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Comprehensive Invited Review

PPARs and the Cardiovascular System

Milton Hamblin, Lin Chang, Yanbo Fan, Jifeng Zhang, and Y. Eugene Chen

Reviewing Editors: John Bright, Adnan Erol, M. Faadiel Essop, Shou Wei Han, and Do-Young Yoon

Cardiovascular Center, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan.

Abstract

Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone-receptor superfamily. Originally cloned in 1990, PPARs were found to be mediators of pharmacologic agents that induce hepatocyte peroxisome proliferation. PPARs also are expressed in cells of the cardiovascular system. PPARγ appears to be highly expressed during atherosclerotic lesion formation, suggesting that increased PPARγ expression may be a vascular compensatory response. Also, ligand-activated PPARγ decreases the inflammatory response in cardiovascular cells, particularly in endothelial cells. PPARα, similar to PPARγ, also has pleiotropic effects in the cardiovascular system, including antiinflammatory and antiatherosclerotic properties. PPARα activation inhibits vascular smooth muscle proinflammatory responses, attenuating the development of atherosclerosis. However, PPARδ overexpression may lead to elevated macrophage inflammation and atherosclerosis. Conversely, PPARδ ligands are shown to attenuate the pathogenesis of atherosclerosis by improving endothelial cell proliferation and survival while decreasing endothelial cell inflammation and vascular smooth muscle cell proliferation. Furthermore, the administration of PPAR ligands in the form of TZDs and fibrates has been disappointing in terms of markedly reducing cardiovascular events in the clinical setting. Therefore, a better understanding of PPAR-dependent and -independent signaling will provide the foundation for future research on the role of PPARs in human cardiovascular biology. *Antioxid. Redox Signal.* 11, 1415–1452.

I. Introduction

Peroxisomes are organelles that participate in fatty acid metabolism. Clofibrate analogues, hypolipidemic agents that control plasma cholesterol and triglyceride levels, can induce proliferation of liver cell peroxisomes (300, 301). In addition, two lipid-lowering compounds structurally different from clofibrate, [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (Wy-14,643) and 2-chloro-5-(3, 5-dimethylpiperidino-sulfonyl)benzoic acid (tibric acid), also were found to stimulate hepatocyte peroxisome proliferation (302). Although hypolipidemic drugs were demonstrated to activate peroxisome proliferation, these studies did not establish a mechanism. Subsequent studies identified a protein whereby peroxisome proliferators bind with affinity (196, 197), and this protein was later identified as a member of the nuclear hormone-receptor superfamily that includes steroid, retinoid, and thyroid hormone receptors (104). The name peroxisome proliferator-activated receptor took origin from the cloning by Issemann *et al.* (172) to identify possible endogenous mediators of peroxisome proliferation–induced gene transcription in rodent livers. The peroxisome proliferator–activated receptors (PPARs) consist of three related transcription factors: PPARalpha (PPARα), PPARbeta/delta (PPARβ/δ), and PPARgamma (PPARγ), encoded by the genes *PPARA*, *PPARD*, and *PPARG*, respectively (96). In addition to the role in peroxisome proliferation, these nuclear transcription factors are involved in numerous cellular functions, including insulin sensitivity, glucose homeostasis, fatty acid oxidation, cytokine production, and vasculoprotection.

II. PPAR and the Mechanism of Action

PPARs were initially shown to recognize and bind a DNA sequence upstream of the PPAR target gene. This sequence was termed the peroxisome proliferator response element (PPRE) (251, 362) (Fig. 1). Acyl-CoA oxidase is a peroxisomal enzyme involved in fatty acid oxidation. The promoter of this enzyme was found to contain a DNA sequence that was responsive to stimulation by Wy-14,643, and this stimulatory response was mediated by PPAR. Of great importance, PPAR was shown to bind to this 5′ flanking portion, or peroxisome proliferator response element of the acyl-CoA oxidase gene (362). PPARs, on activation, heterodimerize with the retinoic X receptor (RXR)-α (22, 121, 182, 190), and this is followed by coactivator recruitment, which eventually leads to transcriptional regulation of gene expression (85, 312) (Fig. 1). Besides being involved in transactivation, PPARs also participate in the negative regulation of certain genes by recruiting co-repressors (233) (Fig. 1). In addition, other molecular mechanisms are found by which PPARs can inhibit gene expression. First, transrepression can be caused by physical interaction with other transcription factors, including nuclear factor-kappa B (NF-κB), Smad-3, activator protein-1 (AP-1), and signal transducers and activators of transcription (STAT) proteins (80, 114, 217, 307). Second, PPARs can modulate transrepression through the mitogen-activated protein kinase (MAPK) pathway (157). Coactivators and co-repressors, in addition to regulating transcriptional activation, are critical for the repression of certain genes (85, 305, 312). Third, PPARs recruit coactivator proteins and often compete with NF-κB and AP-1 for binding to these co-regulators (305). Thus, NF-κB and AP-1 target gene expression is attenuated because of competition with PPARs for coactivator binding.

Finally, PPARs can contribute to transrepression by either inhibiting clearance of co-repressor complexes (123, 287) or releasing co-repressors, which could allow co-repressor binding to NF-κB, eventually inhibiting NF-κB target gene expression (305).

The phosphorylation of PPARs is critical to regulating many of the biologic functions of these nuclear receptors. Initially, insulin-induced phosphorylation of PPARα was shown to increase transcriptional activity (322). Also, stress-activated p38 MAPK has been shown to phosphorylate PPARα and enhance target gene expression in myocardiocytes (24). Several studies demonstrate that MAPK phosphorylation deactivates PPARγ and reduces basal and ligand-dependent transcriptional activity (5, 51, 52, 157). However, one study shows that PPARγ is activated by ERK5 in endothelial cells (ECs), and this particular MAPK does not phosphorylate

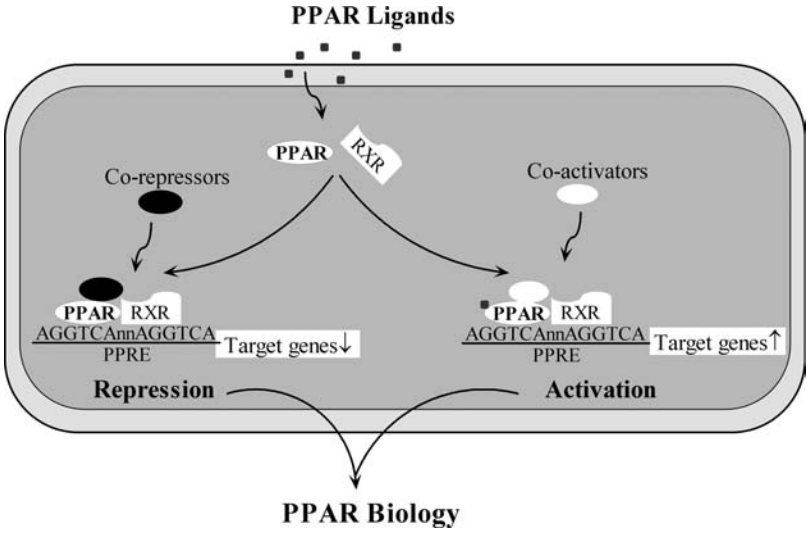

FIG. 1. Schematic view of PPAR action. After a ligand binds to PPAR, PPAR heterodimerizes with the retinoid X receptor (RXR) and then binds to the PPRE. Recruiting coactivators and co-repressors leads to activation and repression of PPAR target genes, respectively.

PPARγ (7). A recent report demonstrates that PPARγ is under the control of Bcr, a serine/threonine kinase that phosphorylates PPARγ and prevents transcriptional activity (9). PPARδ is also considered to be a phosphoprotein because protein kinase A (PKA)-induced phosphorylation of PPARδ, similar to PPARα and PPARγ, has a stimulatory effect on transcription (200). These are just a few of many examples that demonstrate how PPAR signaling may be affected because of phosphorylation by protein kinases.

PPARγ is most abundantly expressed in adipose tissue, with less expression in the colon and immune system. PPARγ has been shown to facilitate differentiation of fibroblasts into adipocytes (59). PPARγ is also involved in the regulation of lipid metabolism, as ligand-dependent activation leads to an increase in genes that regulate fatty acid uptake and storage (320). Furthermore, PPARγ plays a role in glucose homeostasis and insulin sensitivity (110). Although PPARγ was initially found to be critical for adipocyte differentiation and function, over time, PPARγ was discovered to play an important role in the cardiovascular system. As well as in adipocytes and T cells, PPARγ is also expressed in endothelial cells, vascular smooth muscle cells (VSMCs), and macrophages.

III. PPARγ Ligands

PPARs possess varying degrees of responsiveness to certain peroxisome proliferating agents (188). Although several compounds were demonstrated to activate PPARs, initially no reports confirmed direct binding to this receptor. However, in 1995, evidence was provided that thiazolidinediones (TZDs), a class of antidiabetic drugs that improve insulin sensitivity, bind to and activate PPARγ with high affinity (209) (Fig. 2). Furthermore, PPARγ was shown to be the major target of these insulin-sensitizing agents (110).

Troglitazone (Rezulin), the first FDA-approved TZD used in the clinical setting, was discontinued from the market in 2000 because of reports of liver toxicity (125, 206, 259). Rosiglitazone (Avandia) and pioglitazone (Actos), subsequent TZD agents currently approved for clinical use, are not associated with severe hepatotoxicity (357), although weight gain and edema have been reported as side effects (263). Also, rosiglitazone has been reported to be associated with increased risks of myocardial infarction and mortality due to cardiovascular complications (265); however, the results are controversial (155, 369). Clinical data from the PROactive study found that pioglitazone reduces the risk of secondary end points, including all-cause mortality, nonfatal myocardial infarction, and stroke in diabetic patients but nonsignificantly decreases the composite primary end-point risk (95). However, a recent meta-analysis that included 19 clinical trials found that pioglitazone reduces primary end-point components, including risk of death, myocardial infarction, and stroke (225).

