

Review Paper

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ROLE IN CHEMOTHERAPY

Abstract

Peroxisomes are subcellular organelles found in most plant and animal cells that perform diverse metabolic functions including H₂O₂-based respiration, $\hat{1}^2$ -oxidation of fatty acids (FAs), and cholesterol metabolism (Lazarow, and Fujiki, 1985; Lock et al., 1989). 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 (Lock et al., 1989). 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 (Lazarow, and Moser, 1989). Peroxisome proliferator-activated receptors (PPARs) proteins belong to superfamily of phylogenetically related protein termed nuclear hormone factor (Michalic and Wahil, 2006).

Keywords :- PPAR, obesity, inflammation, diabetes, hypertension

INTRODUCTION

Peroxisomes are subcellular organelles found in most plant and animal cells that perform diverse metabolic functions including H₂O₂-based respiration, β -oxidation of fatty acids (FAs), and cholesterol metabolism (Lazarow, and Fujiki, 1985; Lock *et al.*, 1989). 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 (Lock *et al.*, 1989). 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 (Lazarow, and Moser, 1989). Peroxisome proliferator-activated receptors (PPARs) proteins belong to superfamily of phylogenetically related protein termed nuclear

hormone factor (Michallic and Wahil, 2006). 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 (Oliveira *et al.*, 2007). 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 (Tyagi *et al.*, 2011).

STRUCTURE

Structurally, PPARs are similar to steroid or thyroid hormone receptor and are stimulated in response to small lipophilic ligands (Tyagi *et al.*, 2011). The PPARs possess the canonical domain structure common to other nuclear receptor family members, including the amino-terminal AF-1 trans activation domain, followed by a DNA-binding domain, and a dimerization and ligand-binding domain with a ligand-dependent trans activation function AF-2 located at the carboxy-terminal region (Zoete *et al.*, 2007). 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 3 respectively (Lu and Cheng, 2010).

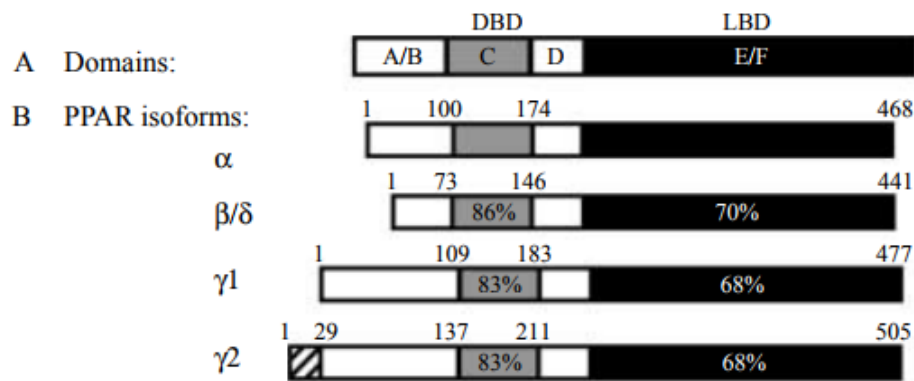


Figure 1.1 Schematic representation of the structures of PPARs

(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.

44

45 MECHANISM OF ACTION OF PEROXISOME PROLIFERATOR-ACTIVATED 46 RECEPTORS

47 To be transcriptionally active, All PPAR form heterodimers with retinoid X receptor (RXR)
48 thereby forming a complex that then binds to a specific DNA response element (Kliwer *et*
49 *al.*, 1992). These DNA sequences are termed PPREs (peroxisome proliferator hormone
50 response elements) present in promoter areas of target genes (Michalic and Wahil, 2006). In
51 this way, PPARs can transactivate specific target genes in a ligand-dependent manner
52 (Berger and Moller, 2002). Their natural activating ligands are lipid-derived substrates (Tyagi
53 *et al.*, 2011). In the absence of the ligands, these heterodimers are associated with co-
54 repressor complex, which block gene transcription. Moreover, PPARs can negatively regulate
55 the expression of genes without binding to DNA (Daynes and Jones, 2002) or inhibit the
56 activities of other transcription factors by direct interaction via a mechanism known as

57 ligand-dependent trans-repression (Abdelrahman *et al.*, 2005). Trans-repression may occur
58 either through physical interaction of PPARs with other transcription factors or co-activators,
59 or through modulation of kinase activity preventing activation of downstream transcription
60 factors (Johnson *et al.*, 1997) It is established that posttranslational modifications by
61 phosphorylation, ubiquitination, or SUMOylation are involved in the regulation of PPAR
62 activity and functions (Wadosky and Willis, 2012). In this context, different kinase signaling
63 pathways, including the Mitogen-activated protein kinase (MAPKs), 5' AMP-activated
64 protein kinase (AMPK), Glycogen synthase kinase 3- beta (GSK3 β), protein kinase (PKA),
65 and protein kinase (PKC), phosphorylate PPARs at several residues to either increase or
66 decrease their transcriptional activity, in a ligand-dependent or ligand-independent manner.
67 Like PPARs, RXR exists as three distinct isoforms: RXR- α , β , and γ , all of which are
68 activated by the endogenous agonist 9-cis retinoic acid (Lemberger *et al.*, 1996).

