

Peroxisome-proliferator-activated receptors regulate redox signaling in the cardiovascular system

Teayoun Kim, Qinglin Yang

Teayoun Kim, Qinglin Yang, Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL 35294-3360, United States

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Correspondence to: Qinglin Yang, MD, PhD, Professor, Department of Nutrition Sciences, University of Alabama at Birmingham, 1675 University Blvd., Webb 435, Birmingham, AL 35294-3360, United States. qyang@uab.edu

Telephone: +1-205-9966022 Fax: +1-205-9347049

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Abstract

Peroxisome-proliferator-activated receptors (PPARs) comprise three subtypes (PPAR α , δ and γ) to form a nuclear receptor superfamily. PPARs act as key transcriptional regulators of lipid metabolism, mitochondrial biogenesis, and anti-oxidant defense. While their roles in regulating lipid metabolism have been well established, the role of PPARs in regulating redox activity remains incompletely understood. Since redox activity is an integral part of oxidative metabolism, it is not surprising that changes in PPAR signaling in a specific cell or tissue will lead to alteration of redox state. The effects of PPAR signaling are directly related to PPAR expression, protein activities and PPAR interactions with their coregulators. 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. Moreover, the intensity and extension of redox

regulation by each PPAR subtype are varied depending on different tissues and cell types. Both beneficial and adverse effects of PPAR ligands against cardiovascular disorders have been extensively studied by many groups. The purpose of the review is to summarize the effects of each PPAR on regulating redox and the underlying mechanisms, as well as to discuss the implications in the cardiovascular system.

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Key words: Peroxisome-proliferator-activated receptor; Redox; Cardiovascular disorders; Oxidative stress; Antioxidant

Core tip: Numerous studies have shown that peroxisome-proliferator-activated receptors (PPARs) ligands can modulate antioxidants *via* various mechanisms. Importantly, direct transcriptional regulation of antioxidant genes, such as *vthioredoxin-1*, *glutathione peroxidase 3*, *sestrin-1*, *catalase*, *superoxide dismutase (SOD)1*, *SOD2*, and *heme oxygenase*, is established by identifying functional PPAR responsive element in promoter regions of the above genes. This review summarizes how these important antioxidant genes are regulated by each subtype of PPARs in response to oxidative stress in the cardiovascular system and how oxidative stress affects PPAR function, as well as the biological implications in the cardiovascular system.

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INTRODUCTION

Mitochondria are the powerhouse for cells and are vulner-

able 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^[1]. 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)^[2,3]. NOXs are membrane-bound enzyme complexes that generate superoxide by transferring electrons from intracellular NADPH across the membrane and coupling these to molecular oxygen^[4]. 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^[5]. Oxidative stress occurs when the balance between ROS/RNS production and the endogenous antioxidant defense. Oxidative stress is associated with major pathological development of cardiovascular disease^[5]. 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^[6,7].

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^-) to O_2 and hydrogen peroxide (H_2O_2), which is further converted into H_2O by catalase^[8], thioredoxin (Trx)^[9], or glutathione peroxidases^[10-12]. In mammals, three isoforms of SOD have been reported: the cytosolic Cu/Zn SOD (SOD1)^[13], the mitochondrial manganese SOD (SOD2 or MnSOD)^[8,12,14], and the extracellular form of Cu/Zn-SOD (SOD3 or ecSOD)^[15]. 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^[9]. 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^[16]. 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.

Peroxisome-proliferator-activated receptors (PPARs) including α , δ and γ , comprise a subfamily of the nuclear receptor superfamily. Similar to other nuclear receptor superfamilies, PPARs share the typical domain structure, including a central DNA-binding domain, an N-terminal ligand-independent activation domain and a C-terminal

ligand binding domain^[17]. Each PPAR subtype mostly forms heterodimer with the retinoid X receptor (RXR) before binding to PPAR responsive element (PPRE) of their target genes and the subsequent synergistic activation of these genes^[18]. Fatty acids and lipid metabolites serve as endogenous PPAR ligands, which exert adaptive metabolic responses to changes in metabolic status in various tissues^[18]. In addition to those identified synthetic compounds *via* high throughput screening, many compounds of natural products and modern medicine have been identified as exogenous PPAR ligands with a wide range of specificities and potencies. Despite the past success of a few of those PPAR subtype specific ligands in the clinical treatment of type II diabetes and dyslipidemia in patients, the potential side effects of these compounds have become a major concern. In-depth understanding of the molecular mechanisms underlying PPAR's action has become even more important in our effort to rescue and improve this class of drugs with clinically proven effectiveness.