GW1929 and GW7845 are examples of non-TZD high-affinity ligands for PPARγ (39, 344) (Fig. 2). In addition, PPARα/γ dual and PPAR$\alpha/\gamma/\delta$ pan agonists have been developed to promote synergistic antidiabetic and cardiovascular protective effects. Muraglitazar, naveglitazar, tesaglitazar, and netoglitazone are several examples of PPARα/γ dual agonists (296) (Fig. 2). GW409544 has been shown to be a potent activator of both PPARα and PPARγ (390) (Fig. 2). Bezafibrate, a lipid-lowering drug that reduces the risk of myocardial infarction in patients with metabolic syndrome, is a PPAR$\alpha/\gamma/\delta$ pan agonist (353) (Fig. 2).

Several natural PPARγ ligands have been identified and can be classified into two major groups of compounds, fatty acids and phospholipids. PPARγ ligands consist of polyunsaturated fatty acids, including linoleic acids (36), linolenic acid (175), arachidonic acid (192), and eicosapentaenoic acid (159) (Fig. 2). Monounsaturated fatty acid compounds that bind PPARγ include oleic acid (317) (Fig. 2). Oxidatively modified lipids also bind PPARγ (Fig. 2). 15-Deoxy-δ 12,14-prostaglandin J_2 (15d-PGJ_2) and other J2 series prostaglandins were identified as natural ligands for PPARγ (110, 189) (Fig. 2). TZDs were demonstrated to be synthetic analogues of 15d-PGJ_2 (110). Other natural PPARγ ligands include 12- and 15-hydroxyeicosatetraenoic acid (HETE) (159) and 9- and 13-hydroxyoctadecadienoic acid (HODE) (254) (Fig. 2), oxidized metabolites of arachidonic and linoleic acids, respectively. 1-*O*-hexadecyl-2-azelaoyl-*sn*-glycero-3-phosphocholine (azPC), an oxidized phospholipid, is also a PPARγ ligand (78) (Fig. 2). In addition, lysophosphatidic acid (LPA) and its naturally

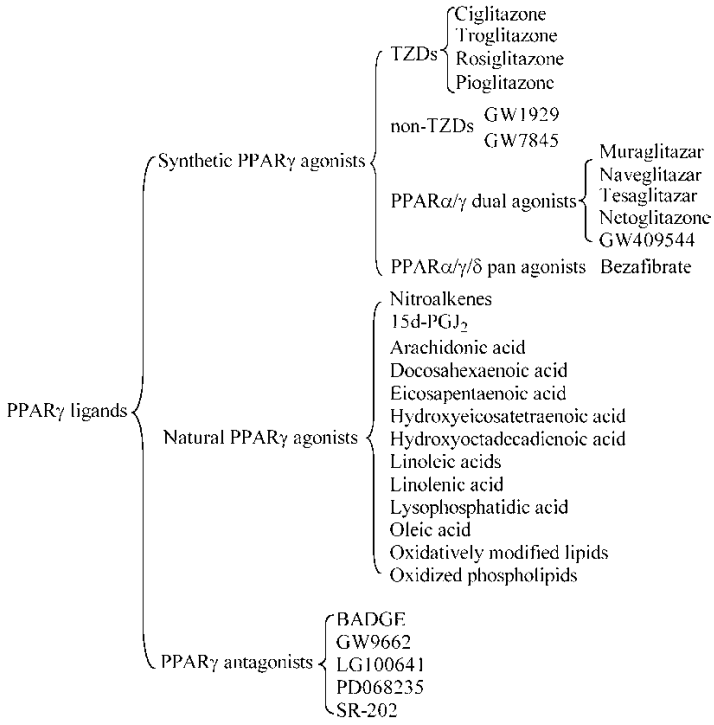

FIG. 2. PPARγ ligands. Natural and synthetic agonists bind and activate PPARγ. Natural PPARγ agonists include 15d-PGJ_2, fatty acids, oxidatively modified lipids, hydroxyeicosatetraenoic acid, hydroxyoctadecadienoic acid, oxidized phospholipids, lysophosphatidic acid, and nitroalkenes. Synthetic PPARγ agonists include TZDs, GW1929, GW7845, PPARα/γ dual agonists, and PPARα/γ/δ pan agonists. Examples of PPARγ antagonists include BADGE, GW9662, LG100641, PD068235, and SR-202.

occurring analogue, 1-*O*-octadecenyl-2-hydroxy-*sn*-glycero-3-phosphate (AGP) also have affinity for PPARγ (361, 406) (Fig. 2).

Finally, our research group identified nitroalkenes 9-, 10-, 12-, and 13-nitro-9,12-*cis*-octadecadienoic acid (LNO_2) (319) and 9- and 10-nitro-9-*cis*-octadecenoic acid (OA-NO_2) (19) as natural PPARγ ligands (Fig. 2). We recently reported the crystal structure of the PPARγ ligand-binding domain bound to LNO_2 and found that LNO_2 promotes PPARγ interaction with coactivator motifs of transcriptional coactivators (218). The two charged residues R288 and E343 of PPARγ that make specific contacts with the NO_2 are not conserved in PPARα and PPARδ (218), explaining why LNO_2 preferentially activates PPARγ rather than the other two PPAR subtypes (319). LNO_2 isomers bind to the two electrostatic regions of the ligand-binding pocket, and these electrostatic clusters allow binding of different ligands at the same time (218, 258). Our studies provide further evidence regarding the interaction between PPARγ and LNO_2 and serve as a basis for the development of novel PPARγ ligands that could not only mimic the interactions of LNO_2 on PPARγ but also extend beyond the current TZD-induced PPARγ-mediated effects in the cardiovascular system.

PPARγ ligands can also participate in signaling independent of PPARγ. Several studies have shown that PPARγ ligands can directly interact and inhibit transcription factors in a PPARγ-independent manner. First, although we have shown that nitroalkenes are PPARγ ligands, nitroalkene-induced inhibition of macrophage proinflammatory cytokine secretion is regulated through nitroalkylation of the p65 subunit, repressing NF-κB transcriptional activity (76) (Fig. 3).

Second, 15d-PGJ_2 inhibits NF-κB transcriptional activity by inhibiting IκB kinase (IKK) (54, 314, 342) and the DNA binding domains of NF-κB (342). In all likelihood, the effects of 15d-PGJ_2 on IKK activity result in the inhibition of IKK-induced Ser32 and Ser36 phosphorylation of IkappaB-α (IκBα) (54) (Fig. 3). Compound G, a non-TZD agonist, also inhibits NF-κB activation by decreasing IKK activity (55). Furthermore, the administration of TZD at higher concentrations attenuates NF-κB target-gene expression in macrophages lacking PPARγ (56, 249).

Pioglitazone can bind to mitoNEET, an integral protein located in the outer mitochondrial membrane that regulates oxidative capacity (71) (Fig. 3). MitoNEET received its name because of the Asn-Glu-Glu-Thr (NEET) sequence located in the carboxyl-terminal domain. Isolated mitochondria from the hearts of mitoNEET-null mice display an overall worsening of complex 1–dependent oxygen consumption (384). Because mitoNEET is an iron-sulfur cluster containing protein, and pioglitazone has been shown to increase mitoNEET 2Fe-2S stability (279), it is possible that pioglitazone could regulate the redox potential or function of the mitoNEET iron-binding CDGSH domain [C-X-C-X(2)-(S/T)-X(3)-P-X-C-D-G-(S/A/T)-H] (385).

PPARγ antagonists are also ligands that can be used as important tools in determining PPARγ signaling and function in basic science. The safety concerns and adverse side effects of TZDs have spurred an increased effort to study possible therapeutic benefits of administering PPARγ antagonists in the clinical setting. Bisphenol A diglycidyl ether (BADGE) is often considered to be the first PPARγ ligand known to inhibit transcriptional activity (386). A potent PPARγ antagonist is GW9662, a compound that covalently modifies the Cys286 residue of the ligand-binding domain (207). Other examples of PPARγ antagonists include LG100641 (252), PD068235 (50), and SR-202 (308).

The use of different methods for studying and screening novel PPAR modulators is an important concept of drug

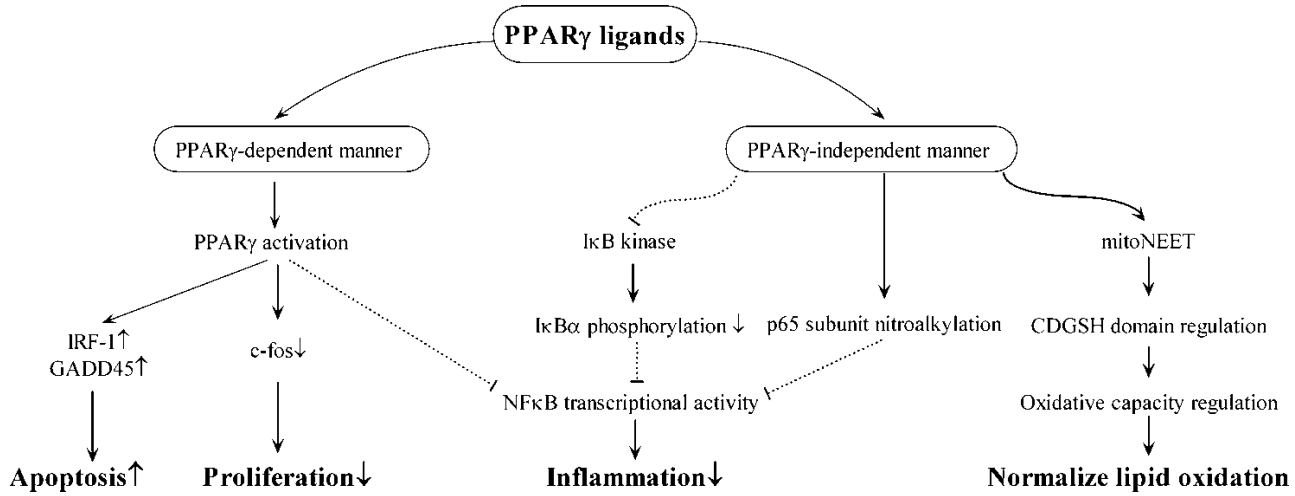

FIG. 3. Schematic view of PPARγ-dependent and -independent signaling pathways. PPARγ ligands can exert their effects in cardiovascular cells through PPARγ-dependent and -independent mechanisms. PPARγ-mediated increases in IRF-1 and GADD45 result in greater VSMC apoptosis. PPARγ-dependent decreases in c-fos expression attenuate VSMC proliferation. Ligand-activated PPARγ inhibits NF-κB transcriptional activity and inflammation in cardiovascular cells. PPARγ ligand–independent signaling can decrease IκB kinase activity, leading to decreased IκBα phosphorylation, NF-κB transcriptional activity, and inflammation. Another example of PPARγ ligand signaling that occurs independent of PPARγ involves nitroalkylation of the p65 subunit and eventual reduction in NF-κB activity and inflammation. Pioglitazone can regulate mitochondrial oxidative capacity and normalize lipid oxidation through direct binding to the mitoNEET protein, independent of PPARγ.