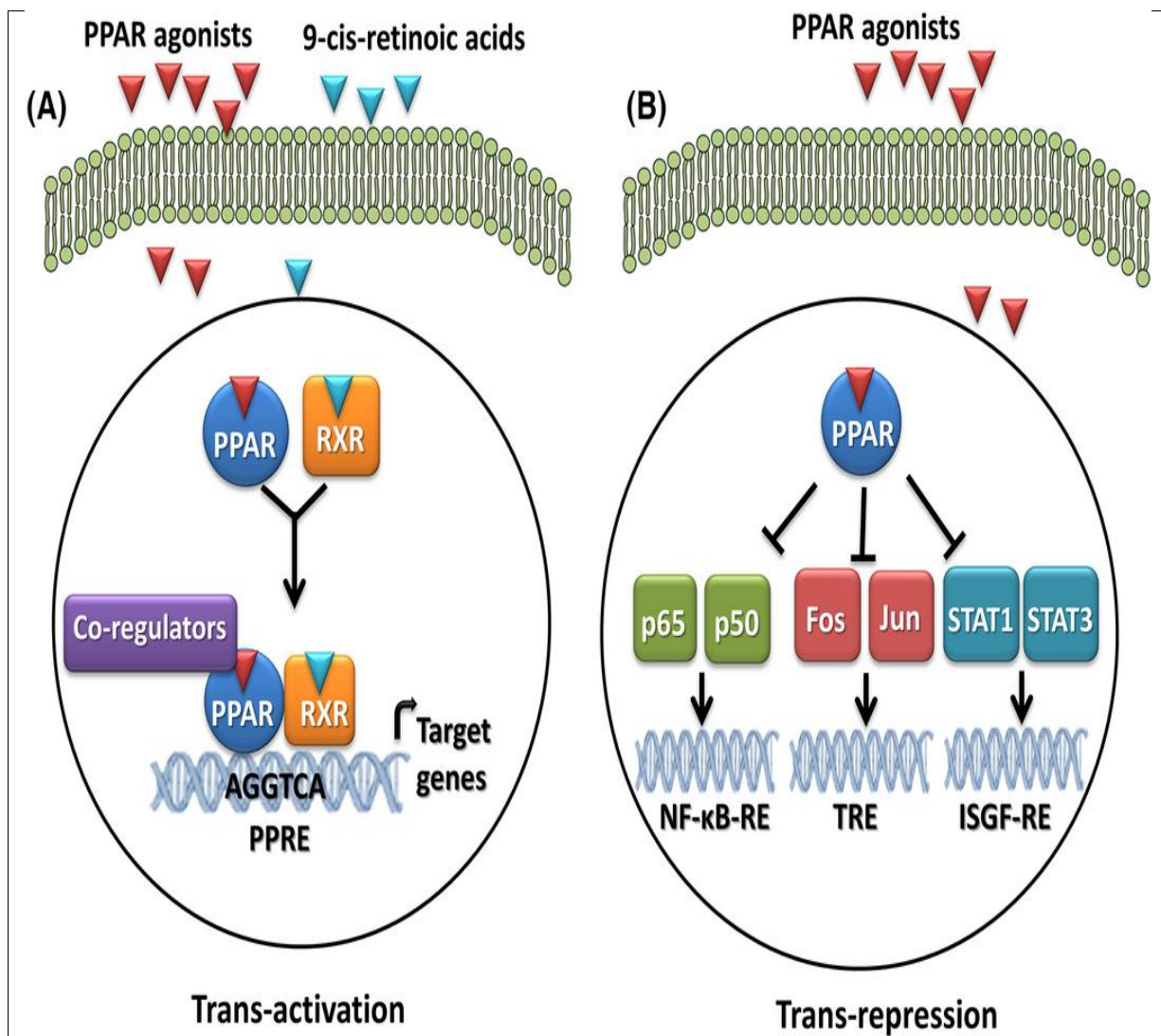


Figure 1.2 Molecular mechanisms of PPAR actions.

(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 by means of coactivators binding (trans-activation). (B) PPARs can also negatively regulate the expression of genes without binding to DNA (trans-repression). Through this mechanism, PPARs inhibit the activity of several transcription factors such as NF- κ B, STATs, cJun, and c-Fos in a DNA-binding-independent manner. PPAR, peroxisome proliferator-activated receptors; NF- κ B-RE, nuclear factor- κ B response element; PPRE, PPAR response element; RXR, retinoid X receptor; STATs, signal transducer and activator of transcription; TRE, TPA (12-O-tetradecanoylphorbol-13-acetate) response element; ISGF-RE, interferon-stimulated gene factor response element.

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 (Tyagi *et al.*, 2011). 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 whole body regulate energy expenditure; expression of PPAR- γ in endothelial cells, vascular smooth muscle cells (Evans *et al.*, 2004).