In the past decades, numerous studies elucidated the main functional role of PPAR as key transcriptional regulators of lipid metabolism, mitochondrial biogenesis, and anti-oxidant defense. While PPAR's role in regulating lipid metabolism is well-established, their role in regulating redox activity remains incompletely understood. 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. The molecular mechanisms underlying PPAR's role in redox regulation are not fully understood. While numerous studies demonstrate the indirect influence of PPAR activation on the redox state, the role of PPAR in direct transcriptional regulation of redox has emerged. Given the importance of redox regulation in the pathophysiology of the cardiovascular system, this review will give an overview of PPAR's function in regulating redox activity, particularly in the cardiovascular system.

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. PPAR expression and functional activity have recently been observed in the vasculature such as endothelial cells^[19] and vascular smooth muscle cells (VSMCs)^[20], sug-

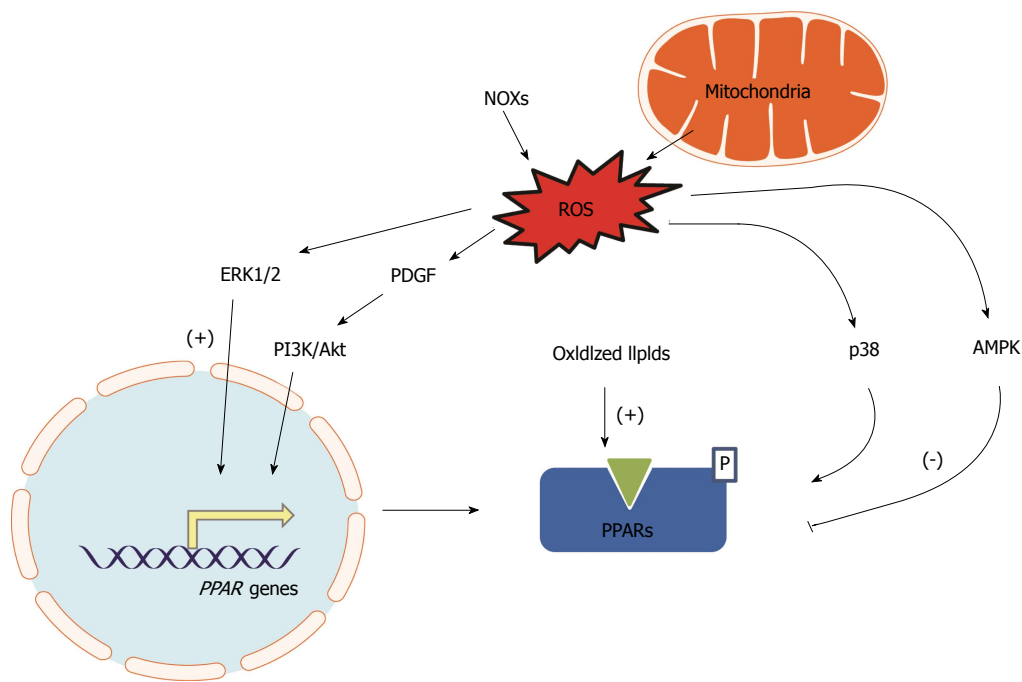


Figure 1 Oxidative stress-induced signaling pathways affecting peroxisome-proliferator-activated receptor transcript and protein activity. Oxidative stress triggers activation of ERK1/2, platelet-derived growth factor (PDGF), and phosphatidylinositol 3-kinase (PI3K)/Akt resulting in increased transcription of peroxisome-proliferator-activated receptors (PPARs) as a defense mechanism. Oxidized lipids activate transcription and activation of PPARs. Oxidative stress increases p38 mitogen-activated protein kinase and 5'AMP-activated protein kinase (AMPK) resulting in the phosphorylation of PPAR proteins resulting in suppressed transcription of PPARs. NOX: Nicotinamide adenine dinucleotide phosphate oxidase; ROS: Reactive oxygen species.

