PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS AND CARDIOVASCULAR REMODELING

Ernesto L. Schiffrin

CIHR Multidisciplinary Research Group on Hypertension,
Clinical Research Institute of Montreal, Montreal, Quebec, Canada.

Running Title: Cardiac and vascular effects of PPARs

No. of words: Abstract 210; total manuscript 6337.

Correspondence:

Ernesto L. Schiffrin, MD, PhD, FRCPC
Clinical Research Institute of Montreal,
110 Pine Avenue West,
Montreal, Quebec, Canada H2W 1R7.
Tel: 1 (514) 987-5528
Fax: 1 (514) 987-5602
E-mail: ernesto.schiffrin@ircm.qc.ca
Abstract

Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors that heterodimerize with the retinoid X receptor (RXR) and then modulate the function of many target genes. Three PPARs are known, α, β/δ and γ. The better known are PPARα and PPARγ that may be activated by different synthetic agonists, although the endogenous ligands are unknown. PPARα is involved in fatty acid oxidation and expressed in liver, kidney and skeletal muscle, whereas PPARγ is involved in fat cell differentiation, lipid storage and insulin sensitivity. However, both have been shown to be present in variable amounts in cardiovascular tissues, including the endothelium, smooth muscle cells, macrophages and the heart. The activators of PPARα (fibrates), and PPARγ (thiazolidinediones or glitazones) antagonized the actions of angiotensin II actions in vivo and in vitro, and exerted cardiovascular antioxidant and anti-inflammatory effects. PPAR activators lowered blood pressure, induced favorable effects on the heart, and corrected vascular structure and endothelial dysfunction in several rodent models of hypertension. Activators of PPARs may become therapeutic agents useful in the prevention of cardiovascular disease beyond their effects on carbohydrate and lipid metabolism. Some side effects such as weight gain as well as documented aggravation of advanced heart failure through fluid retention by glitazones may however limit their therapeutic application in cardiovascular prevention.

Key words: PPAR, arteries, endothelium, heart, inflammation
Introduction

Peroxisome proliferator-activated receptors (PPARs) are nuclear factors initially shown to respond to xenobiotics with peroxisomal proliferation in the rodent liver [30]. Later they were demonstrated to modulate genes that regulate lipid and glucose metabolism (reviewed in ref. 40). More recently, PPARs have been shown to participate in the regulation of cell growth and migration [36], oxidant stress [15,59] and inflammation [13] in the cardiovascular system. PPARα is found in tissues where fatty acid catabolism is important (liver, kidney, heart, and muscle) and is stimulated by natural ligands such as fatty acids and eicosanoids (e.g.: leukotriene B₄), and by synthetic ligands, the lipid lowering fibrates [14]. PPARα affects target genes that participate in ω- and β-oxidation of fatty acids. PPARβ/δ is expressed in many tissues [6,34]. Recent evidence suggests that PPARβ/δ is involved in fatty acid and lipid metabolism, particularly in skeletal muscle [9,40,60]. This may also occur in cardiovascular tissues [24]. PPARγ controls adipocyte differentiation and lipid storage [60] and is accordingly highly expressed in adipose tissue. Through its effects on adipose tissue and skeletal muscle, PPARγ regulates the action of insulin. Selective activators of PPARγ are the insulin sensitizers thiazolidinediones or glitazones, such as troglitazone, pioglitazone and rosiglitazone.

PPARs have an N-terminal domain that regulates PPAR activity, a DNA binding domain that binds to the PPAR response element (PPRE) in the promoter region of target genes, a domain for a cofactor, and a C-terminal ligand-binding domain that determines ligand specificity [62]. PPARs are bound to co-repressor proteins when inactive. After stimulation by PPAR activators, PPARs dissociate from co-repressors and recruit co-activators, which include a PPAR-binding protein and the steroid receptor coactivator-1 [37], and
heterodimerize with retinoid X receptors (RXRα). They then bind to PPRE in target genes to modulate gene transcription [27]. Gene regulation by this mechanism results in the action that PPARs have on carbohydrate and lipid metabolism (figure 1). Both PPARα and γ also exert numerous effects by interaction with different transcription factors to repress pro-inflammatory genes (figure 1). Whereas the effects on carbohydrate and lipid metabolism affect the cardiovascular system mainly through their impact on atherogenesis, the anti-inflammatory and antioxidant actions of PPARs affect cardiovascular remodeling in many ways. Effects of PPARs on cardiovascular remodeling are the main subject of the present review, beyond their regulatory effects on glucose and lipid metabolism that have been reviewed recently [40].