discovery. Several examples are known by which cell-free assays can be used for PPAR-modulator screening. A cell-free competition radioreceptor assay uses recombinant PPAR along with a radioisotope-labeled ligand and competitor ligands (110, 400). The premise of coactivator-dependent receptor ligand assays (CARLAs) includes coactivator recruitment and the use of a pull-down approach to determine the amount of ligand-bound PPAR-coactivator complex. The practice of radioactive labeling is not a requirement in CARLAs, allowing a large, quantitative screening of PPAR compounds (68, 192). The scintillation proximity assays (SPAs) measure receptor–ligand interaction. *Beta emission* from the radioactively labeled ligand is measured, and this is advantageous because of high sensitivity, high reliability, and the lack of a required separation step (100, 262).

The use of radioisotope-free assays is an alternative approach to previous cell-free methods. Surface plasmon resonance (SPR) techniques can be beneficial for detecting ligand–nuclear receptor interactions (401) and ligand-binding effects on nuclear-receptor dimerization (402), as well as screening for ligands from ligand-bound nuclear receptor–coactivator interactions (116). Fluorescence resonance energy transfer (FRET) is a radioisotope-free assay that is used to detect and quantitate PPAR ligand binding. A ligand-induced PPAR conformational change results in coactivator recruitment, allowing the fluorescence donor indirectly linked to PPAR and the fluorescence acceptor indirectly linked to the coactivator to draw into close proximity as the excited fluorescence donor transfers energy to the acceptor (68, 411). A simple ELISA has been developed in which unliganded PPAR weakly binds to the coactivator LXXLL motifs, while ligand-bound PPAR strongly binds to these LXXLL peptides. This radioisotope-free assay uses a specific anti-PPAR antibody to detect PPAR binding (69).

IV. PPARγ and Endothelial Cells

The first evidence of PPARγ expression in endothelial cells (34, 179, 235, 387) came from several studies examining the interaction of PPARγ and plasminogen activator inhibitor type-1 (PAI-1). The expression of PAI-1 in both endothelial cells and adipoctyes is involved in limiting fibrinolysis in humans. Elevated PAI-1 has been associated with myocardial ischemia and thrombosis in mice (228). PPARγ agonists are generally found to increase PAI-I expression in endothelial cells (235, 387), although one study suggests the opposite (179). A later study provided evidence that PPARγ1 and not PPARγ2 mRNA is present in human umbilical vein endothelial cells (HUVECs) (198).

A. PPARγ and the regulation of EC inflammatory response

Adhesion molecules can bind to inflammatory cells involved in signaling and regulation on the surface of endothelial cells. These adhesion molecules include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), platelet–endothelial cell adhesion molecule (PECAM-1), E-selectin, and integrins. Along with monocyte chemoattractant protein-1 (MCP-1) and other chemoattractant molecules, adhesion molecules are responsible for attachment of immune cells to the endothelial layer, followed by eventual immune cell migration across the endothelium (313).

Much evidence demonstrates PPARγ inhibitory and anti-inflammatory effects in endothelial cells. Several studies have reported that activation of PPARγ inhibits expression of cellular adhesion molecules, including VCAM-1, ICAM-1, PECAM, and E-selectin, in addition to inflammatory cell migration and adhesion to atherosclerotic plaques (87, 173, 241,

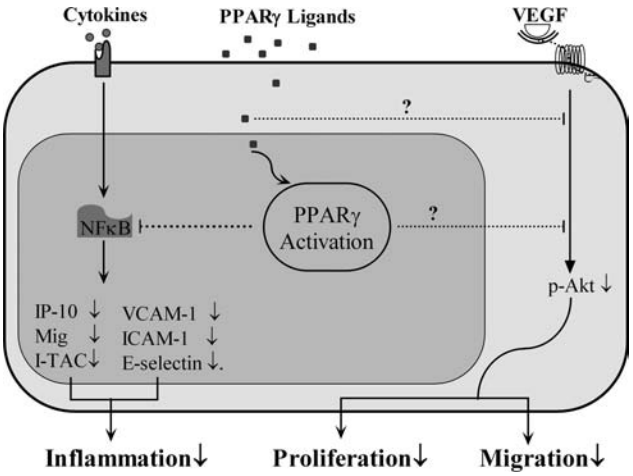

FIG. 4. Schematic view of PPARγ activation in ECs. Natural or synthetic PPARγ ligands attenuate VEGF-induced Akt phosphorylation, inhibiting EC proliferation and migration. Ligand-activated PPARγ exerts its antiinflammatory effects by inhibiting cytokine-induced NF-κB activation in ECs.

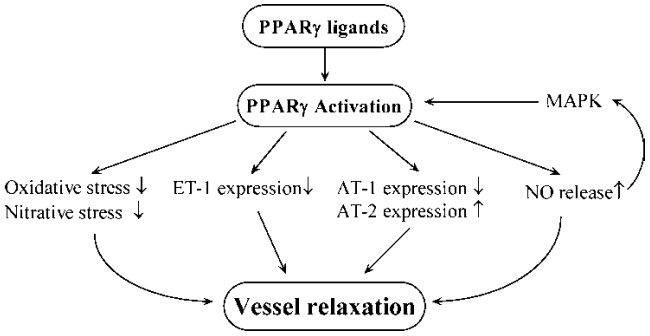

FIG. 5. Schematic view of PPARγ activation in vascular tone regulation. PPARγ ligands decrease ET-1 and AT-1R expression and increase AT-2R expression. PPARγ ligands stimulate NO release, and NO can activate endothelial cell PPARγ through MAPK. TZDs can also decrease oxidative and nitrative stress.

257, 286, 378) (Fig. 4). NF-κB plays an important role in regulating leukocyte adhesion molecule expression. Cytokines activate NF-κB in endothelial cells, thereby allowing NF-κB binding to promoters of adhesion molecule genes. Through NF-κB binding, cytokine-induced gene expression of ICAM-1, VCAM-1, and E-selectin occur in the endothelium (73). Constitutively active PPARγ inhibits NF-κB– and AP-1–regulated gene expression and binding activity in ECs, and PPARγ activation inhibits adhesion molecule expression by inhibiting NF-κB and AP-1 signaling, considered the most important transcription factors in endothelial cell signaling (378). Another mechanism that may suppress endothelial cell inflammatory signaling is the inhibition of the diacylglycerol-protein kinase C (PKC) pathway (368). A study examined the effects of PPAR-γ ligands on chemokine expression that is induced by interferon-gamma (IFN-γ) in cultured human endothelial cells. PPARγ activators decrease IFN-inducible protein of 10 kDa (IP-10), monokine induced by IFN-γ (Mig), and IFN-inducible T-cell α-chemoattractant (I-TAC) expression through the likely inhibition of NF-κB (237) (Fig. 4). However, expression of MCP-1 is not changed in this study (237), in contrast to a previous report showing that TZDs inhibit tumor necrosis factor-alpha (TNF-α)- and interleuken-1beta (IL-1β)-induced MCP-1 mRNA expression and secretion (253).

In cultured endothelial cells, TZDs may reduce superoxide production and inflammation (162, 244) by suppressing expression of NAD(P)H oxidase subunits that are critical for superoxide generation (162). Furthermore, a recent study found that mice expressing a dominant negative PPARγ mutation show elevated oxidative stress and impaired endothelial function in cerebral arteries (32). Next, in cultured endothelial cells, TZDs, along with 15d-PGJ_2, attenuate IFNγ-induced major histocompatibility complex class II (MHC-II), a protein involved in regulating immune responses and T-cell activation (194). Finally, in HUVECs, TZDs promote expression of heme-oxygenase 1 (HO-1), a PPARγ target gene with antiinflammatory properties (193).

B. PPARγ and the regulation of vascular tone

Endothelin-1 (ET-1) is a vasoconstrictive protein that can also regulate VSMC proliferation. PPARγ ligands attenuate both ET-1 expression and secretion in endothelial cells by blocking AP-1 signaling (83, 118, 163, 234, 318) (Fig. 5). Angiotensin II (AngII) is also a potent vasoconstrictor that increases angiotensin II type 1 (AT1) receptor expression, leading to narrowing of blood vessels and elevations in oxidative stress. In Sprague–Dawley rats, rosiglitazone and pioglitazone blunt AngII-induced increases in blood pressure by downregulating AT1 receptors and increasing angiotensin II type 2 receptor (AT2) expression (87) (Fig. 5). Both TZDs improve AngII-induced endothelial dysfunction (87). Subsequently, another study reported that in male apoE-knockout ($apoE^{-/-}$) mice, endothelial dysfunction occurs after AngII treatment in association with decreased PPARγ gene and protein expression (355). Because human PPARγ dominant negative mutations are associated with hypertension (27), TZD-induced PPARγ activation may be one method of treatment for the effects of elevated blood pressure.