gesting that PPARs could be redox sensitive transcription factors in the vasculature and could be selectively activated by oxidized-fatty acids. PPAR γ is abundantly expressed in macrophage/foam cells of atherosclerotic lesions^[21,22]. *In vitro* experiments confirmed that ROS-related increase of oxidized low-density lipoprotein in macrophage up-regulates PPAR γ expression^[21]. In contrast, H₂O₂ induced oxidative stress in vascular endothelial cells attenuates PPAR γ expression and activity through suppression of PPAR γ transcription, potentially *via* activating inhibitory redox-regulated transcription factors^[19]. Similar ROS-related alteration of PPAR γ expression may occur in other tissues too. Increased lipid oxidation not only causes oxidative stress, but also increases PPAR γ expression in the skeleton (osteoblasts)^[23]. Moreover, peroxidized polyunsaturated fatty acids promote PPAR γ -mediated transcription and binding of PPAR γ to specific target genes, including PPAR γ itself^[23]. PPAR γ is inhibited by histone deacetylase 4 in cortical neurons under oxidative stress in neurons^[24]. Treating the cultured cells with a glutathione-depleting agent diethylmaleate reduces DNA-binding activity of PPAR α ^[25]. Supplement of an antioxidant, vitamin E, can effectively restore PPAR α expression in aged mice to levels seen in younger mice^[26]. This may also occur in cells of the cardiovascular system. This observation implicates that balancing the cellular redox state may serve as an essential transcriptional regulation for PPAR α . ERK1/2 activation is one of the common consequences of oxidative stress^[27]. Activation of ERK1/2 signaling can induce the expression of PPAR γ during the differentiation of 3T3-L1 preadipocytes^[28]. Another oxi-

datve stress induced factor, Platelet-derived growth factor (PDGF), has been shown to upregulate PPAR δ gene expression in VSMCs by the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway^[29]. Therefore, it appears that oxidative stress may influence individual PPAR activity in a tissue specific manner.

The transcriptional activity of PPARs can be regulated by post-translational modifications such as phosphorylation, SUMOylation, and ubiquitination^[30,31]. Increase in ROS levels is accompanied by p38 mitogen-activated protein kinase and 5'AMP-activated protein kinase (AMPK) activation in the heart^[32-34]. The PPAR α phosphorylation by the p38 MAPK decreases the transcriptional activity of PPAR α ^[35].

As summarized in Figure 1, 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.

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. Many studies revealed the beneficial effects of PPAR ligands against cardiovascular disorders, although recent studies demonstrate potential adverse effects of synthetic PPAR ligands on cardiovascular disease models. This section summarizes how each PPAR regulates redox mainly in the cardiovascular system.

PPAR α and oxidative stress

PPAR α is expressed in various cell types related to the cardiovascular system, including cardiomyocytes^[36], endothelial^[37,38], smooth muscle cells^[20] and monocytes/macrophages^[39]. The role of PPAR α in lipid and lipoprotein metabolism is well established^[36,40]. Fibrates are drugs that selectively target PPAR α and have been clinically used to lower hypertriglyceridemia, a risk factor of cardiovascular disease. Moreover, PPAR α is a critical regulator of intra- and extracellular lipid metabolism. In addition, the therapeutic efficacy of fibrates in inhibiting atherogenesis may also in part attribute to its capacity to regulate cholesterol efflux^[41] and redox signaling. Activation of PPAR α protects the heart from ischemia/reperfusion injury^[40,42,43].

Evidence supporting the role of PPAR α in regulating redox pathways remains relatively superficial and paradoxical. Most of the early studies are based on *in vitro* and *in vivo* experiments using PPAR α -selective ligands, such as clofibrate, fenofibrate and Wy14643. It has been shown that clofibrate protects rat hearts from coronary artery occlusion-induced myocardial ischemia by reducing ROS production and lipid peroxidation. These protective effects are mainly attributed to significantly increased expression and activity of SOD1, SOD2, and catalase in the heart tissue^[43]. Furthermore, clofibrate is able to suppress the upregulation of Ang II, Ang II AT1-receptor and subsequently the related oxidative stress in the heart, at least partially contributing to the improved cardiac function^[43]. 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^[44]. In human macrophage, PPAR α activation by another subtype selective ligand, GW647, can upregulate the transcript and protein expression of Trx-1^[45]. 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^[45]. Therefore, stimulation of PPAR α could exert a beneficial effect against the development of atherosclerosis. The remaining questions are whether PPAR α ligand treatments could alleviate specifically oxidative stress and contribute to their beneficial effects *via* a PPAR α dependent or independent mechanism. Studies on mouse models of transgenic overexpression and/or knockout of PPAR α specifically in the cardiovascular system solved some of the puzzles. However, discrepancies among different studies exist. PPAR α knockout mice showing minimal phenotypic changes in the heart are probably in different genetic backgrounds from those showing major pheno-