**Vascular effects of PPAR alpha**

PPARα and PPARγ are expressed in the cardiovascular system [5]. PPARα are found in endothelial cells [28], vascular smooth muscle cells (VSMC) [56] and in monocytes/macrophages [10]. The role that these nuclear factors play in the vasculature and the heart has been revealed over the past few years [40]. PPARα ligand docosahexanoic acid (DHA) was shown to have proapoptotic effects on cultured VSMCs [19] which were mediated by activation of p38 mitogen-activated protein kinase (MAP kinase) [21]. Anti-inflammatory effects were demonstrated by the inhibition by PPARα ligands of interleukin (IL)-1β-induced production of IL-6 and prostaglandins, and expression of cyclooxygenase-2. These effects occurred as a consequence of PPARα inhibition of signaling by the proinflammatory mediator nuclear factor (NF)-κB and induction of apoptosis [10]. Antagonism of signaling by NF-κB was also demonstrated by other investigators [12, 46]. PPARα activators also down-regulated cytokine-induced genes, such as vascular cell
adhesion molecule (VCAM)-1 and tissue factor in endothelial cells [42]. PPARα-deficient mice demonstrated enhanced inflammatory responses to lipopolysaccharide (LPS) administration, and in these mice fibrates were unable to affect LPS-induced IL-6 [12]. The PPARα activator fenofibrate also reduced plasma concentrations of the cytokines interferon-γ and tumor necrosis factor α (TNFα) in hyperlipoproteinemia IIb patients [38].

Because PPARs might antagonize angiotensin II (Ang II) effects, the action of the PPARα activator DHA was investigated in angiotensin II-infused rats [15]. DHA reduced Ang II-induced oxidative stress (as demonstrated by NADPH oxidase activity measured by chemiluminescence) and expression of inflammatory mediators (the adhesion molecules intercellular adhesion molecule or ICAM-1 and VCAM-1) in blood vessels of Ang II-infused rats. Blood pressure (BP), elevated by Ang II, was reduced by DHA. The remodeling of small resistance arteries induced by Ang II was abrogated by the PPARα activator. Concomitantly, endothelial dysfunction typically found under Ang II infusion was prevented by DHA, together with reduction in NADPH oxidase-dependent superoxide anion formation.

Although these effects cannot be conclusively and unambiguously shown to be unrelated to BP reduction, in some models such as the DOCA-salt hypertensive rat, they have occurred in response to PPARα activators in absence of significant BP lowering [26]. This suggests that they are probably not dependent on reduction of BP.

Recent studies have elucidated some of the mechanisms involved in the beneficial effects of PPARα activation on endothelial function. Goya et al. demonstrated that fenofibrate increases endothelial nitric oxide synthase (eNOS) expression in bovine aortic endothelial cells. Interestingly this does not occur through effects on eNOS gene promoter activity but rather through increases in mRNA stability [25].
Vascular effects of PPAR gamma

Like PPARα, PPARγ has been reported to be present in the vasculature [40] and was demonstrated in endothelial cells [52], VSMCs [20,35] and in monocytes/macrophages [50]. PPARγ activators inhibited proliferation and migration of VSMCs [35,36]. They enhanced the expression of PPARγ in macrophages and inhibited expression of inducible nitric oxide synthase (iNOS), matrix metalloproteinase (MMP)-9 and scavenger receptor A. These effects of PPARγ were mediated in part by inhibition of transcription factors AP-1, STAT and NF-κB. PPARγ activators inhibited expression of tumor necrosis factor (TNF)α, interleukin (IL)-6, IL-1β [31], iNOS, MMP-9 and scavenger receptor A in monocytes [49]. PPARγ activators attenuated TNF-induced VCAM-1 and ICAM-1 expression in endothelial cells, and reduced monocyte/macrophage homing to atherosclerotic plaques in apoE-deficient mice [45]. PPARγ expression has indeed been demonstrated in human atherosclerotic plaques [48]. However, 15-deoxy-Δ^{12,14}-prostaglandin J₂ (15d-PGJ₂) may stimulate the synthesis of IL-8 in endothelial cells in a PPARγ-independent manner [32]. Mechanisms whereby PPARγ activation may induce anti-inflammatory effects include interactions with CCAAT/enhancer-binding protein (C/EBP)-δ present in tandem repeats in the PPARγ gene promoter. C/EBP induces expression of inflammatory cytokines, but is inhibited by PPARγ in the vasculature by transactivation [58].