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

PPAR- 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 (Moreno *et al.*, 2004; Heneka and Landreth, 2007). In the liver, PPAR- α plays a crucial role in fatty acid oxidation, 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 (Lefebvre *et al.*, 2006; Rigamonti 2008). PPAR- α ligands can be either synthetic or endogenous fatty acids and fatty acid-derived compounds are natural ligands for PPAR- α (Willson *et al.*, 2000).

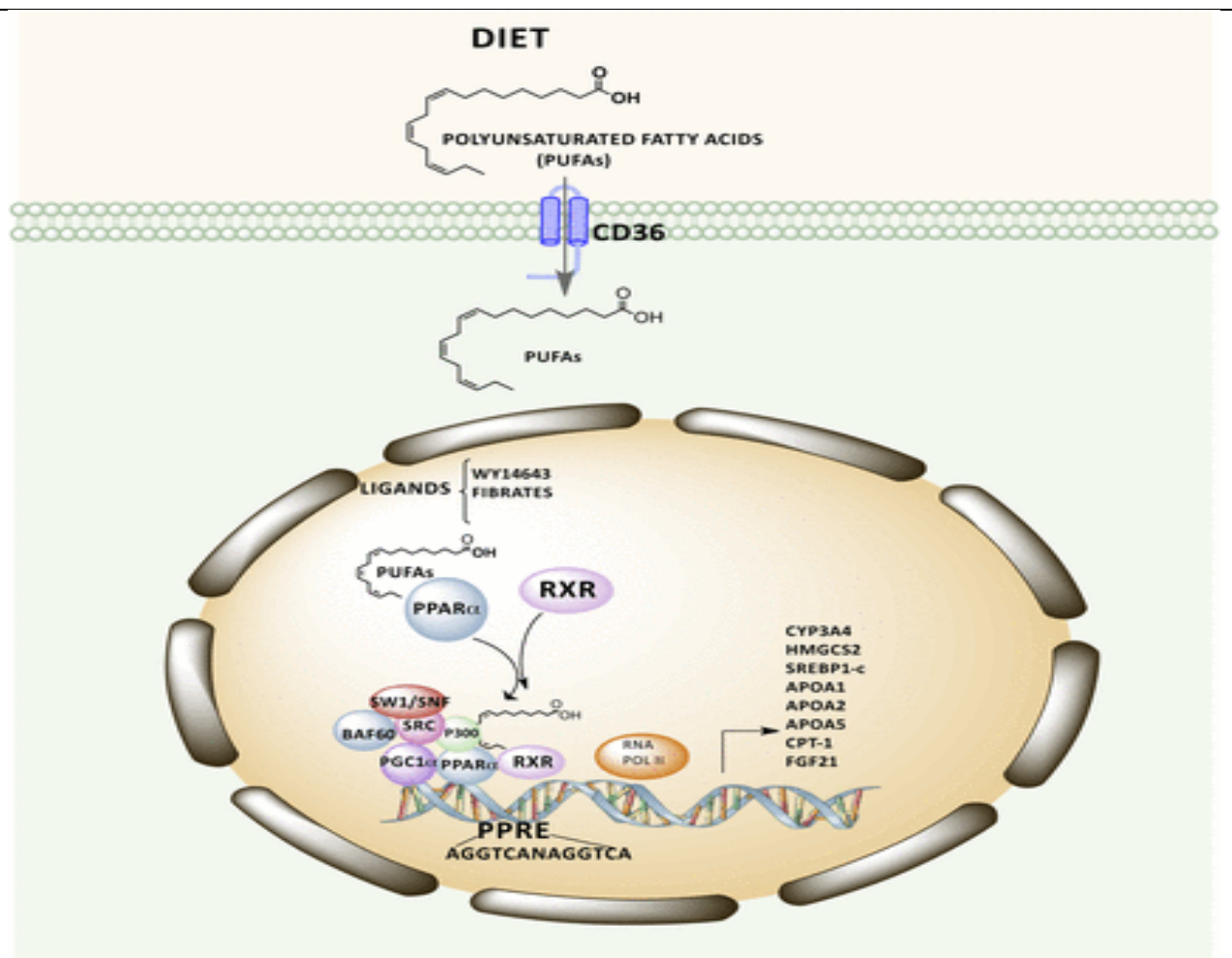


Figure 1.3 Schematic representation of PPAR- α target gene transcription dependent on ligand binding and recruitment of coactivators.

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 is able to 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; **HMGCS2**, hydroxymethylglutaryl CoA synthase 2; **p300**, histone acetyltransferase p300; **PGC1 α** , 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 nonfermentable chromatin-modifying complex.*

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 (Berger *et al.*, 2005; Jay and Ren, 2007; Barter and Rye, 2008). 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 (Mukherjee *et al.*, 1997).