typic changes. In a study reporting cardiac contractile dysfunction in PPAR α null mice, a mechanism of oxidative damage in sarcomere proteins and lipid peroxidation was proposed based on the observation that a significant decrease of SOD2 protein and the corresponding activity with no change of other antioxidant enzymes such as Cu/ZnSOD (SOD1), catalase, and glutathione peroxidase (GPx) was reported^[46]. It is not clear if the repression of SOD2 protein level and activity also occurred at the transcript level. Moreover, another study could not confirm the downregulation of SOD2 transcript and protein in the PPAR α null heart^[47]. Therefore, strong evidence of a direct interplay between cardiac SOD2 and PPAR α is still lacking and whether the observation recorded is due to a lack of genuine regulation by PPAR α or a long-term developmental adaptation to the absence of PPAR α remains yet to be established.

It is well established that PPAR α specific ligands activate fatty acid oxidation. However, it remains unclear, at least in cardiovascular tissues, whether this increased lipid oxidation would subsequently lead to oxidative stress due to the augmented respiration. There is evidence that activation of PPAR α in the heart either by transgenic overexpression or PPAR α selective ligand treatment causes increased fatty acid oxidation^[48,49]. Activation of PPAR α may be associated with the repression of estrogen related receptors (ERRs). ERRs are members of another nuclear receptor subfamily that governs mitochondrial biogenesis^[50], thus exacerbating pressure overload-induced cardiac hypertrophy and heart failure due to mitochondrial dysfunction^[51]. However, the subsequent changes of ROS in the heart have not been well characterized. In human and murine macrophages, different PPAR α , but not PPAR γ , agonists increase the production of ROS (H₂O₂ and superoxide)^[52]. Most importantly, this study excluded the potential off-target effects of the tested PPAR α ligands by showing the mediating role of PPAR α agonists. 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. The consequences of PPAR α activation on ROS production in macrophage are not clear. Overwhelming evidence supports the fact that PPAR α activation suppresses atherogenic inflammation in macrophage^[39,53]. It is likely that ROS will be reduced in PPAR α ligand treated macrophages.

Overall, it is likely that PPAR α plays certain roles in regulating redox state in the cardiovascular system. However, supporting evidence will be needed to further address the mechanistic aspects of PPAR α related redox changes.

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 of the cardiovascular system, since PPAR γ is expressed in the heart and vasculature^[42,54]. Activation of PPAR γ may exert anti-atherogenic^[41,55] and anti-hypertrophic effects^[56]. Despite the relatively low expression in the myocardium, cardiomyocyte-restricted PPAR γ knockout in mice leads to cardiac hypertrophy and even heart failure^[57,58]. On the other hand, PPAR γ activation substantially reduces myocardial infarct size, significantly improve aortic flow during reperfusion in both normal and diabetic hearts and substantially ameliorate post-ischemic functional recovery in rats^[42,59,60]. These observations suggest an important role of PPAR γ in the heart.

While the transcriptional transrepression of nuclear factor kappa-B (NF- κ B) signaling by PPAR γ has been suggested as a mechanism in most of above studies, the role of PPAR γ as a transcriptional regulator of endogenous antioxidants is another mechanism. Our previous study on the cardiomyocyte-restricted PPAR γ knockout mice unveiled that oxidative stress plays an essential role in the development of progressive cardiac hypertrophy and dilated cardiomyopathy in these mice^[58]. However, further study from our group on adult mice with short term cardiac-specific PPAR γ knockout showed only modest cardiac hypertrophy without oxidative stress, though fatty acid utilization was impaired and cardiac performance was compromised. Neither the mitochondrial ultrastructure nor mitochondrial copy number was altered compared with control mice^[61]. These two contrast outcomes of PPAR γ knockout suggest that cardiac oxidative stress may cause chronic damage instead of acute lethality. The deteriorating phenotype of PPAR γ knockout was prevented by administration of MnTBAP, which mimics SOD by scavenging superoxide. Therefore, 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.