Conversely, endothelial cell–derived nitric oxide (NO) is a molecule that is a key participant in vasodilatory activity (280). In 1998, it was found that troglitazone causes vasodilation in humans (117). Subsequent studies showed that PPARγ ligands increase NO production and release (49, 67, 294) (Fig. 5), although it appears that PPARγ ligands may stimulate production of endothelial cell NO through different pathways (294). Ligand-activated PPARγ was found to be critical to heat-shock protein 90/endothelial nitric oxide synthase (eNOS) interaction and eNOS phosphorylation in HUVECs (294). Furthermore, NO was recently reported to activate PPARγ in endothelial cells through a p38 MAPK signaling pathway (297) (Fig. 5). TZDs possess vasculoprotective effects through the attenuation of oxidative and nitrative stresses (Fig. 5), and elevated NO levels. One study in male hypercholesterolemic rabbits suggests that rosiglitazone protects the endothelium by inhibiting superoxide, peroxynitrite, and excess NO production (351). Similar to adipocytes and VSMCs (94, 165), TZD-induced reduction in

elevated NO levels may be the result of inducible nitric oxide synthase (iNOS) inhibition in endothelial cells (351).

C. PPARγ and VEGF

PPARγ activators have been shown to modulate *in vivo* vascular endothelial growth factor (VEGF)-induced angiogenesis and also *in vitro* differentiation of endothelial cells into tubelike structures. In addition, VEGF is known to play a role in endothelial cell proliferation, migration, vascular permeability, and atherosclerosis. Several studies demonstrated that PPARγ agonist inhibition of VEGF-induced angiogenesis may be PPARγ dependent (Fig. 4), part of which includes the inhibition of VEGF receptors and urokinase plasminogen activator expression along with increased PAI-1 expression, NO, and apoptosis (185, 387). Rosiglitazone has been shown to decrease VEGF secretion and indirectly to inhibit angiogenesis in tumor endothelial cells (282). However, a recent study found that administration of GW1929, through PPARγ-mediated signaling, increases *in vitro* endothelial cell tube formation and *in vivo* neovascularization that is associated with elevated VEGF (33).

D. PPARγ and EC migration

PPARγ ligands are also involved in antimigratory actions of endothelial cells. VEGF-induced migration of HUVECs is inhibited by troglitazone and ciglitazone, providing evidence of PPARγ ligand antimigratory effects on endothelial cells. Moreover, the effects of PPARγ ligands on EC migration include inhibition of Akt phosphorylation (129) (Fig. 4). Leptin, through endothelial *ob* receptor activation, has been shown to promote endothelial cell proliferation, survival, and vascular angiogenesis (38, 331). In addition, leptin can regulate endothelial cell Akt phosphorylation (366) and migration (128). The administration of PPARγ ligands inhibits leptin-stimulated Akt phosphorylation and EC migration (128). The tumor-suppressor phosphatase and tensin homologue (PTEN), a modulator of the PI3K/Akt signaling pathway, has been reported to attenuate VEGF-induced EC migration through the inhibition of Akt phosphorylation (158), and PTEN levels were found to be elevated after administration of PPARγ ligands, suggesting the possibility that PTEN plays a role in the inhibitory actions of TZDs on VEGF- and leptin-induced Akt phosphorylation and endothelial cell migration (128) (Fig. 4). Another study, by using scrape-wound and chemotactic assays, found that troglitazone inhibits endothelial cell migration in high-glucose media (146). Troglitazone was shown to accelerate endothelial cell coverage and repair after rat aortic balloon injury. However, the *in vivo* data suggest that endothelial repair may have occurred as a result of troglitazone-induced suppression of endothelial cell apoptosis rather than a reduction in endothelial cell migration (146). A PPARγ-mediated mechanism for TZD-induced migratory activity is not suggested in this study. Moreover, further evidence suggests that the effects of TZD treatment pertaining to endothelial cell migration might occur through PPARγ-independent signaling (204).

E. PPARγ and EC apoptosis

Previous studies suggest that 15d-PGJ_2 and ciglitazone may induce endothelial cell apoptosis through a PPARγ-mediated signaling pathway (34, 213). Our laboratory found that administering a PPARγ antagonist did not block 15d-PGJ_2–induced inhibition of platelet-derived growth factor (PDGF), providing evidence that 15d-PGJ_2 apoptotic and antiproliferative effects may be PPARγ independent in endothelial cells (409). However, PPARγ1 was reported to induce apoptotic genes in HUVECs (169), and a study with PPARγ gain- and loss-of-function techniques found PPARγ to be critical to endothelial cell apoptosis (10). Rosiglitazone was shown to inhibit angiogenesis through a PPARγ-dependent proapoptotic pathway in HUVECs (185). The induction of apoptosis is possibly beneficial, because activated cells may produce cytokines. In cases of severe pulmonary hypertension, lung arterioles consist of phenotypically altered endothelial cells that reduce blood flow and elevate blood pressure. PPARγ-mediated EC apoptosis could be beneficial in alleviating lumen-obliterating endothelial cell growth (10).

F. PPARγ and endothelial progenitor cells

Endothelial progenitor cells (EPCs) are circulating vascular progenitor cells that have been shown to stimulate reendothelialization and decrease neointima formation (376). *In vitro* and *in vivo* studies demonstrated that rosiglitazone stimulates angiogenic progenitor cell (APC) differentiation to endothelial cells to promote reendothelialization and vascular protection against injury (377). Rosiglitazone was shown to improve impaired EPC function in diabetic individuals (292). In EPCs isolated from male subjects, rosiglitazone and 15d-PGJ_2 prevented C-reactive protein–induced EPC dysfunction and promoted angiogenesis (367). Rosiglitazone returns migratory activity to baseline in cultured EPCs from diabetic individuals, which may improve impaired EPC function associated with diabetes (291). Pioglitazone has been shown to increase migratory activity of cultured EPCs from patients with coronary artery disease through PPARγ-dependent signaling (383), as well as to enhance circulating and bone marrow EPC migratory activity (122). Rosiglitazone may also reduce NAD(P)H oxidase and the resultant increase in oxidative stress while enhancing EPC reendothelialization, promoting vessel repair, and improving vascular function (338). Rosiglitazone and pioglitazone, in addition to improving EPC-induced angiogenesis, can attenuate EPC apoptosis (122, 367). A reduction in EPC apoptosis may be of great benefit to individuals with vascular disease (122). PPARγ inhibition of EPC apoptosis may have significant clinical relevance because previous studies showed that different types of EPCs have different morphology, proliferation rates, survival rates, and gene-expression profiles that contribute to different functions in neovasculogenesis (160, 398). Finally, it has been suggested that many of the beneficial cardiovascular effects from TZD treatment in patients may be due to the positive effects on EPCs (367). The proapoptotic data in ECs and antiapoptotic data in EPCs may be due to different PPARγ functions in these cells. The role of PPARγ-independent effects on apoptosis in these cells is a possibility and also should be considered.

V. PPARγ and Vascular Smooth Muscle Cells

In 1998, three investigative groups reported evidence of PPARγ expression in rat aortic and human VSMCs (164, 239, 340). Similarly, a later study observed that PPARγ expression is present in early human vascular lesions and is upregulated

in rat aortic smooth muscle cells after balloon injury (198). Another study reported that both human coronary artery and aortic VSMCs express PPARγ1 and PPARγ2 isoforms (29). PPARγ mRNA levels were reported to increase in mesenteric arteries of both young and adult spontaneously hypertensive rats (SHRs), suggesting that PPARγ expression is differentially regulated in SHRs (88). Similar data regarding mRNA expression in SHRs were reported from our laboratory. However, we found PPARγ protein expression and function from SHR vascular smooth muscle cells to be lower compared with those in Wistar–Kyoto rats. It is likely that the suppressed PPARγ function is a result of decreased protein expression, which could explain the increased VSMC proliferative activity in SHRs (388).

A. PPARγ and VSMC proliferation

TZDs were reported to attenuate VSMC proliferation and regulate vascular tone well before being identified as PPARγ ligands (98, 337, 407). Troglitazone was initially found to suppress basic fibroblast growth factor (bFGF)-induced vascular smooth muscle cell growth, preventing rat aortic neointima formation after endothelial injury (199) (Fig. 6). Further studies also confirmed the antiproliferative activity of troglitazone on human VSMCs (29, 250). However, these initial studies did not examine whether the vasculoprotective effects of troglitazone were PPARγ mediated. A later study with a balloon-injury model confirmed that the inhibitory effect of troglitazone on VSMC proliferation occurs through a PPARγ-mediated pathway (198). TZDs (troglitazone, rosiglitazone, and pioglitazone) inhibit VSMC proliferation in several human vascular cell beds. The particular TZD administered rather than the vascular source is critical for the potential suppression of VSMC proliferation (79).

C-fos is involved in the MAPK pathway, which plays a role in cell proliferation. Troglitazone attenuates bFGF-induced c-fos expression in cultured VSMCs by inhibiting the MAPK signaling pathway (199) (Fig. 6). A later study also found troglitazone to inhibit PDGF-induced c-fos mRNA expression (29) (Fig. 6). Finally, a recent report demonstrated that rosiglitazone and PPARγ overexpression suppress bFGF-induced c-fos mRNA expression (Fig. 6). Moreover, PPARγ dominant negative gene transfer attenuates rosiglitazone-induced inhibition of c-fos mRNA expression (223).

Connective tissue growth factor (CTGF) has the ability to regulate many transforming growth factor-beta (TGF-β) responses in VSMCs, including proliferation, migration, and fibrosis. Data from our laboratory demonstrated that PPARγ interrupts the Smad3 signaling pathway, inhibiting TGF-β–stimulated CTGF expression in human aortic smooth muscle cells (HASMCs) (114) and suggesting crosstalk between PPARγ and TGF-β pathways (Fig. 6). We found that TGF-β induces early PPARγ stimulation and late PPARγ inhibition of gene expression and that growth factor– and cytokine-induced PPARγ expression is inhibited by TGF-β. Early activation of TGF-β–induced PPARγ is mediated by early growth response-1 (Egr-1) signaling, whereas inhibition of PPARγ by TGF-β is mediated by Smad3, AP-1, and Nab2 (112) (Fig. 6).

Studies from our laboratory also provided the first evidence that the PI3-kinase/Akt-dependent pathway is a regulator of PPARγ1 gene expression in VSMCs. We reported that PPARγ1 is upregulated by PDGF *via* PI3-kinase/Akt signaling (115) (Fig. 6). Dominant negative overexpression of the p85 subunit from PI3-kinase or Akt proteins also suppresses PDGF-induced PPARγ expression (115). We also found Egr-1 to be the transcriptional regulator of both growth factor– and cytokine-induced VSMC PPARγ1 gene expression. Our results demonstrate that PPARγ is involved in a feedback mechanism that negatively controls VSMC activation (111).