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. PPAR γ is predominantly expressed in adipose tissue and also in vasculature including vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) (Braissant *et al.*, 1996). PPAR γ forms a heterodimer with RXR and binds to the PPAR response elements (PPREs) in the promoter region of target genes (Schoonjans *et al.*, 1996). PPAR- γ acting as sensors of hormones, vitamins, endogenous metabolites, and xenobiotic compounds, the nuclear receptors control the expression of a very large number of genes (Lehman *et al.*, 1995). When activated by various natural and synthetic ligands such as prostaglandin metabolite 15d-PGJ2 (Forman *et al.* 1995) and the insulin sensitizer rosiglitazone (Lehmann *et al.* 1995), PPAR γ transactivates the gene expression and regulates adipogenesis (Farmer, 2006) and insulin response (Nehlin *et al.*, 2006). 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 (Lehman *et al.*, 1995). PPAR- γ agonist improves insulin resistance by opposing the effect of Tumor necrosis factor- α (TNF- α) in adipocytes (Kubota *et al.*, 2006). PPAR- γ enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism (Ferre, 2004). In addition, PPAR γ possesses antiatherogenic and anti-inflammatory actions in

ECs (Reiss and Vagell, 2006). 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 J₂ (15d-PGJ₂), a naturally occurring agonist can modulate inflammatory responses in brain by reducing iNOS expression and neuronal cell death whereas the anti-inflammatory actions of PPAR γ are not attributable to inhibition of cyclooxygenase because injection of selective cyclo-oxygenase inhibitor NS-398 had no effect (Heneka *et al.*, 2000).

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 (Barish *et al.*, 2006). Newly synthesized compounds such as GW501516, GW610742, and GW0742X are shown to have high selectivity to PPAR δ (Nagasawa *et al.*, 2006). PPAR- δ has been noted to reduce the expression of inflammatory mediators and adhesion molecules, suggesting their potential role in attenuating atherogenesis (Graham *et al.*, 2005). Few studies have shown that PPAR- δ ligands have the potential to inhibit cardiac hypertrophy due to their inhibitory activity on nuclear factor- κ B (NF κ B), a transcription factor which produces inflammatory cytokines (Tyagi *et al.*, 2011).

138 **Table 1. Tissue distribution and main functions of PPAR isoforms**

PPAR α	PPAR β/δ	PPAR γ
<i>Tissue distribution</i> 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
<i>Function</i> ↑ 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

139 (↑ Increase, ↓ decrease); FA-fatty acids.

140 INTERACTION BETWEEN FATTY ACID BINDING PROTEINS WITH PPAR

141 Intracellular long-chain fatty acids (FAs) are key components in the synthesis of cellular
142 membranes as well as being utilized as signalling molecules and for energy delivery (Kaikaus
143 *et al.*, 1990). The preservation of a proper balance between absorption, secretion, and storage
144 of FA is therefore, integral for cellular physiology (Glatz and Storch, 2001). Increasingly
145 prominent diseases such as obesity, cardiovascular diseases, type II diabetes, and
146 atherosclerosis, to a large extent, all evolve from disorders of lipid metabolism. In vivo, due
147 to their poor aqueous solubility, FAs are bound and transported by a class of intracellular
148 lipid binding proteins (iLBPs) termed fatty acid binding proteins (FABPs) (Storch and

Thumser, 2000). 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 maintenance of cellular homeostasis through the transcriptional regulation of metabolic enzymes and transporters that target the activating ligand (Velkov, 2013). 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) (Dreyer *et al.*, 1993). PPARs are ligand-activated transcription factors that respond to FA and eicosanoids (Hostetler *et al.*, 2005). The most prevalent iLBPs in the enterocyte, the innate intestinal- (I-) FABP and L-FABP together, constitute 3%–6% of the total cytosolic protein (Poirier *et al.*, 1997). 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 (Velkov *et al.*, 2007). In enterocytes, all three PPAR sub-types are present, the PPAR α and PPAR δ subtypes are predominantly expressed, and to a lesser extent PPAR γ (Escher *et al.*, 2001). Whereas, in hepatocytes, L-FABP is highly expressed together with PPAR α , PPAR δ and PPAR γ are also expressed to a lesser extent (Lowe *et al.*, 1985). 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 (Velkov, 2013).

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 (Cronet *et al.*, 2001). 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 (Bourguet *et al.*, 2000).

Table 2. Natural and synthetic agonists of PPARs

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

Natural and synthetic ligands have been reported for the three PPAR isotypes (Balakumar *et al.*, 2007; Bensinger and Tontonoz, 2008). **For PPAR α** , ligands include natural unsaturated fatty acids (FAs), leukotriene, hydroxyeicosatetraenoic acids (HETEs), and synthetic hypolipemia-inducing drugs such as fibrates (Fyffe *et al.*, 2006). The fibrate hypolipidemic drug classes preferentially bind PPAR α (Noy, 2007). **For PPAR δ** , ligands are less well known, but FAs have been suggested to be natural ligands for this subtype of PPAR (Fyffe *et*

al. 2006). Recent studies identified a few more PPAR δ agonists, namely tetradecylthioacetic acid (TTA), L-165041, and GW501516 (Berger *et al.*, 1999; Oliver *et al.*, 2001; Westergaard *et al.*, 2001). **For PPAR γ** , endogenous ligands include polyunsaturated FAs, prostanoids, and oxidized FAs found in low-density lipoproteins (Forman *et al.*, 1995, Kliewer *et al.*, 1995, Davies *et al.*, 2001). Synthetic ligands for PPAR γ include anti-diabetic drugs, such as rosiglitazone and pioglitazone of the thiazolidinedione class (Nolte *et al.*, 1998) and NSAIDs (Lehmann *et al.*, 1997).