Treatment of PPAR γ -specific ligands, rosiglitazone and pioglitazone, can ameliorate H₂O₂-induced oxidative damages in the newborn rabbit heart. These oxidative damages feature repressed left ventricular developed pressure, sarcomere shortening, decreased catalase expression level, and increases lactate dehydrogenase. 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^[62]. Studies also have shown that PPAR γ ligands have protective effects against hypertrophy, induced by ischemia/reperfusion or angiotensin II, in rodents *via* various mechanisms^[63]. Ang II inhibits PPAR γ transcriptional activity, which in turn suppresses expression of antioxidant enzymes. PPAR γ agonists, pioglitazone and 15d-PGJ₂, reverse the Ang II-induced suppression of catalase in adventitial fibroblasts of rat aorta^[64]. Pioglitazone also attenuates atrial fibrillation, in which oxidative stress plays an important role in the pathophysiology and often complicated by ischemic heart

disease, valvular disease, and left ventricular hypertrophy^[65]. PPAR γ plays an important role in macrophage inflammatory homeostasis, partly by regulating cholesterol efflux^[41]. On the other hand, lipopolysaccharide and IFN- γ in macrophages upregulates PPAR γ activity and attenuates the oxidative burst^[66]. 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^[67]. This effect is also found in the vasculature of diabetic mice independent of correction of diabetic metabolic derangements^[68]. Moreover, another PPAR γ ligand rosiglitazone can attenuate high glucose induced oxidative stress and subsequent monocyte-endothelial interactions by attenuating NF- κ B/p65 activation and NOX4 expression, thus favorably modulating endothelial responses in the diabetic vasculature^[69]. Therefore, it is clear that PPAR γ is an essential regulator of redox signaling in the cardiovascular system and can protect against many cardiovascular disorders *via* transcriptional activation of antioxidant genes.

PPAR δ and oxidative stress

PPAR δ is ubiquitously expressed with differential expression abundances in various tissues depending on pathophysiological condition. PPAR δ is abundantly expressed in the heart and plays an essential role in regulating fatty acid oxidation in cardiomyocytes^[70]. The essential role of PPAR δ in the heart is further demonstrated by the striking cardiac pathological development in mice with cardiomyocyte-restricted knockout of PPAR δ ^[71]. Several other studies confirmed the myocardial protective effects either with the treatment of PPAR δ ligands in rats^[72,73] or cardiomyocyte-restricted overexpression in transgenic mice^[74,75]. PPAR δ is also expressed in VSMCs and up-regulated after vascular injury^[76]. 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^[76,77]. A PPAR δ -specific ligand compound promotes lipid accumulation in human macrophages by increasing the expression of genes involved in lipid uptake and storage, whereas this treatment represses lipid metabolism and efflux^[78]. However, another PPAR δ -specific ligand GW501516 increases expression of the reverse cholesterol transporter, ATP-binding cassette A1, and induced apolipoprotein A1-specific cholesterol efflux in macrophages^[79]. This observation of PPAR δ activation is similar to the effects of PPAR α and PPAR γ activation in macrophages by which cholesterol is removed from foam cells^[41]. In addition, it has been reported that PPAR δ ligand L-165041 inhibits VCAM-1 expression and cytokine-induced MCP-1 secretion in endothelial cells and increases high-density lipoprotein (HDL) levels in *db/db* mice^[80]. Since the increased HDL levels are well associated with decreased risk of atherosclerosis, it appears PPAR δ activation may inhibit atherogenesis.