Angiotensin II plays a crucial role in controlling the proliferation and migration of VSMCs. Troglitazone blocks AngII-induced MAPK activation of VSMCs (140) (Fig. 6). One possible mechanism includes the attenuation of PKC nuclear activity and PKC-mediated extracellular signal regulated kinase 1/2 (ERK 1/2) translocation to the nucleus (132). Another mechanism of AngII-induced VSMC proliferation involves the upregulation of AT1 receptors. PPARγ ligands have been reported to be responsible for the inhibition of AT1 expression in VSMCs (343, 349). Further, it was suggested that ligand-activated PPARγ inhibits AT1 transcription by blocking Sp1, leading to the suppression of AT1-receptor expression (343). Finally, telmisartan, an AT1-receptor antagonist with partial PPARγ activator properties, inhibits AT1-receptor expression. Conversely, administration of the PPARγ antagonist GW9662 attenuates telmisartan-induced inhibition of AT1, confirming a participatory role for PPARγ in this signaling cascade (167). Both 15d-PGJ_2 and rosiglitazone were shown to decrease

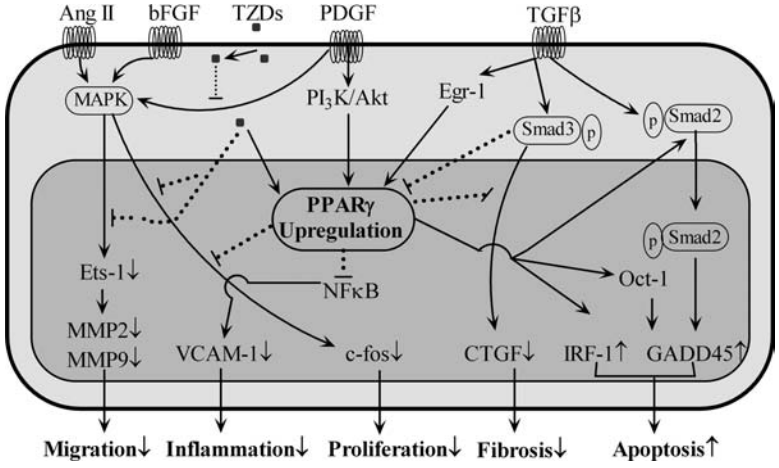

FIG. 6. Schematic view of PPARγ activation in VSMCs. In VSMCs, TZDs attenuate growth factor–induced (e.g., AngII) cell migration, proliferation, and fibrosis in either a PPARγ-dependent or -independent manner by interfering with growth factor–stimulated signaling pathways. PPARγ activation exerts antiinflammatory roles by inhibiting the NF-κB pathway; PPARγ activation promotes apoptosis *via* inducing IRF-1 or GADD45 expression.

AngII-stimulated eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and Src homology (SH) 2–containing inositol phosphatase 2 (SHIP2) phosphorylation, suppressing Ang II–induced VSMC growth (28). Rosiglitazone may directly decrease SHIP2 activity (28). A recent study suggests that pioglitazone and rosiglitazone inhibit AngII-induced Rho kinase, a known modulator of VSMC tonicity and proliferation. This may be accomplished through increased cytosolic Src homology region 2–containing protein tyrosine phosphatase-2 (SHP-2) expression and reduced Vav phosphorylation (372). However, the effects of PPARγ activators on AngII cell signaling and growth are still unclear.

One of the most important mechanisms in preventing VSMC growth involves suppression of cell-cycle signaling. In PDGF- or insulin-stimulated cultured rat VSMCs, PPARγ ligands prevent proliferation by inhibiting the G_1/S phase, a rate-determining step in cell-cycle progression (373). Cell-cycle suppression likely occurs through decreased phosphorylation of the retinoblastoma protein (Rb) (373), a mediator of G_1/S progression (327). Moreover, PPARγ agonists prevent mitogen-induced p27(Kip1) degradation (373), a known inhibitor of cdk and Rb phosphorylation (328). A non-TZD partial PPARγ agonist can attenuate mitogen-induced downregulation of p27(Kip1) and proliferation in rat aortic vascular smooth muscle cells. Furthermore, functional PPARγ is necessary to obtain maximal antiproliferative effects in VSMCs (42). PPARγ ligands also attenuate PDGF-induced p21(Cip1) expression through the likely inhibition of PKC-δ phosphorylation and activity in cultured rat aortic smooth muscle cells (374). p21(Cip1) promotes activation of the cyclin/cdk complex that eventually results in G_1/S phase progression (195, 328). Repression of p21(Cip1) may be another mechanism by which PPARγ attenuates VSMC proliferation. Minichromosome maintenance proteins (MCMs) 6 and 7 participate in the initial stages of DNA replication (231) and are considered to be E2F target genes (272). On retinoblastoma phosphorylation, E2F dissociates from Rb and is released for transactivation of DNA synthesis target genes (151). PPARγ ligands attenuate MCM 6 and 7 expression in VSMCs through the prevention of E2F release from Rb transactivation, further demonstrating that PPARγ agonists inhibit G_1/S cell-cycle progression, in this case by curtailing pRb/E2F/MCM signaling (43).

Telomerase is important for many cellular functions, including VSMC proliferation. PPARγ ligand administration was shown to downregulate telomerase activity in cultured VSMCs, because of likely inhibition of telomerase reverse transcriptase (TERT) expression, the catalytic subunit of telomerase. Overexpression of TERT abolishes PPARγ-ligand inhibition of VSMC proliferation. In addition, the Ets-1 transcriptional factor regulates TERT, and PPARγ agonists inhibit both Ets-1 mRNA expression and binding to the TERT promoter. Thus, it is likely that PPARγ ligands target TERT for downregulation to counteract the proliferative properties of vascular smooth muscle cells (269).

Another mechanism suggests that PPARγ ligands inhibit insulin-induced mitogenic signaling by preventing phosphorylation of the Elk-1 transcription factor (130). A recent *in vitro* study showed that troglitazone attenuates LDL-induced VSMC proliferation and production of superoxide, a contributor to proliferation of VSMCs (153). Finally, PPARγ has also been shown to induce a differentiated phenotype in proliferative VSMCs. PPARγ-dependent signaling increases smooth muscle α-actin (SM-α-actin) and smooth muscle myosin heavy chain (SM-MHC), markers of differentiated VSMCs. Moreover, the effects of PPARγ on VSMC differentiation appear to be mediated by the GATA-6 transcription factor (4).

B. PPARγ and VSMC migration

Troglitazone has been shown to inhibit PDGF-induced vascular smooth muscle cell migration (29, 199). In addition to troglitazone, 15d-PGJ_2 (198, 239) and rosiglitazone (198) attenuate PDGF-induced VSMC migration. CTGF is known to be involved in VSMC migration, and data from our laboratory provide evidence that PPARγ inhibits CTGF expression (114). These studies provide strong support for the involvement of activated PPARγ in the prevention of VSMC migration that leads to subsequent neointima formation.

Angiotensin II is involved in the control of VSMC proliferation and migration. Troglitazone can block AngII-induced MAPK activation of VSMCs, resulting in the inhibition of VSMC migration (140) (Fig. 6). PPARγ activators can also inhibit PDGF-, thrombin-, and insulin-like growth factor-1 (IGF-1)-induced VSMC migration through MAPK and downstream nuclear signaling (133). Furthermore, PPARγ ligands were reported to inhibit PDGF-induced Ets-1 nuclear expression in cultured VSMCs (Fig. 6) or from rat aortic balloon injury. Ets-1 is a transcription factor that is part of ERK/MAPK cell migratory signaling. Moreover, Ets-1 is involved in the transcriptional regulation of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), facilitators of VSMC migration (131) (Fig. 6). PPARγ activators decrease MMP-9 mRNA and protein expression, along with activity, whereas PPARγ inactivation through phosphorylation reverses agonist-induced inhibition of MMP-9 expression (239).

C. PPARγ and VSMC apoptosis

In VSMCs, PPARγ can signal both growth inhibition (405) and apoptosis (44, 148). PPARγ activation increases GADD45 expression and caspase-mediated apoptosis (Fig. 6). The Oct-1 protein, a transcription factor regulated by PPARγ, is critical for PPARγ-induced GADD45 protein expression (44) (Fig. 6). PPARγ ligand administration and PPARγ overexpression have been reported to upregulate interferon regulatory factor (IRF-1) expression, mediating PPARγ-induced apoptosis in VSMCs (Fig. 6). Further evidence of proapoptotic effects is provided by using an anti-sense approach to suppress IRF-1 expression in VSMCs (224). Pioglitazone is shown to increase apoptosis through PPARγ-dependent TGF-β release in cultured VSMCs, likely facilitating phosphorylated Smad2 nuclear translocation (303) (Fig. 6). TGF-β–induced apoptosis is mediated, in part, by Smad-dependent GADD45 expression, providing further evidence that GADD45 mediates VSMC apoptosis (397) (Fig. 6). Pioglitazone is also reported to induce apoptosis through Smad2 phosphorylation in cultured VSMCs from both nondiabetic and diabetic patients, usually resistant to induced apoptosis (315). Furthermore, troglitazone can induce apoptosis by activating GADD45 and p53 expression independent of PPARγ activation (275). Rosiglitazone at high concentrations can more potently induce

apoptosis in intimal compared with medial smooth muscle cells (35).

D. PPARγ and the regulation of VSMC inflammatory response

CCAAT/enhancer-binding proteins (C/EBPs) are involved in transcriptional regulation of inflammatory cytokines and other proteins. PPARγ ligands attenuate C/EBPδ expression, and C/EBPδ overexpression reverses PPARγ ligand inhibition of cytokine gene expression (346). Interestingly, elevations in C/EBPδ levels due to inflammation increase PPARγ expression and strengthen its antiinflammatory effect in VSMCs (347). In addition, PPARγ ligands suppress C/EBPδ mRNA and protein levels by dephosphorylating STAT-3 (347), suggesting that PPARγ and C/EBPδ participate in negative autoregulation feedback. Moreover, PPARγ overexpression decreases C/EBPδ promoter activity, further indicating the presence of receptor-dependent signaling in C/EBPδ expression (347). This mechanism is likely involved in the suppression of inflammatory cytokines during atherosclerosis (347). Other antiinflammatory responses involving PPARγ activation include the suppression of TNF-α–induced expression of VCAM-1 (Fig. 6), MCP-1, and fractalkine (CX3CL1) in cultured VSMCs through inhibition of NF-κB (283).