PPARγ activators (rosiglitazone and pioglitazone) prevented the BP rise, and the structural, functional and molecular changes induced by Ang II in blood vessels, inhibiting cell growth and inflammation [18]. Ang II-induced small resistance artery remodeling and endothelial dysfunction were prevented. Vascular DNA synthesis, expression of cell cycle proteins, Ang AT₁ receptors, VCAM-1, and platelet and endothelial cell adhesion molecule
(PECAM); and NF-κB activity all of which were increased by Ang II infusion, were blunted by pioglitazone or rosiglitazone.

In DOCA-salt hypertensive rats, a hypertensive model associated with enhanced expression of preproendothelin (preproET)-1, BP increase was prevented in part by the PPARγ activator rosiglitazone but not by the PPARα activator fenofibrate [26]. Both PPAR activators however abrogated the increase of preproET-1 mRNA in mesenteric blood vessels of these hypertensive rats, and prevented the hypertrophic remodeling typically found in DOCA-salt rats. Rosiglitazone but not fenofibrate prevented endothelial dysfunction, but both abrogated the enhanced production of reactive oxygen species that occurs in blood vessels in DOCA-salt hypertensive rats.

Spontaneously hypertensive rats (SHR) exhibit insulin resistance that has been associated with a mutation of cd36, which encodes for a fatty acid translocase. Insulin resistance thus results in decreased fatty acid translocation [1]. cd36 is a target of PPARγ. It has been speculated that expression of PPARs could be decreased in blood vessels of SHR, which would exacerbate proliferation, migration, inflammation and fibrosis, as found in this hypertensive model. Indeed, human mutations of PPARγ have been associated with diabetes, insulin resistance and hypertension, all of which are accompanied by vascular disease [4]. However, rather than decreased expression of PPARα and γ in blood vessels and cultured VSMC from SHR, their expression was increased [20]. This may result from a feedback response to the decreased activity of the mutant cd36 of SHR.

Mechanisms whereby PPARγ activation improves endothelial function were investigated by Calnek et al [8]. These authors demonstrated that PPARγ ligands, 15d-PGJ2 or ciglitazone increased NO release by porcine and human aortic endothelial cells. PPARγ
activation did not increase eNOS expression. Overexpression of PPARγ or treatment with 9-cis retinoic acid also enhanced NO release. Neither 15d-PGJ2 nor ciglitazone altered eNOS mRNA. Thus, PPARγ ligands stimulated NO release from endothelial cells through a transcriptional mechanism unrelated to eNOS expression [8].

Many studies have pointed toward an inhibitory role of PPARs in atherogenesis [40]. The effect of rosiglitazone treatment on mechanisms involved in the initial stages of atherogenesis was evaluated in rabbits fed a high cholesterol diet [59]. Treatment with rosiglitazone enhanced the down-regulated PPARγ expression, improved endothelium-dependent vasodilatation, suppressed gp91phox and iNOS expression, reduced superoxide and total NO production, and inhibited nitrotyrosine formation. The endothelial protective effects of PPARγ activators may reduce leukocyte accumulation in the vascular wall, contributing to anti-atherosclerotic effects.

Ishibashi et al. [29] studied effects of pioglitazone in rats receiving \( \text{N}^\omega \)-nitro-L-arginine methyl ester (L-NAME) to inhibit eNOS. The PPARγ activator pioglitazone did not affect blood pressure, the metabolic state or serum NO levels, but prevented L-NAME–induced coronary inflammation and arteriosclerosis. Pioglitazone did not reduce local expression of monocyte chemoattractant protein (MCP)-1 but attenuated the expression of the MCP-1 receptor C-C chemokine receptor 2 (CCR2) in monocytes in the vascular wall and in the circulation. It prevented coronary arteriosclerosis, possibly by down-regulation of CCR2, which could represent a novel anti-inflammatory mechanism of PPARγ activation independent of insulin sensitization.