While the role of PPAR δ activation in protecting

against pathogenesis in the cardiovascular system is established, how much of the protective mechanisms are involved in the anti-oxidation effects remains obscure. However, the role of PPAR δ activation in anti-oxidant defense of the cardiovascular system is unraveling. A recent study demonstrated that the PPAR δ counteracts Ang II-induced ROS production in VSMCs. 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^[81,82]. Activation of PPAR δ suppresses the translocation of Rac1 to the plasma membrane, a key step in NOXs-induced ROS production, in VSMCs^[82]. Another recent study focusing on human endothelial cells demonstrates similar findings. PPAR δ activation by GW501516 inhibits angiotensin II-induced premature senescence featured with elevated ROS production in human coronary artery endothelial cells^[83]. These results illustrate that ligand-activated PPAR δ plays an important role in the cellular response to oxidative stress by decreasing Ang II-induced ROS in vascular cells. In addition, we have recently demonstrated that 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^[84]. Cardiomyocytes-restricted PPAR δ knockout from adult heart leads to oxidative damages with repressed expression of SOD1 and SOD2^[84]. Interestingly, the PPAR α null mice with additional PPAR δ knockout from the heart showed similar results. Both the transcript and protein expression of SOD1 and SOD2 was repressed in PPAR δ , but not PPAR α deficient hearts^[47]. In this study, none of the endogenous antioxidants appears to be affected at basal condition in the PPAR α null heart. Therefore, it appears repressed antioxidant expression is the main reason for the major oxidative damages in the hearts of PPAR δ knockout and PPAR δ /PPAR α double knockout mice. The effects of PPAR δ activation in regulating cardiac antioxidant defense have also been proven in mouse models with cardiomyocyte-restricted overexpression of a constitutively active PPAR δ . The enhanced antioxidant defense in these mice enables them to have improved cardiac performance under left ventricular pressure overload condition^[75]. However, the transcriptional regulation of antioxidants by PPAR δ in the heart may depend on various metabolic conditions with different pathological development. The myocardial protective effects of PPAR δ ligand treatment and transgenic PPAR δ overexpression have been attributed to their roles in ameliorating lipid profile by increasing fatty acid β -oxidation^[72] and in enhancing myocardial glucose utilization^[74]. Nevertheless, it is likely that the PPAR δ mediated upregulation of the antioxidants defense may also contribute to the beneficial effects.

The effects of each of the three PPARs on redox signaling in the cardiovascular system are generally beneficial in the cardiovascular system. However, contradicting results from various studies exist. It is far from clear as how each of the three PPARs differentially regulates

redox signaling in various tissues and cells of the cardiovascular system.

MECHANISMS OF ACTION OF PPARS IN REGULATING REDOX

The molecular mechanisms underlying the PPAR-mediated regulation of redox signaling have been extensively studied. There is emerging evidence supporting that PPAR activation exerts direct transcriptional regulation on the expression of several key endogenous antioxidants, including SOD1^[13], SOD2^[14], catalase^[58,85,86], GPx, OH-1 and Trx-1^[45].

Rat SOD1, which is analogous to human SOD1, has PPRE consensus sequence in its promoter region^[87]. SOD1 is induced in HepG2 human hepatoma cells by arachidonic acid (polyunsaturated fatty acid), one of the peroxisome proliferators, as a defense system. A promoter analysis of *SOD1* gene revealed a conserved PPRE sequence located in -797 and -792 nt, which is able to induce CAT reporter gene activity. The HepG2 nuclear extract showed PPRE-binding in gel mobility shift assay and nuclear extract from retinoic acid-treated HepG2 cells increased the intensity of the DNA-protein complex indicating *SOD1* gene is induced by arachidonic acid through the binding of PPAR to the PPRE of the *SOD1* gene^[85]. PPAR γ ligands have been shown to reduce superoxide by stimulating both activity and expression of SOD1 in human umbilical vein endothelial cell and suppressing NOXs^[67].

Our previous study showed that PPAR γ is essential for the full expression of SOD2 transcript in the heart^[58]. SOD2 expression level in cardiac-specific PPAR γ knockout mice heart is significantly decreased, and mitochondrial superoxide production was significantly increased compared to that in control mice. We have further confirmed that the PPRE sequence found between -985 and -935 nt in the *SOD2* promoter region is functioning. The truncated promoter fragments did not transactivate luciferase reporter gene by rosiglitazone^[58]. Therefore, both SOD1 and SOD2 are regulated by direct interaction of PPARs on the PPRE of their promoters under specific conditions.