PHARMACOLOGICAL POTENTIALS OF PPARS RECEPTORS

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 PPAR α on obesity and lipid metabolism through its effects on PPAR α -dependent regulation of target genes (Badr, 2009). There are evidences that suggest that PPARS may be interesting therapeutic targets to modulate obesity-induced inflammation (Planavila *et al.*, 2005).

Inflammation

Inflammatory conditions are mainly characterized by activation of macrophages and monocytes at the injury site which subsequently increase the release of proinflammatory mediators like Tumor necrosis factor- α (TNF- α), Interleukin 6 (IL-6), and Interleukin 1 beta

(IL-1 β) which in turn stimulates the production of cyclooxygenase (COX) products. PPAR- α and fenofibrate reduces 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) (D'Agostino *et al.*, 2007; DeFilippis *et al.*, 2009). More recently, 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, PPAR γ has been suggested to play an important role as an endogenous inhibitor of NF- κ B-mediated inflammation (Suzawa *et al.*, 2003). 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 (Majdalawieh and Ro, 2010).

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) (Schoonjans *et al.*, 1996). PPAR- γ has also been shown to control expression of fatty Acid Transport Protein 1 (FATP-1) and 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 (Wu *et al.*, 1999). 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 (Matsusue *et al.*, 2004).

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 PPAR δ) in epithelial homeostasis have been described including the regulation of keratinocyte differentiation, apoptosis and cell proliferation, inflammation, and wound healing (Colin *et al.*, 2010). PPAR- γ not only controls the expression of genes involved in differentiations but also negatively regulates the cell cycle (Grommes *et al.*, 2004). 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 (Rubin *et al.*, 2000). Prostate carcinoma, colorectal carcinoma, non-small-cell lung carcinoma, pancreatic carcinoma, bladder cancer, gastric carcinoma, and glial tumors of the brain (Chattopadhyay *et al.*, 2000). Sarraf *et al.* (1998) also demonstrated that troglitazone and rosiglitazone suppress the growth of human colonic cancer cells.

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 (Racke and Drew, 2008). *In vivo* oral administration of the PPAR- γ agonist pioglitazone reduced glial activation and the accumulation of A β -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 (Swerdlow, 2007).

Lung Pathophysiology and Disease

PPARs plays 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 (Badr, 2009).

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 (Terauchi and Kadowaki, 2005).

Pain Reduction

Synthetic PPAR- α receptor agonists produce broad-spectrum analgesia in a dose-dependent manner (LoVerme *et al.*, 2006). It was recently reported that supraspinal (intracerebroventricular) administration of PPAR- α ligands (perfluorooctanoic acid) reduced peripheral edema and/or inflammatory hyperalgesia (D'Agostino *et al.*, 2007) and that intrathecal administration of PPAR γ ligands, rosiglitazone and 15d-PGJ2, reduced behavioral signs of neuropathic pain (Churi *et al.*, 2008). 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 (Maeda *et al.*, 2008).

Neuroprotective properties

Synthetic PPAR α and PPAR γ ligands have neuroprotective properties, Recently, PPAR β/δ activation emerged as the focus of a novel approach for the treatment of a wide range of neurodegenerative diseases.

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 (Kim and Yang, 2013).

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 (Murphy, 2009) 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) (Hamanaka and Chandel, 2009). NOXs are membrane-bound enzyme complexes that generate superoxide by transferring electrons from intracellular NADPH across the membrane and coupling these to molecular oxygen (Lassègue and Griendling, 2012). 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 (Sawyer, *et al.*, 2002). **Oxidative stress:** occurs when there is imbalance between ROS/RNS production and the endogenous antioxidant defense. Oxidative stress is associated with major pathological development of cardiovascular disease (Sawyer, *et al.*, 2002). 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 (Takimoto and Kass, 2007). **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 (Kunau *et al.*, 1995). thioredoxin (Trx) (Tanaka *et al.*, 2000), or glutathione peroxidases (Wallace, 2002). In mammals, three isoforms of SOD have been reported: the cytosolic Cu/Zn SOD (SOD1) (Francke and Taggart, 1979). The mitochondrial manganese SOD (SOD2 or MnSOD) (Kunau *et al.*, 1995; Wallace, 2002), and the extracellular form of Cu/Zn-SOD (SOD3 or ecSOD) (Fukai and Ushio-Fukai, 2011). 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 (Tanaka *et al.*, 2000). In addition, 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 (Wu *et al.*, 2011). These multiple endogenous antioxidants are crucial in maintaining cellular redox balance. If this balance is interrupted, oxidative stress increases, resulting in damage of essential cellular components.