A mechanism for improved endothelial function recently reported is the ability of PPARγ activators to modulate bone marrow (BM)–derived angiogenic progenitor cells
(APCs) to promote endothelial lineage differentiation and early re-endothelialization after vascular intervention. Rosiglitazone treatment attenuated neointima formation in mice after femoral angioplasty [65]. Rosiglitazone caused a 6-fold increase in colony formation by human endothelial progenitor cells, promoted the differentiation of APCs toward the endothelial lineage in mouse BM in vivo and in human peripheral blood in vitro, and inhibited the differentiation toward the SMC lineage. Within the neointima, rosiglitazone stimulated APCs to differentiate into mature endothelial cells and caused early re-endothelialization compared with controls. Thus PPARγ activators are able to promote differentiation of APCs toward endothelial lineage and attenuate restenosis. Elevated levels of C-reactive protein (CRP) have been recognized as a powerful predictor of cardiovascular disease. Verma et al. [64] have now demonstrated that human recombinant CRP, at pathophysiologically relevant concentrations that predict adverse cardiovascular outcomes, inhibits endothelial progenitor cell (EPC) differentiation, survival, and function. The effects of CRP on EPC cell number, expression of endothelial cell–specific markers Tie-2, EC-lectin, and VE-cadherin, increased EPC apoptosis, and impaired eNOS expression and EPC-induced angiogenesis, were attenuated by treatment with rosiglitazone, which may represent a mechanism that explains in part PPARγ activation-induced cardioprotective effects.

VSMC proliferation is involved in vascular injury, restenosis and atherosclerosis. Antiproliferative effects of the PPARγ agonists troglitazone, rosiglitazone, and pioglitazone were investigated on cells derived from the internal mammary and radial artery and saphenous veins, vessels employed for coronary artery by-pass grafting [11]. The three activators of PPARγ inhibited cell proliferation with troglitazone being the most potent and
rosiglitazone similar to pioglitazone. Potency was therefore dependent on the PPARγ activator independently of the vascular source of the cells.

Markers of systemic inflammation (CRP and IL-6), considered "nontraditional" risk factors for cardiovascular disease, are enhanced in patients with type 2 diabetes mellitus. MMP-9 may participate in atherosclerotic plaque rupture. Subjects treated with rosiglitazone for 26 weeks experienced reductions in CRP, MMP-9, and white blood cell count which was significantly correlated with insulin resistance as estimated by the homeostasis model (HOMA) index, indicating potentially beneficial effects on cardiovascular risk in this patient population [23]. Another emerging “nontraditional” risk factor implicated in atherosclerosis is the proinflammatory cytokine CD40 ligand (CD40L). Diabetic patients were shown to have elevated plasma levels of soluble CD40L (sCD40L) independent of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, blood pressure, body mass index, gender, C-reactive protein, and soluble ICAM-1 [63]. Treatment with troglitazone for 12 weeks lowered sCD40L plasma levels in type 2 diabetic patients, suggesting a novel anti-inflammatory mechanism for limiting diabetes-associated arterial disease. Other investigators have also shown similar results in patients with type 2 diabetes and coronary artery disease (CAD). Thirty-nine patients with diabetes and angiographically proven CAD received rosiglitazone for 12 weeks [41]. Rosiglitazone treatment, but not placebo, significantly reduced sCD40L serum levels. This further underscores the ability of PPARγ-activating thiazolidinediones to reduce sCD40L serum levels and exert anti-inflammatory and anti-atherogenic effects.

Rosiglitazone has also been shown to reduce endothelial markers such as E-selectin and von Willebrand factor in non diabetic CAD subjects [54]. Eighty-four patients with
stable, angiographically documented CAD without diabetes mellitus were given rosiglitazone for 12 weeks. Rosiglitazone treatment significantly reduced E-selectin, von Willebrand factor, CRP, fibrinogen and insulin resistance as measured by HOMA index in comparison to placebo. Thus, PPARγ activation reduced markers of endothelial cell activation and levels of acute-phase reactants in CAD patients without diabetes. In addition to this, other studies have shown that these agents improve endothelial function of patients with the metabolic syndrome. Wang et al. [67] studied 50 nondiabetic patients who met a definition for the metabolic syndrome and received rosiglitazone for 8 weeks. These patients experienced significant reductions in fasting plasma insulin levels, HOMA index, blood pressure and high-sensitivity CRP. Rosiglitazone treatment significantly improved both endothelium-dependent flow-mediated and endothelium-independent nitroglycerin-induced vasodilatation of the brachial artery. Carotid intima-media thickness (IMT) has been considered a surrogate of endothelial function. In 92 non diabetic subjects with angiographically documented CAD studied by Sidhu et al. [55], rosiglitazone administration for 48 weeks resulted in reduced IMT progression compared with the placebo group, associated with reduced insulin resistance (estimated by HOMA index). Thus, PPAR activation improves endothelial dysfunction, thought to be a mechanism for initiation and progression of atherosclerosis, a risk factor and a participant in the triggering of cardiovascular events.