Cat (catalase; EC 1.11.1.6) plays an important role in cellular protection against oxidative stress by scavenging H₂O₂ generated from peroxisomal fatty acid β -oxidation. Numerous studies have shown that ligands of PPAR α , PPAR δ , and PPAR γ increase catalase expression level and activity. Catalase has been characterized as PPAR γ target gene with a PPRE consensus sequence on its promoter region. One study reported that *in vitro* translated protein PPAR γ /RXR α heterodimer binds 5'-proximal promoter region (5 kb) of catalase. The putative PPRE fragment increased reporter gene activity in the presence of PPAR γ ligands and deletion of the region containing PPRE abolished the response to the ligand. Further promoter deletion assay revealed that the PPRE was located between -1027 and -1015 nt. Tandem repeated 3 \times PPRE significantly increased PPAR γ -stimulated promoter

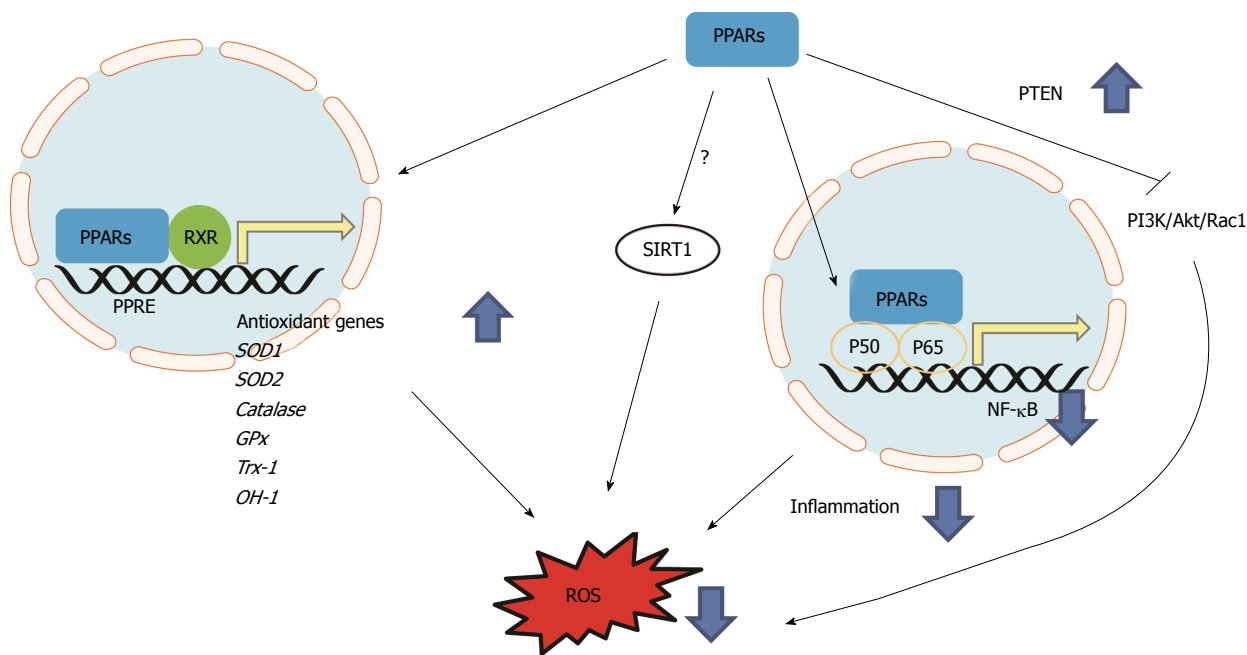


Figure 2 Antioxidant mechanisms of peroxisome-proliferator-activated receptors. Peroxisome-proliferator-activated receptors (PPARs) activate antioxidant genes via transcriptional regulation by binding on PPAR response element (PPRE) of promoter region of target genes. PPARs suppress nuclear factor kappa-B (NF-κB)-light-chain-enhancer of activated B cells via interaction with p50 and p65 resulting in decreased inflammatory response and oxidative stress. PPARs suppress phosphatidylinositol 3-kinase (PI3K)/Akt/Rac1 signaling axis via activation of PTEN resulting in decreased reactive oxygen species (ROS). RXR: Retinoid X receptor; *sod*: Superoxide dismutase; *trx*: Thioredoxin; *gp*x: Glutathione peroxidase; *ho*: Heme oxygenase.

activity, suggesting that PPRE alone is enough to induce transactivation of target gene^[86].

The selective PPAR α ligand GW647 significantly increases Trx-1 expression and activity in human macrophage. A luciferase reporter assay on human macrophage and detailed computer analysis revealed that PPRE is located between -2185 and -2198 nt of Trx-1 promoter. Mutated PPRE abolished transactivation activity on luciferase reporter assay. In an electrophoretic mobility shift assay, *in vitro* translated RXR α and PPAR α proteins bind this PPRE by heterodimerization.

