:3–54.
91. Francke U, Taggart RT. Assignment of the gene for cytoplasmic superoxide dismutase (Sod-1) to a region of chromosome 16 and of Hprt to a region of the X chromosome in the mouse. Proc Natl Acad Sci USA. 1979;76:5230–5233.
92. Fukai T, Ushio-Fukai M. Superoxide dismutases: Role in redox signaling, vascular function, and diseases. Antioxid Redox Signal. 2011;15:1583–1606.
93. Wu ML, Ho YC, Yet SF. A central role of heme oxygenase-1 in cardiovascular protection. Antioxid Redox Signal. 2011; 15:1835–1846.
94. Wang X, Liu JZ, Hu JX, Wu H, Li YL, Chen HL, Bai H, Hai CX. ROS-activated p38 MAPK/ERK-Akt cascade plays a central role in palmitic acid-stimulated hepatocyte proliferation. Free Radic Biol Med. 2011; 51:539–551.
95. Fu M, Zhu X, Wang Q, Zhang J, Song Q, Zheng H, Ogawa W, Du J, Chen YE. Platelet-derived growth factor promotes the expression of peroxisome proliferator-activated receptor gamma in vascular

smooth muscle cells by a phosphatidylinositol 3-kinase/Akt signaling pathway. Circ Res. 2001;89:1058–1064.

96. Almeida M, Ambrogini E, Han L, Manolagas SC, Jilka RL. Increased lipid oxidation causes oxidative stress, increased peroxisome proliferator-activated receptor-gamma expression, and diminished pro-osteogenic Wnt signaling in the skeleton. J Biol Chem. 2009;284: 27438–27448.
97. Barger PM, Browning AC, Garner AN, Kelly DP. p38 mitogen-activated protein kinase activates peroxisome proliferator-activated receptor alpha: A potential role in the cardiac metabolic stress response. J Biol Chem. 2001;276:44495–44501.
98. Ibarra-Lara L, Hong E, Soria-Castro E, Torres-Narváez JC, Pérez-Severiano F, Del Valle-Mondragón L, Cervantes-Pérez LG, Ramírez-Ortega M, Pastelín-Hernández GS, Sánchez-Mendoza A. Clofibrate PPARα activation reduces oxidative stress and improves ultrastructure and ventricular hemodynamics in no-flow myocardial ischemia. J Cardiovasc Pharmacol. 2012; 60:323–334.
99. Yeh CH, Chen TP, Lee CH, Wu YC, Lin YM, Lin PJ. Cardiomyocytic apoptosis following global cardiac ischemia and reperfusion can be attenuated by peroxisome proliferator-activated receptor alpha but not gamma activators. Shock. 2006;26:262–270.
100. Billiet L, Furman C, Cuaz-Pérolin C, Paumelle R, Raymondjean M, Simmet T, Rouis M. Thioredoxin-1 and its natural inhibitor, vitamin D3 up-regulated protein 1, are differentially regulated by PPAR alpha in human macrophages. J Mol Biol. 2008; 384:564–576.
101. Sekulic-Jablanovic M, Petkovic V, Wright M, Kucharava K, Huerzeler N, Levano S, Brand Y, Leitmeyer K, Glutz A, Bausch A, Bodmer D. Effects of peroxisome proliferator activated receptors (PPAR)-γ and -α agonists on cochlear protection from oxidative stress. PLOS ONE. 2017; 12(11):e0188596.
102. Chen T, Jin X, Crawford BH, Cheng H, Saafir TB, Wagner MB, Yuan Z, Ding G. Cardioprotection from oxidative stress in the newborn heart by activation of PPARγ is mediated by catalase. Free Radic Biol Med. 2012;53:208–215.
103. Hwang J, Kleinhenz DJ, Lassègue B, Griendling KK, Dikalov S, Hart CM. Peroxisome proliferator-activated receptor-gamma ligands regulate endothelial membrane superoxide production. Am J Physiol Cell Physiol. 2005;288:C899–C905.
104. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. Diabetes. 1996;45:1661–1669.
105. Platt C, Coward RJ. Peroxisome proliferating activator receptor-gamma and the podocyte. Nephrol Dial Transplant. 2017;32:423-433.
106. Cheng L, Ding G, Qin Q, Xiao Y, Woods D, Chen YE, Yang Q. Peroxisome proliferator-activated receptor delta activates fatty acid oxidation in cultured neonatal and adult cardiomyocytes. Biochem Biophys Res Commun. 2004; 313:277–286.
107. Zhang J, Fu M, Zhu X, Xiao Y, Mou Y, Zheng H, Akinbami MA, Wang Q, Chen YE. Peroxisome proliferator-activated receptor delta is up-regulated during vascular lesion formation and promotes post-confluent cell proliferation in vascular smooth muscle cells. J Biol Chem. 2002; 277:11505–11512.
108. Lee H, Ham SA, Kim MY, Kim JH, Paek KS, Kang ES, Kim HJ, Hwang JS, Yoo T, Park C. Activation of PPARδ counteracts angiotensin II-induced ROS generation by inhibiting rac1 translocation in vascular smooth muscle cells. Free Radic Res. 2012;46:912–919.
109. Wang P, Liu J, Li Y, Wu S, Luo J, Yang H, Subbiah R, Chatham J, Zhelyabovska O, Yang Q. Peroxisome proliferator-activated receptor {delta} is an essential transcriptional regulator for mitochondrial protection and biogenesis in adult heart. Circ Res. 2010;106:911–919.
110. Lebovitz RM, Zhang H, Vogel H, Cartwright J, Dionne L, Lu N, Huang S, Matzuk MM. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. Proc Natl Acad Sci USA. 1996;93:9782–9787.

111. Girnun GD, Domann FE, Moore SA, Robbins ME. Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. Mol Endocrinol. 2002;16:2793–2801.
112. Westergaard M, Henningsen J, Johansen C, Rasmussen S, Svendsen ML, Jensen UB, Schrøder HD, Staels B, Iversen L, Bolund L. Expression and localization of peroxisome proliferator-activated receptors and nuclear factor kappa B in normal and lesional psoriatic skin. J Invest Dermatol. 2003;121: 1104–1117.

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