In a study of 136 Japanese type 2 diabetic subjects, pioglitazone was administered for 3 months and changes in glycolipid metabolism, plasma high-sensitivity CRP, leptin, adiponectin, and pulse wave velocity (PWV, a parameter that increases with the stiffness of blood vessels and is indicative of the presence of vascular injury) were evaluated to investigate the relationship between the anti-atherogenic and anti-diabetic effects of
pioglitazone [51]. Pioglitazone treatment improved glucose metabolism, and increased plasma adiponectin concentrations, and decreased CRP and PWV. Treatment with pioglitazone was associated with a low CRP and PWV independently of changes in carbohydrate metabolism. Thus, the PPARγ agonist exerted anti-atherogenic effects independent of its anti-diabetic action by lowering CRP that contributes to vascular injury, and the stiffness of blood vessels, which is a measure of vascular disease and contributes to enhance pulse pressure, another risk factor for vascular events.

**Cardiac effects of PPARs**

PPARα regulates cardiac energy and lipid metabolism and plays a role in mitochondrial fatty acid β-oxidation, which is critical for fuel generation in the heart [7]. It serves as a molecular 'lipostat' through the induction of target genes involved in fatty acid metabolism [22]. PPARα controls myocardial lipid metabolism through activation of transcription of carnitine palmitoyltransferase I (CPT I) [7]. In PPARα-null mice the capacity for constitutive myocardial β-oxidation of medium and long-chain fatty acids was markedly reduced [68]. Constitutive β-oxidation of very long chain fatty acids such as lignoceric acid was unaffected in PPARα-deficient mice. This suggests that PPARα is not involved in the constitutive expression of enzymes that mediate β-oxidation.

During cardiac hypertrophy PPARα is inhibited [3], which reduces the capacity of hypertrophied myocytes to metabolize myocardial lipids, resulting in intracellular fat accumulation. PPARα activators inhibited cardiac expression of TNFα and NF-κB induced by LPS [57]. Fenofibrate reduced preproET-1 mRNA expression and collagen type I and type III mRNA, associated with decreased in interstitial and perivascular cardiac fibrosis after pressure-overload induced by abdominal aortic banding [44], probably through
suppression of AP-1-mediated preproET-1 gene activation. Additionally, fenofibrate reduced cardiac hypertrophy and inflammation, associated with an increase in the anti-inflammatory cytokine IL-10 [39]. Fenofibrate had beneficial effects on inflammation and collagen deposition in the heart of Ang II-infused rats [16]. NF-κB activity, VCAM-1, PECAM, ICAM-1 and ED-1 (macrophage antigen) expression were all decreased, and AT₁ receptors down-regulated and AT₂ receptors upregulated, which may be considered a beneficial change since AT₁ are pro-hypertrophic, proinflammatory and pro-fibrotic, whereas AT₂ are generally shown to exert opposite effects.

The role of PPARγ in the heart is less clear than that of PPARα. Expression of PPARγ in the heart is very low [33]. PPARγ activators inhibited hypertrophy and brain natriuretic peptide expression in cultured cardiomyocytes [70]. Aortic banding induced enhanced cardiac hypertrophy in heterozygous PPARγ-deficient mice [2], suggesting an inhibitory effect of PPARγ on cardiac growth. Pioglitazone, however, blunted myocardial hypertrophy in both wild-type and PPARγ-/- mice, suggesting an effect independent of activation of PPARγ. Angiotensin II-induced gene expression and cardiomyocyte hypertrophy were attenuated in vitro by thiazolidinediones. These data suggest that PPARγ inhibits cardiac hypertrophy. In diabetic rats, PPARγ improved left ventricular diastolic function and decreased collagen accumulation [61,72], and also protected the myocardium from ischemic injury [53,71]. On the other hand, PPARγ activators may trigger an aggravation of congestive heart failure [66,69], which is counterintuitive with respect to the cardiovascular preventive potential of these drugs. This appears to be mainly due to fluid retention as a consequence of their insulinomimetic action on the kidney, rather than a negative inotropic effect. Thus, caution has been urged in the use of thiazolidinediones in
diabetic patients with advanced heart failure [43], even though these agents may have cardiovascular protective properties in patients with less advanced cardiovascular disease.