The GPx3 expression level in the skeletal muscles is significantly decreased in *db/db* relative to control mice^[88]. Additionally, the plasma GPx3 levels are significantly decreased in type 2 diabetic patients compared to normal subjects. PPAR γ ligands troglitazone, rosiglitazone, and pioglitazone decrease extracellular H₂O₂ levels and prevent H₂O₂-induced insulin resistance by increasing the expression of GPx3 in human skeletal muscle cells^[88]. This increase of GPx3 is PPAR γ -specific and exclusive to GPx3, but not other GPx family. Whereas the PPAR γ siRNA represses TZD-induced GPx3 expression, GPx3 siRNA inhibits the H₂O₂ scavenging antioxidant effect of TZD. These data indicate that GPx3 is regulated by PPAR γ playing cellular protective role against oxidative stress. In the luciferase reporter assay GPx3 promoter -2294 nt region shows strong trans-activation of reporter gene and PPRE is found between -2186 and -2174 nt^[88].

In addition to the direct transcriptional effects of PPARs, the interaction of PPAR signaling with many other cell signals can also mediate PPAR's effects on regulating redox state in cells of the cardiovascular system.

PPAR δ can act through inhibiting the PI3K/Akt signaling pathway to suppress the marked increase in ROS levels induced by Ang II. Ligand-activated PPAR δ also blocked Ang II-induced translocation of Rac1 to the cell membrane, inhibiting the activation of NOXs and consequently ROS generation^[82]. The activation of NF-κB is the main signaling event that triggering the inflammatory responses and the subsequent oxidative stress. It has been well recognized that PPAR can exert transrepression effects on the NF-κB signaling and suppress inflammatory responses; hence oxidative stress is ameliorated^[89-92]. Therefore, it appears that 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 (Figure 2). However, the mechanisms of how PPARs as a transcription factor would perturb these signaling pathways remain incompletely understood. This is especially the case in understanding how each of the three PPARs exerts antioxidant effects. While PPAR δ activation appears to exert most of the direct and indirect inhibitory effects on ROS production in the cardiovascular system, the effects of PPAR α and PPAR γ appear to be more complicated depending on cell types and specific conditions. Investigations on the potential beneficial effects of dual or triple PPAR ligands are emerging. This novel class of PPAR ligands may be able to avoid potential side effects of each single ligand^[93]. Phase II clinical trials for a dual PPAR α/γ agonist, aleglitazar, validate their hypoglycemic and hypolipidemic effects^[94]. An ongoing phase III clinical trial^[95] will reveal the efficacy against cardiovascular event. However, a few dual agonists, such

as ragaglitazar, MK-0767, and naveglitazar, cause bladder cancer in rodents suggesting tissue-specific response should be meticulously tested. However, whether these upcoming new agonists modulate oxidative stress in cardiovascular system remains unclear. Further studies should be conducted.

Another difficulty involved in dissecting the antioxidant role of PPARs is the potent effects of PPAR activation in many other metabolic pathways, which all pose major influences on the redox balance. Therefore, we will have to interpret many of the current findings in contexts of specific cell types, specific animal strain/species and specific disease states.

FUTURE PERSPECTIVES AND CONCLUSIONS

The PPARs are one of the most extensively studied members among the nuclear hormone receptor family. Compounds (fibrate and TZD drugs) targeting PPAR α and PPAR γ have been used broadly in treating diabetes and dyslipidemia. While the effects of PPAR signaling on redox regulation in the cardiovascular system are major indications of the therapeutic potential, use of clinically available PPAR agonists for heart failure and atherosclerosis remains controversial for major safety concerns^[96,97]. The main issues concern whether the risk outweighs the benefit. Current literatures strongly support a key role of PPARs as regulators of redox signaling in response to oxidative stress in the cardiovascular system by exerting antioxidative effects through transcriptional or post-translational regulations. It remains crucial to confirm many of the *in vitro* findings on the role of PPARs as redox regulators in intact animals under normal physiological and pathological conditions. Preclinical studies on animal models with temporal and spatial genetic manipulations have emerged as powerful tools for preclinical understanding of PPAR's roles in regulating redox signaling in the cardiovascular system. Most importantly, these studies will provide insights into the potential development of partial PPAR modulators that regulate specific cellular redox state without major unwanted effects.

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