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 (Kim and Yang, 2013). 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 (Wang *et al.*, 2011); 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 (Fu *et al.*, 2001). Increased lipid oxidation not only causes oxidative stress, it activates transcription and activation of PPARs causing increases expression of PPAR γ in the skeleton (osteoblasts) (Almeida *et al.*, 2009). The transcriptional activity of PPARs can be regulated by post-translational modifications such as phosphorylation, SUMOylation, and ubiquitination (Burns and Vanden Heuvel, 2007). Increase in ROS levels during oxidative stress is accompanied by increases p38 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 PPAR α phosphorylation by the p38 MAPK decreases the transcriptional activity of PPAR α (Barger *et al.*, 2001).

As shown below in Figure 1.4 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 an adaptive feedback or a maladaptive feedback that leads to a vicious cycle (Kim and Yang, 2013).

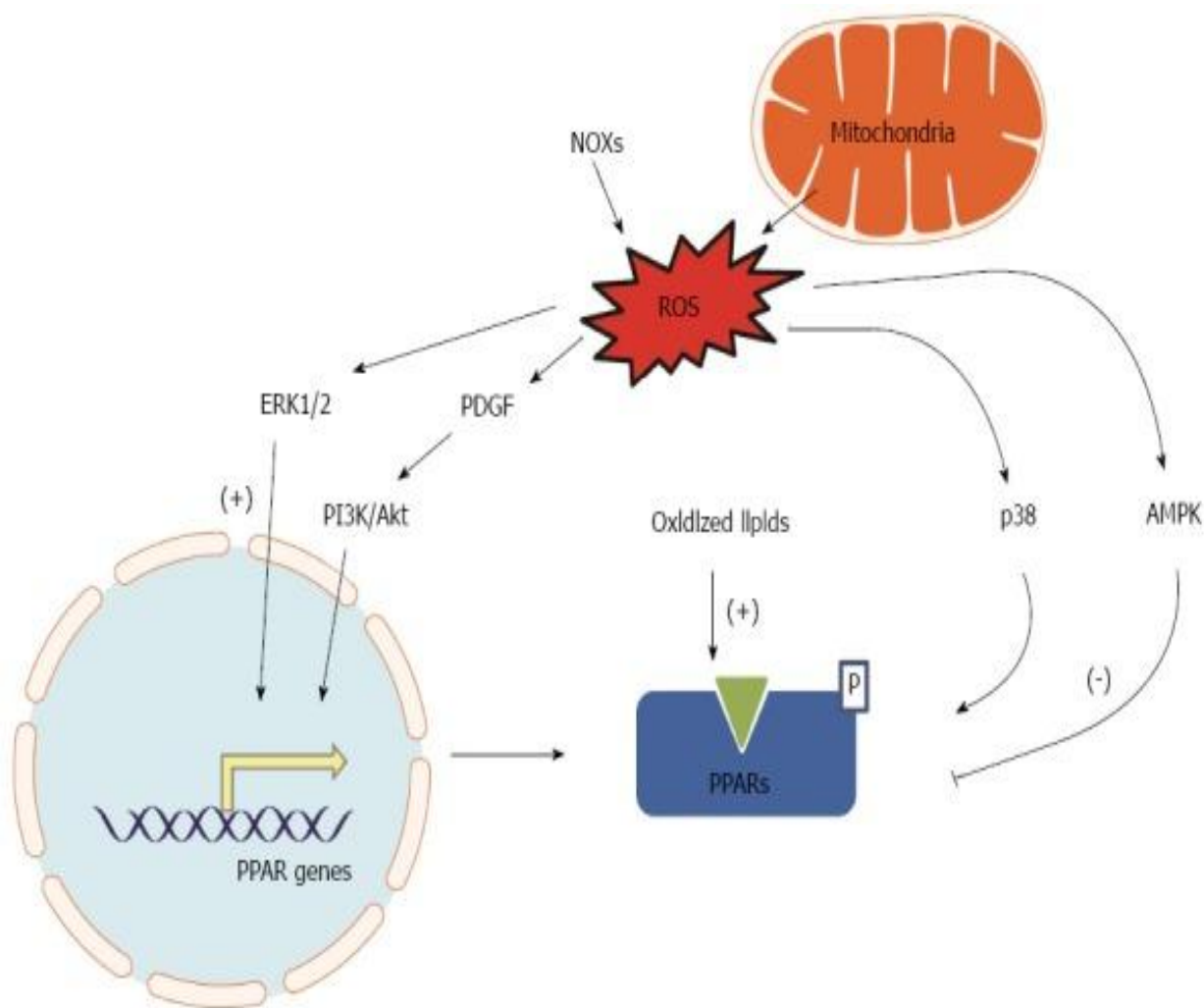


Figure 1.4 Effect of oxidative stress-induced signaling pathways on peroxisome-proliferator-activated receptor transcript and protein activity

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 a specific tissue. Adding to the complexity, specific ligands of each PPAR subtype may also display different potencies and specificities of their role on regulating the redox pathways. Each PPAR subtype regulates redox status with various intensity and extension in a tissue and cell type specific manner (Kim and Yang, 2013).