The hypertrophic heart typically experiences an increase in glucose utilization and decreased fatty acid oxidation. It is unclear whether PPARγ has effects on fatty acid metabolism comparable to those of PPARα. PPARα and PPARγ have partially overlapping ligand binding profiles. Thus, PPARγ may mediate some intracellular signaling in cardiomyocytes similarly to PPARα, which could attenuate cardiac remodeling via signaling pathways not involved in the control of lipid and energy metabolism. Inflammation plays a critical role in the progression of cardiac remodeling and dysfunction. In macrophages, PPARγ participates in the regulation of inflammatory responses by inhibition of transcription factors NF-κB and AP-1 [50]. NF-κB is required for the hypertrophic response of neonatal rat cardiomyocytes in vitro [47]. Recently, the PPARγ activator pioglitazone was shown to have beneficial long-term effects on cardiac hypertrophy and cardiac inflammation without affecting cardiac function in stroke-prone SHR [17]. However, whether PPARγ effects on the heart are exerted directly on cardiomyocytes, or via infiltrating macrophages and other blood-borne cells, or result from hormonal effects mediated from other organs has not yet been demonstrated [33].

Conclusion

PPARα and PPARγ modulate inflammatory, fibrotic and hypertrophic responses in the cardiovascular system. The signaling pathways mediating the anti-inflammatory effect of PPARs, particularly in the heart, remain to be demonstrated. The contrast between the beneficial effect of PPARγ activators on the heart in experimental models and clinical reports of decompensated heart failure in some diabetic patients treated with PPARγ activators
requires clarification. It is possible that salt and water retention induced by the insulin-sensitizing action of PPARγ activators unmasks latent left ventricular dysfunction and precipitates heart failure not directly induced by actions of PPARγ activators on the heart [66]. Selective PPARα or γ activators, partial agonists or dual α/γ activators may become interesting cardiovascular protective therapies in hypertension or other forms of cardiovascular disease in the near future. Currently, numerous clinical trials are evaluating this promising potential of PPAR activators.

Acknowledgements

Work from the author’s laboratory has been supported by grant 13570 and 37917, and a Group grant to the Multidisciplinary Research Group on Hypertension, all from the Canadian Institutes of Health Research..

References


38. **Madej A, Okopien B, Kowalski J, Zielinski M, Wysocki J, Szygula B, Kalina Z and Herman ZS.** Effects of fenofibrate on plasma cytokine concentrations in patients


**Figure legend**

**Figure 1.** Mechanism of action of PPARs. After activation by ligand binding, PPARs heterodimerize with RXR and bind to specific PPAR response elements (PPRE) on the promoter of target genes to regulate glucose and lipid metabolism (right). This aspect of PPAR alpha and gamma action which has cardiovascular protective effects through effects on atherosclerosis and diabetes, is not discussed in the present review. Both PPAR alpha and gamma also interact with different transcription factors to repress pro-inflammatory genes (left), which is the subject of the present review. VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; PECAM, platelet and endothelial cell adhesion molecule; NF-kappaB, nuclear factor kappaB; AP, activator protein; CCAAT/EBP, CCAAT/enhancer binding protein; CRP, C-reactive protein; TNF, tumor necrosis factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; CD40L, CD 40 ligand; MMP, matrix metalloproteinase; iNOS, inducible nitric oxide synthase; VSMCs, vascular smooth muscle cells; FA, fatty acid; VLDL, very low density lipoprotein; HDL, high density lipoprotein.
Transrepression (anti-inflammatory)

- VCAM, ICAM, PECAM
- NF-κB, AP-1
- CCAAT/EBP
- CRP, TNF-α, IFN-γ
- IL-1β, IL-6, MCP-1, CD40L
- MMP-9
- iNOS
- Growth and migration of VSMCs

Liver (PPAR-α)
- FA oxidation
- VLDL
- Lipolysis
- HDL & reverse cholesterol transport

Adipocytes & muscle (PPAR-γ)
- Insulin sensitivity

PPAR → RXR → PPRE (carbohydrate and lipid metabolism)