VI. PPARγ and Monocytes/Macrophages

PPARγ expression is present in murine macrophages (8, 307), neointimal lesions (198), macrophage-derived foam cells in both early and advanced stages of atherosclerotic lesions (240, 306), and differentiated human monocyte–derived macrophages (64). However, PPARγ expression, critical for macrophage lipid metabolism, is not a determinant for macrophage differentiation *in vivo* or *in vitro* (56, 249). PPARγ is also found in other inflammatory cells, including human peripheral blood T cells (395), human $CD4^+$ T cells (236), and mature dendritic cells from the spleen (106). PPARγ expression is also confirmed in mouse T-helper cells (70). The PPARγ1 isoform is found in THP-1 and RAW 264.7 cells (306).

A. PPARγ and monocyte/macrophage inflammatory signaling

Macrophages are often considered to be heterogeneous and respond to various signaling cascades (365). Different cytokines determine the type of stimulatory or inhibitory response on inflammatory signaling by inducing either a "classic" or "alternative" activation pathway in macrophages. Th1 cytokines, including lipopolysaccharide (LPS), IFN-γ, and IL-1β, tend to be involved in "classic" activation, whereas Th2 cytokines, including IL-4 and IL-13, likely activate the "alternative" pathway. M1 macrophages are involved in proinflammatory cytokine expression and oxidative stress, whereas M2 macrophages play a role in apoptotic cell phagocytosis, sequestering of pathogens, and wound healing (267, 341). Moreover, macrophages demonstrate functional plasticity because they have the ability to switch between M1 and M2 states of activation (295).

PPARγ was shown to be necessary for monocyte-derived M2 macrophage phenotype expression (37). PPARγ is also upregulated during M1 switching to an M2 phenotype, which is critical for increased expression of CD36 (31), arginase I (267), and the mannose receptor (37). PPARγ has been shown to regulate M1/M2 switching, in part by reducing inflammatory cytokine expression normally associated with an M1 phenotype, such as TNF-α, IL-1β, and IL-6 (174), and suppressing *in vitro* macrophage activation (307). The suggestion that PPARγ is an inflammatory regulator is further illustrated by the belief that PPARγ may reverse suppression of cytotoxic T lymphocytes, normally a function of M2 activation (364). In addition, specific genes from both M1 and M2 macrophages were found to be unaltered when administering TZD (56, 154, 382).

PPARγ participates in antiinflammatory signaling to protect against atherosclerotic lesion formation, in part, through negative regulation of macrophage transcriptional activity. PPARγ ligands, in a PPARγ-dependent manner, attenuate monocyte and macrophage MMP-9 expression and secretion (186, 240, 307, 330), iNOS, and scavenger receptor-A (SR-A) through the likely inhibition of AP-1, STAT, and NF-κB transcription factor signaling (307). In addition, PPARγ negatively regulates a specific population of pro-inflammatory genes controlled by these transcription factors (307, 330) (Fig. 7). PPARγ activation also inhibits macrophage osteopontin (OPN) expression by interfering with nuclear factor binding to the homeobox-like A/T rich region of the OPN promoter, providing another example of PPARγ inhibition of macrophage gene expression (277, 278). Similarly, PPARγ ligands were shown to inhibit proinflammatory cytokine (IL-6, IL-1β, TNF-α) expression in monocytes (174) (Fig. 7). However, PPARγ may not be required for IFN-α– or LPS-induced proinflammatory cytokine secretion in macrophages (56, 249). Moreover, it is possible that PPARγ ligands can upregulate antiinflammatory cytokines (Fig. 7), such as the IL-1–receptor antagonist (IL-1Ra), suggesting another way by which PPARγ can suppress proinflammatory activity (245). PPARγ also regulates inflammatory signaling in cells other than monocytes and macrophages. PPARγ activators can suppress IL-2 (70, 236, 395, 396), IFN-γ (236), and TNF-α (236) in human and animal lymphocytes. PPARγ ligands also decrease CD40-induced IL-12 secretion in dendritic cells (106).

B. PPARγ and monocyte/macrophage migration and apoptosis

In addition to antiinflammatory properties, PPARγ ligands inhibit monocyte/macrophage migration. Troglitazone or rosiglitazone administration results in the inhibition of MCP-1–induced monocyte migration (186). Furthermore, oxidized low-density lipoproteins (oxLDLs) may attenuate MCP-1–dependent monocyte migration by inhibiting chemokine receptor 2 (CCR2) expression (145). Both 9-HODE and 13-HODE, components of oxLDL that stimulate monocyte differentiation to macrophages, inhibit macrophage migration and enhance macrophage adhesion to VSMCs by upregulating CX3CR1 and decreasing CCR2 expression through a PPARγ pathway (26), suggesting a proinflammatory role for macrophage PPARγ that may lead to the development of atherosclerosis. Moreover, a recent study showed that PPARγ-dependent signaling increases CXCR2 receptor expression in primary human macrophages, providing further evidence that PPARγ can also have proinflammatory properties (309). Next, PPARγ ligands can also induce apoptotic activity by blocking the NF-κB antiapoptotic signaling

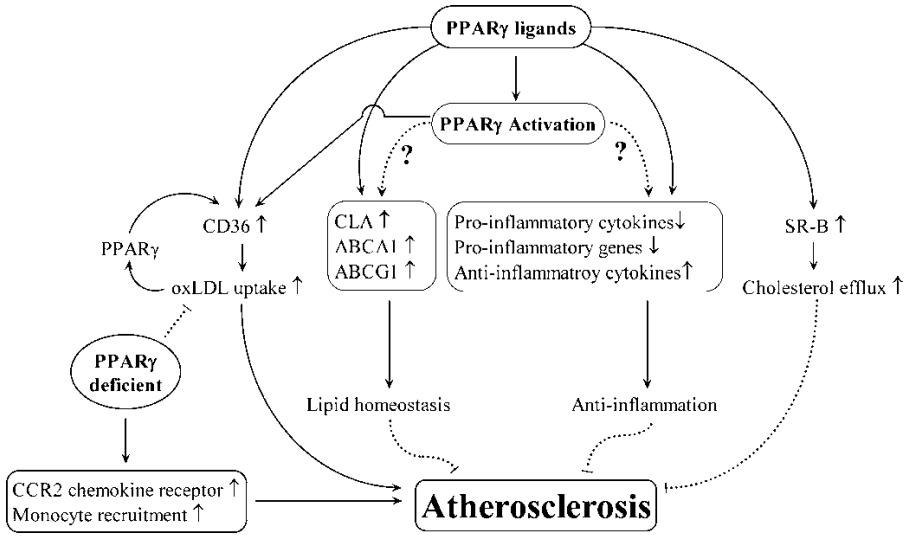

FIG. 7. Schematic view of PPARγ roles in atherosclerosis. PPARγ ligands increase CLA, ABCA1, and ABCG1 expression, leading to improved lipid homeostasis. PPARγ agonists also decrease proinflammatory cytokine and gene expression and increase antiinflammatory cytokine expression. PPARγ ligands increase SR-B expression, which promotes cholesterol efflux. Conversely, PPARγ activation upregulates CD36 expression, resulting in increased oxLDL uptake. Increased oxLDL levels further stimulate PPARγ expression, which leads to increased CD36 expression. Finally, loss of PPARγ increases CCR2 expression and monocyte recruitment.

cascade in human macrophages (64). Finally, PPARγ activation during differentiation of human monocytes to macrophages decreases the ability to engulf apoptotic neutrophils (232).

C. PPARγ and monocyte/macrophage iNOS expression

Studies have shown that the ability of PPARγ to repress iNOS expression (159, 217, 307) may occur through direct interaction with the CREB-binding protein (CBP) (217). Furthermore, a recent provocative report suggested another mechanism by which PPARγ represses iNOS and other proinflammatory genes in murine macrophages. SUMO-1 covalently modifies several transcription factors, including PPARγ (271). SUMOylation of PPARγ results in binding to the nuclear-receptor co-repressor (N-CoR)-histone deacetylase-3 (HDAC-3) complex, repressing proinflammatory signaling, particularly NF-κB target genes (270, 287). Furthermore, PPARγ and the glucocorticoid receptor were found to inhibit iNOS expression through at least two different signaling pathways (270).

D. PPARγ and monocyte/macrophage CD36 expression

CD36 is a scavenger receptor that promotes uptake of oxLDL (101). Ligand-dependent PPARγ has been shown to increase CD36 expression through various signaling pathways in both cultured monocytes and macrophages (159, 254, 358). By using embryonic stem cell–derived macrophages, two studies reported that PPARγ is required for ligand-activated CD36 gene regulation (56, 249). Macrophages from PPARγ conditional knockout mice are shown to have decreased CD36 expression compared with wild-type macrophages (8). However, although CD36 is a PPARγ target gene, PPARγ is not mandatory for oxLDL uptake in differentiated macrophages (56). Moreover, an *in vivo* study showed that TZDs decrease macrophage CD36 protein expression in *ob/ob* mouse models that display characteristics of insulin resistance, diabetes, and obesity, all of which are risk factors for atherosclerosis (219). TGF-β phosphorylation of PPARγ has been suggested as an inhibitory mechanism of action regarding PPARγ-mediated CD36 expression (143).