PPAR α and Oxidative Stress

Activation of PPAR α protects the heart from ischemia/reperfusion injury (Ibarra-Lara *et al.*, 2012). It has been shown that clofibrate a PPAR α ligand protects rat hearts from coronary artery occlusion-induced myocardial ischemia by reducing ROS production and lipid peroxidation. These protective effects of PPAR α ligand are mainly attributed to significantly increased expression and activity of SOD1, SOD2, and catalase in the heart tissue (Ibarra-Lara *et al.*, 2012). Another synthetic ligand of PPAR α , Wy14643, also protects rabbit hearts from ischemia/reperfusion injury by increasing HO-1 expression and decreasing caspase-3 activation (Yeh *et al.*, 2006). In human macrophage, PPAR α activation by another subtype selective ligand, GW647, can upregulate the transcript and protein expression of Trx-1 (Billiet *et al.*, 2008). Moreover, PPAR α activation could also enhance the Trx-1 activity by indirect down-regulation of the natural Trx-1 inhibitor, vitamin D3 up-regulated protein 1 (Billiet *et al.*, 2008). Therefore, stimulation of PPAR α could exert a beneficial effect against the development oxidative damage (Kim and Yang, 2013). PPAR α agonists induce ROS production by increasing NOXs expression and stimulating its activity, which will generate more endogenous PPAR α ligands. This vicious cycle will lead to augmented oxidative stress in macrophages. It has become obvious that the activation of PPAR α in macrophage could have opposite effects on regulating redox state in other tissues showing increase in the expression and activity of either Trx-1 or NOXs.

PPAR γ and oxidative stress

PPAR γ 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 (Billiet *et al.*, 2008). The PPAR γ has been suggested in signalling the transcriptional transrepression of nuclear factor kappa-B (NF- κ B) and it also serve as a transcriptional regulator of endogenous

antioxidants (Kim and Yang, 2013). PPAR γ is an essential regulator of redox signaling and can protect against oxidative damages *via* transcriptional activation of antioxidant genes. Both PPAR α and PPAR γ are involved in the regulation of mitochondrial SOD2 under specific conditions, playing a crucial role in cardiac redox balance (Kim and Yang, 2013). Sekulic-Jablanovic *et al.* (2017) shows that the PPAR α 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 loss of all causes. Pioglitazone (PPAR γ -specific), tesaglitazar (PPAR γ/α -specific), and fenofibric acid (PPAR α -specific) all provided >90% protection from gentamicin toxicity by regulation of overlapping subsets of genes controlling ROS detoxification. Treatment of PPAR γ -specific ligands, rosiglitazone and pioglitazone, can ameliorate H₂O₂-induced oxidative damages in the newborn rabbit heart. The protective effect of PPAR γ ligands against oxidative damage seems to be mediated by catalase, since the effect is abolished by PPAR γ blocker or catalase inhibitor, indicating that the PPAR γ -regulated catalase is crucial for cardioprotective effect of PPAR γ ligands (Chen *et al.*, 2012). 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 (Hwang *et al.*, 2005).

PPAR δ and oxidative stress

PPAR δ is ubiquitously expressed with differential expression abundances in various tissues depending on pathophysiological condition (Cheng *et al.*, 2004). PPAR δ is also expressed in VSMCs and up-regulated after vascular injury (Zhang *et al.*, 2002). PPAR δ activation facilitates VSMC proliferation causing matrix modulation and vascular remodeling. This is an opposite outcome to the activation of PPAR α and PPAR γ by which inflammation is decreased (Zhang *et al.*, 2002). Ligand-activated PPAR δ plays an important role in the cellular response to oxidative stress by decreasing Ang II-induced ROS production in

vascular cells. A PPAR δ -specific ligand GW501516 significantly reduced Ang II-induced ROS generation in VSMCs via inhibiting PTEN-mediated modulation of PI3K/Akt/Rac1 signaling. Activation of PPAR δ suppresses the translocation of Rac1 to the plasma membrane, a key step in NOXs-induced ROS production, in VSMCs (Lee *et al.*, 2012). In addition, PPAR δ is essential for not only the constitutive function of fatty acid metabolism and mitochondrial biogenesis, but also in maintaining antioxidant defense of the heart. Cardiomyocytes-restricted PPAR δ knockout from adult heart leads to oxidative damages with repressed expression of SOD1 and SOD2 (Wang *et al.*, 2010).