E. PPARγ and monocyte/macrophage lipid homeostasis

A role for PPARγ activation in macrophage cholesterol homeostasis has been established. CLA-1 is a high-density lipoprotein (HDL) receptor involved in cellular cholesterol removal. CLA-1 was shown to be upregulated by PPARγ ligands in differentiated human macrophages (63) (Fig. 7). PPARγ ligands also demonstrate a role in reverse-cholesterol transport by upregulating expression of ATP-binding cassette (ABC) transporters ABCA1 (11, 57, 65) and ABCG1 (8, 11) in monocytes and macrophages (Fig. 7), possibly through an LXR-α–mediated transcriptional signaling pathway (57) that may include caveolin-1 (227). This is important, because an atheroprotective role for granulocyte–macrophage colony-stimulating factor (GM-CSF) may involve PPARγ and ABCA1 signaling (92). Providing further evidence, a PPARγ conditional knockout mouse model displays a reduction in macrophage cholesterol efflux, although this study found that troglitazone attenuates cholesterol efflux and ABCA1 expression in macrophages from both PPARγ knockout and wild-type mice, suggesting some PPARγ-independent effects (8). Finally, although PPARγ is not required for oxLDL uptake in differentiated macrophages (56), oxLDL uptake is worsened in PPARγ-deficient macrophages (249). This finding further indicates an important role for PPARγ in oxLDL lipid trafficking.

VII. PPARγ and Atherosclerosis

Diabetes has been estimated to increase the risk of developing atherosclerosis by twofold (178). Increasing evidence suggests that failure to maintain normal glycemic control influences the development of atherosclerosis (142, 356). As previously mentioned, PPARγ is expressed in atherosclerotic lesions (240, 306). Monocytes differentiate into macrophages on migration into the vessel wall. In macrophages, oxLDL uptake occurs through scavenger receptors, promoting the expression of foam cells (127, 254). Initially, PPARγ was

thought to be proatherosclerotic. PPARγ ligand administration, combined with an RXR agonist, upregulates oxLDL uptake through increased CD36-receptor expression (Fig. 7). Furthermore, oxLDL exposure increases SR-A and CD36 mRNA expression through a PPARγ-dependent mechanism, signaling further oxLDL cellular uptake (254) (Fig. 7). Moreover, PPARγ is highly expressed in foam cells (358). PPARγ also is found to be highly expressed in cultured $CD36^+$ HASMCs, and troglitazone treatment upregulates CD36 expression only in $CD36^+$ smooth muscle cells, suggesting that VSMCs may be able to obtain a macrophage-like phenotype and differentiate into foam cells (242). Furthermore, LPA, a PPARγ ligand synthesized during mild oxidation of LDL (332), and other PPARγ agonists were also shown to increase neointima formation in rats (406). Collectively, these studies suggest that PPARγ is involved in the development of atherosclerosis. Another study found that oxLDL uptake was decreased in PPARγ-deficient macrophages, partly due to loss of CD36 expression. However, troglitazone treatment had no effect on intracellular oxLDL levels (249). A likely explanation is that troglitazone stimulates CD36 while suppressing SR-A expression (249). It is likely that TZD increases neither macrophage intracellular cholesterol levels nor foam cell formation.

However, the majority of studies suggest an atheroprotective role for TZDs and PPARγ. PPARγ-ligand treatment increases scavenger receptor B (SR-B) expression in atherosclerotic lesion macrophages of $ApoE^{-/-}$ mice, potentially facilitating cholesterol efflux (63) (Fig. 7). Treatment with rosiglitazone and GW7845 inhibits atherosclerosis in male low-density lipoprotein receptor knockout ($LDL\text{-}R^{-/-}$) mice although CD36 expression is increased. Interestingly, PPARγ ligand treatment did not reduce atherosclerosis in female mice. Hormonal differences could be an explanation for the dissimilar outcome between genders (215). In male $LDL\text{-}R^{-/-}$ mice fed either a high-fructose or high-fat diet, troglitazone can suppress atherosclerotic lesion formation (72). Next, rosiglitazone reduces aortic atherosclerotic lesions in both diabetic and nondiabetic $apoE^{-/-}$ male mice (212). Finally, rosiglitazone treatment is associated with increased ABCA1 gene expression (Fig. 7) and decreased macrophage accumulation in diabetic mice, providing further evidence of an antiatherosclerotic role (48).

$LDL\text{-}R^{-/-}$ mice given transplants with bone marrow deficient in PPARγ demonstrate an overall worsening of atherosclerosis (57). Next, bone marrow generated from macrophage PPARγ knockout (MacPPARγ KO) mice was transplanted to $LDL\text{-}R^{-/-}$ and wild-type mice. Mice reconstituted with macrophage PPARγ knockout bone marrow display increased lesion formation in both strains compared with respective controls. In cases of mild or severe hypercholesterolemia, loss of PPARγ results in increased atherosclerosis, possibly due to increased CCR2 chemokine receptor expression and monocyte recruitment (18) (Fig. 7).

In vitro studies show that functional PPARγ is more prevalent in intimal VSMCs compared with medial smooth muscle cells. Therefore, intimal vascular smooth muscle cells are a likely target for PPARγ in regulating antiatherosclerotic effects (35). Another study showed that transfer of the PPARγ wild-type gene in a rat carotid artery balloon injury model results in decreased neointima formation and that rosiglitazone-induced inhibition of VSMC proliferation and migration is blunted by PPARγ-dominant negative gene transfer. However, the effects of rosiglitazone primarily, but not entirely, occur through PPARγ-mediated signaling (223). In human atherosclerotic plaques, PPARγ is associated with M2 macrophage marker expression, although PPARγ activation does not switch M1 macrophages, foam cells, or already differentiated resting macrophages *in vitro* or atherosclerotic plaque macrophages *in vivo* to an M2 phenotype (37).

PPARγ ligands may also reduce atherosclerotic development by inhibiting IFN-γ–induced increases in MHC-II expression that normally activate T lymphocytes and control immune responses (194). Increased expression of iNOS has been shown in coronary atherosclerotic plaques of patients with unstable angina (84). Troglitazone and 15d-PGJ_2 are found to suppress IL-1β–induced iNOS production and cytokine-induced NO synthesis in vascular smooth muscle cells. NF-κB, critical for iNOS transactivation, is downregulated by both PPARγ activators in VSMCs (165). Finally, osteoprotegrin (OPG) is involved in the regulation of atherosclerotic lesion calcification. In our laboratory, we demonstrated that PPARγ ligands or PPARγ overexpression inhibits OPG expression in human aortic smooth muscle cells (113). The role of PPARγ in atherosclerosis is controversial, with much of the literature providing the rationale that PPARγ plays a regulatory role against the development of atherosclerosis. However, several considerations must be taken into account. Pioglitazone binds with less affinity to PPARγ compared with rosiglitazone, yet has been shown to be more effective at improving patient lipid profiles (135). Many of the beneficial effects of TZD-induced activation of PPARγ-mediated transcription are still unclear, particularly because the effects of TZDs on PPARγ-mediated transcriptional activity are tissue specific. Moreover, the biologic effects of PPAR target genes remain largely unestablished, and because PPAR agonists tend to participate in both gene activation and repression, the known biologic effects of PPAR target genes tend to be rather complex. Thus, a need exists for further research regarding the role of PPARγ and its ligands in atherosclerotic plaque formation, although the literature provides compelling evidence that PPARγ activation is important for the attenuation of atherosclerosis.

VIII. PPARγ and the Heart

The role of PPARγ in the heart is controversial and often paradoxical. First, myocardial PPARγ expression seems to vary between studies (16, 124, 392, 394). Next, although several reports have demonstrated beneficial effects of PPARγ agonist administration on the heart (3, 16, 136, 394) (Fig. 8), the effects of TZDs on cardiac function are in question, particularly in humans. A recent study reported that patients who receive rosiglitazone display an increased risk for myocardial infarction and possibly death from cardiovascular events (265) (Fig. 8). *In vivo* administration of TZDs appears to decrease PPAR target gene expression (47, 336). Nonetheless, it is likely PPARγ agonists exert an indirect action on the heart because PPARγ has minimal effects on cardiac fatty acid oxidation or PPAR gene expression in cultured myocytes (124). However, a direct role for PPARγ must be considered because ciglitazone increases insulin-induced glucose transport in cardiomyocytes. Moreover, phosphorylation of Akt residues, Thr308 and Ser473, is required for insulin stimulation of

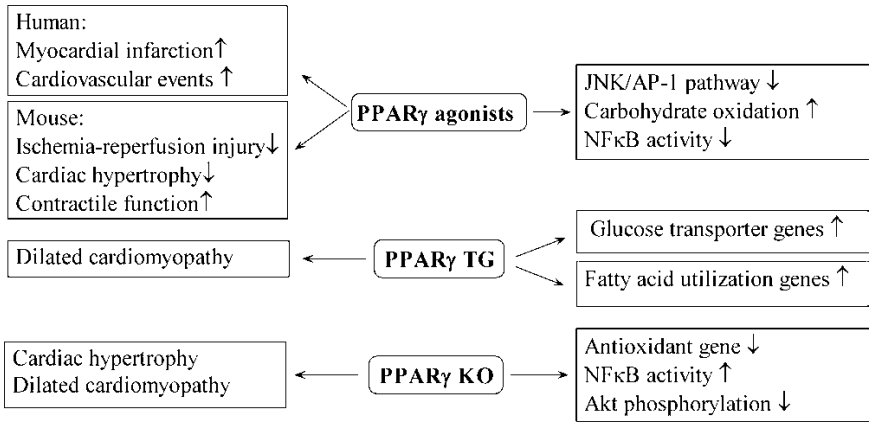

FIG. 8. Schematic view of PPARγ roles in the heart. PPARγ agonists are associated with increased myocardial infarction and cardiovascular events in humans. PPARγ agonists decrease ischemia/reperfusion injury and cardiac hypertrophy while increasing contractile function in mice. Administration of PPARγ agonists decreases JNK/AP-1 and NF-κB signaling pathways and increases carbohydrate oxidation in mice. Mice with cardiac-specific PPARγ overexpression show a dilated cardiomyopathy phenotype. Moreover, these mice have increased expression of genes involved in glucose transport and fatty acid utilization. Myocardial PPARγ-knockout mice display characteristics of cardiac hypertrophy and dilated cardiomyopathy along with increased NF-κB activity, decreased Akt phosphorylation, and decreased antioxidant gene expression.

glucose transport and is decreased in insulin-resistant cardiomyocytes (248). In particular, because active Akt has been shown to be necessary for glucose transporter 4 (GLUT4) fusion with adipocyte plasma membranes (191), this may support a role for PPARγ ligand–induced Akt phosphorylation in cardiomyocytes. The possible discrepancy found in endothelial cells (128, 129) and cardiomyocytes may be explained by the use of different stimuli.