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 (Kim and Yang, 2013). PPAR activation exerts direct transcriptional regulation on the expression of several key endogenous antioxidants, including SOD1 (Francke and Taggart, 1979), SOD2 (Lebovitz *et al.*, 1996), catalase (Girnun *et al.*, 2002), GPx, OH-1 and Trx-1 (Billiet *et al.*, 2008). PPARs activate antioxidant genes *via* transcriptional regulation by binding on PPAR response element (PPRE) of promoter region of target genes. PPARs suppress nuclear factor kappa-B (NF- κ B)-light-chain-enhancer of activated B cells *via* interaction with p50 and p65 resulting in decreased inflammatory response and oxidative stress (Westergaard *et al.*, 2003). PPARs suppress phosphatidylinositol 3-kinase (PI3K)/Akt/Rac1 signaling axis *via* activation of

PTEN resulting in decreased reactive oxygen species (ROS) (Kim and Yang, 2013).

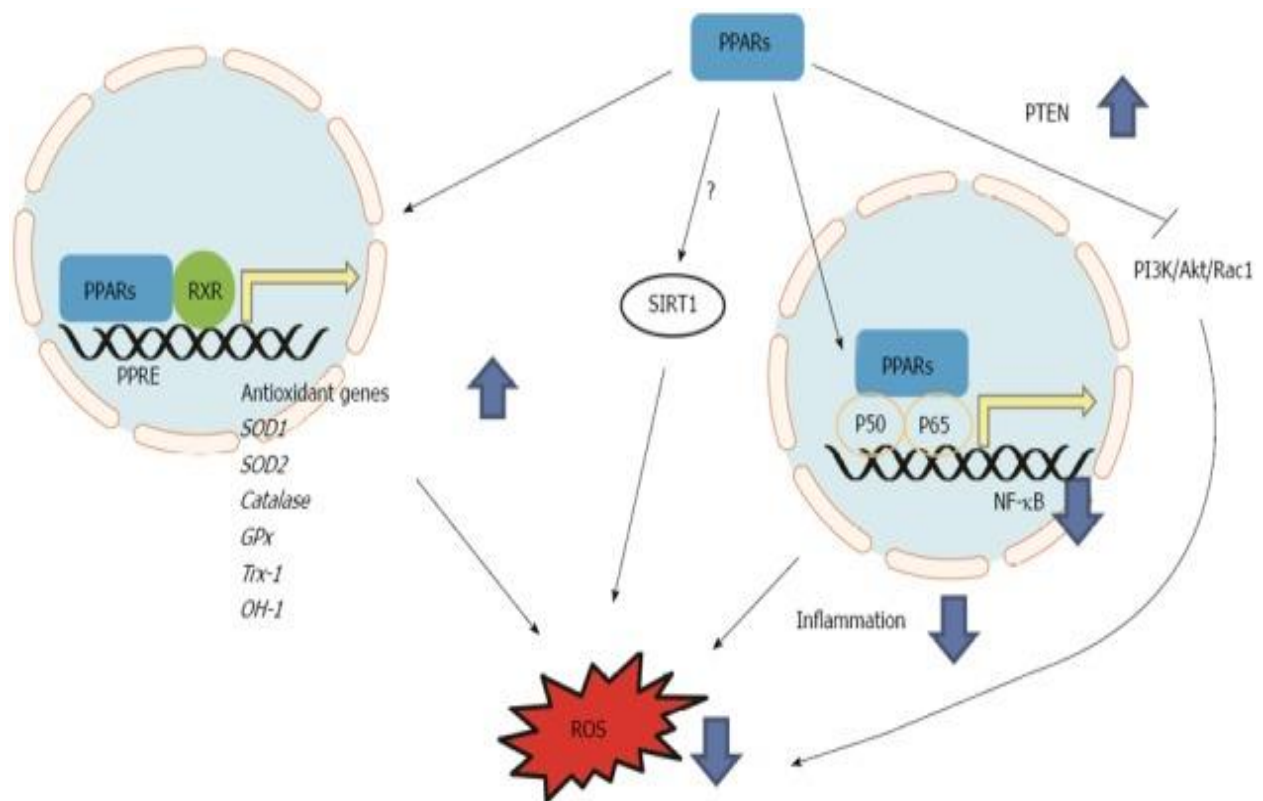


Figure 1.5 Antioxidant mechanisms of peroxisome-proliferator-activated receptors.

ROS: Reactive oxygen species; RXR: Retinoid X receptor; SOD: Superoxide dismutase; TRX: Thioredoxin; GPX: Glutathione peroxidase; HO: Heme oxygenase.

CONCLUSIONS

PPAR are involved in various independent and DNA-dependent molecular and enzymatic pathways in adipose tissue, liver, and skeletal muscles. These pathways are affected in disease condition and cause the metabolic energy imbalance. Thus, intervention of PPAR agonist can provide therapeutic targets for range of diseases such as dyslipidemia, diabetes, obesity, inflammation, neurodegenerative disorder, and cancer. Current literatures strongly support a key role of PPARs as regulators of redox signaling in response to oxidative stress by exerting antioxidative effects through transcriptional or post-translational regulations. Most importantly, there is need for further study to provide insights into the potential

development of partial PPAR modulators that regulate specific cellular redox state without major unwanted effects.

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