Although ciglitazone enhances insulin-stimulated glucose transport, ciglitazone does not improve insulin-stimulated GLUT4 expression in neonatal rat cardiomyocytes (363), adult rat cardiomyocytes (248), or cardiomyoblasts (124). One possible explanation for increased glucose transport is that elevated glucose transporter 1 (GLUT1) expression, not usually seen with insulin-induced glucose uptake, may be a contributing factor, although the mechanisms remain unclear. The cardiomyocyte microtubule network may be important in regulating insulin signaling. Disruption of the microtubule network may prevent the convergence of insulin signaling and GLUT4 vesicle trafficking (248). Conversely, ligand-independent PPARγ represses GLUT4 gene expression in adipocytes, and rosiglitazone not only alleviates PPARγ-induced repression of GLUT4, but also facilitates transcription (15). Similarly, PPARγ1 and PPARγ2 have been shown to repress GLUT4 expression in cardiomyocytes, and this is enhanced by hyperlipidemia, as free fatty acids bind to PPARγ and further repress GLUT4 transcription (12). Overall, these results suggest that the regulation of glucose transport by insulin may involve PPARγ-dependent and -independent signaling pathways.

Another proposed mechanism of action involving insulin signaling and PPARs in the cardiovascular system may include the forkhead-box class O (FOXO) family of transcription factors. FOXO1 is highly expressed in adipocytes and may enhance insulin sensitivity (13, 14) through inhibition of PPARγ1 and PPARγ2 (13). Insulin signaling results in phosphorylation of FOXO1 by Akt (360). FOXO phosphorylation may repress PPARγ1 and PPARγ promoter activity, directly or indirectly leading to increased GLUT4 expression and subsequent improved insulin sensitivity in adipocytes and cardiomyocytes (14).

Transgenic mice overexpressing PPARγ (MHC-PPARγ) in the heart were recently generated and characterized (336). However, cardiomyopathy is present at 2 months of age in these mice, with 100% mortality occurring at 5 months. Subsequently, a new transgenic line was generated to circumvent the problem, as these mice display characteristics suggestive of milder cardiomyopathy (Fig. 8). PPARγ transgenic mice show increases in expression of fatty acid–utilization genes (Fig. 8), similar to MHC-PPARα mice. Conversely, similar to MHC-PPARδ mice, glucose-transporter expression is increased in the PPARγ transgenic model (Fig. 8). Thus, it is possible that combined elevations in cardiac lipid and glucose levels may further potentiate the development of cardiomyopathy (399).

Whole-body PPARγ deletion is embryo-lethal in murine models (21). To study the function of PPARγ in the heart, two cardiac-specific PPARγ-knockout murine models were generated (91, 97); however, these two lines manifest different phenotypes. The first mouse line shows evidence of mild ventricular hypertrophy (Fig. 8) that is further increased by rosiglitazone treatment, suggesting off-target TZD effects on hypertrophy. Systolic function does not seem to be impaired in these cardiac-specific PPARγ-null mice. NF-κB activity is increased, and surprisingly, Akt phosphorylation is decreased despite the presence of a hypertrophic phenotype (97) (Fig. 8). The second cardiac-specific murine knockout model demonstrates progressive dilated cardiomyopathy (Fig. 8) in association with mitochondrial oxidative damage and a reduction in the mitochondrial antioxidant, manganese superoxide dismutase (91) (Fig. 8). These models suggest a likely role for PPARγ in cardiac function as well as in maintaining a proper oxidation/reduction balance.

IX. PPARα

PPARα is highly expressed in the liver, with expression in other tissues including heart, kidney, skeletal muscle, small intestine, and brown adipose tissue. Similar to PPARγ, PPARα is also expressed in the cardiovascular cells. PPARα is involved in the expression of genes involved in lipid metabolism, including fatty acid uptake and oxidation. Moreover,

PPARα, similar to PPARγ, can play a role in transcriptional repression of certain genes by inhibiting signaling pathways of other transcription factors. The attenuation of proinflammatory signaling is accomplished through this method by downregulating expression of genes involved in promoting the inflammatory response.

In rodent models, PPARα was shown to be activated by fibrates, hypolipidemic drugs that are involved in peroxisome proliferation and fatty acid oxidation (172). Fibrates include clofibrate, bezafibrate, fenofibrate, and gemfibrozil. Wy-14,643, nafenopin, and clofibric acid are other hypolipidemic compounds that are PPARα-activating agents. Warfarin, an anticoagulant, and trichloroacetic acid were also initially described to be stimulators of PPARα (96). Fatty acids, including linoleic acid and arachidonic acid, were also shown to activate PPARα and to regulate gene function (138).

A. PPARα ligands

However, these studies did not demonstrate whether fibrates or fatty acid compounds could directly bind to PPARα. A ligand-binding assay found that fibrates and certain fatty acids do indeed have binding affinity for PPARα (109). In addition, GW7647 (40), GW9578 (41), and LY-518674 (393) are known to be PPARα ligands. PPARα antagonists are limited in number and include GW6471 (391) and the *N*-acylsulfonamide compounds A and B (325).

B. PPARα and endothelial cells

PPARα is expressed in human endothelial cells (83, 170, 240). Moreover, PPARα activators are involved in several endothelial cell functions. For example, PPARα agonists can prevent leukocyte recruitment and adhesion to endothelial cells, in part by decreasing VCAM-1 (6, 173, 241, 321), along with ICAM-1 and E-selectin expression (321) (Fig. 9). Downregulation of adhesion molecules by PPARα activators is likely through inhibition of NF-κB (241, 321) (Fig. 9). In addition to decreased adhesion molecule expression, PPARα activators impair leukocyte binding to endothelial cells (6, 173, 241, 321).

PPARα has been demonstrated to play a role in vascular function. PPARα ligands inhibit ET-1 synthesis and secretion in endothelial cells through negative regulation of AP-1 (83) (Fig. 9). A possible explanation is that PPARα activators may suppress, at least in part, PKC activity involved in endothelial cell ET-1 secretion (234). In DOCA-salt rats, fenofibrate prevents increased ET-1 synthesis in mesenteric arteries (163). PPARα ligands stimulate eNOS expression by PPARα-mediated signaling (139).

PPARα has been shown to be involved in endothelial cell inflammatory signaling. One mechanism for endothelial cell PPARα participation in antiinflammatory pathways may include oxLDL and a phospholipase A2 (PLA2)-dependent-pathway, potentially stimulating fatty acid transport protein-1 (FATP-1) expression (81). Another antiinflammatory mechanism suggests that PPARα ligands may decrease VEGFR2 expression through direct PPARα/Sp1 interaction in endothelial cells (246). Finally, bezafibrate increases the CuZn superoxide dismutase antioxidant and decreases NAD(P)H oxidase subunit expression in endothelial cells (168). PPARα ligands have also been shown to attenuate MCP-1 and IL-8 expression in endothelial cells, possibly by PPARα suppressing NF-κB (247, 285). Conversely, another study suggests that PPARα ligands increase MCP-1 and IL-8 expression through a PPARα-dependent signaling cascade in human aortic endothelial cells (203). Overall, these studies suggest that PPARα is primarily involved in antiinflammatory signaling, although it is likely that PPARα may also exert proinflammatory effects.

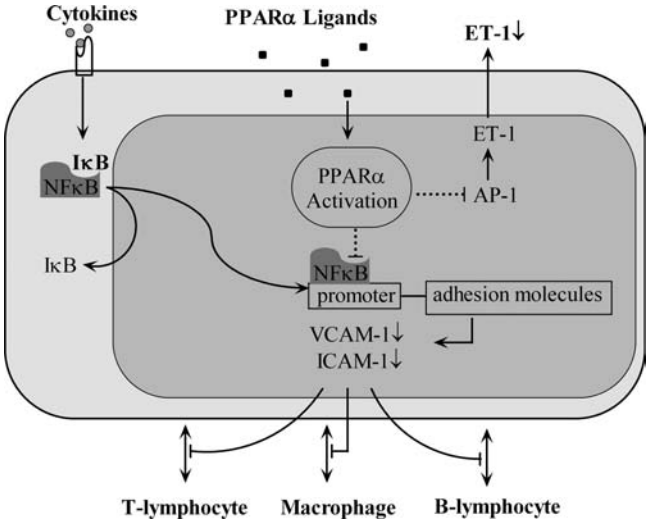

FIG. 9. Schematic view of PPARα activation in ECs. PPARα activation attenuates NF-κB signaling and transcription in ECs, leading to decreased adhesion-molecule expression and inhibition of leukocyte interaction with ECs. PPARα ligands inhibit ET-1 synthesis by negatively regulating AP-1.

C. PPARα and VSMCs

PPARα is also expressed in human vascular smooth muscle cells (239, 340). As in endothelial cells, PPARα has an antiinflammatory role in VSMCs. PPARα activators suppress IL-6 (80, 340), 6-keto-$PGF_{1\alpha}$ (340), along with COX-2 protein and mRNA expression by negatively regulating NF-κB signaling (340) (Fig. 10). PPARα agonists may increase VSMC IκBα, an inhibitory protein that suppresses NF-κB nuclear translocation (82). HO-1, a PPARα target gene, is upregulated by PPARα and contributes to the antiinflammatory effects in VSMCs (193) (Fig. 10). Group IIA secretory phospholipase A2 (sPLA2-II2) is a proinflammatory mediator of atherosclerosis. PPARα has been shown to repress IL-1β–induced sPLA2-IIA expression in VSMCs (298).

In vitro studies have shown that PPARα ligands inhibit VSMC proliferation (264, 404). One possible mechanism may involve PPARα activation of $p16^{INK4a}$ (Fig. 10), a cdk inhibitor that blocks phosphorylation of the retinoblastoma protein and subsequent G_1/S cell-cycle progression (126). Next, epoxide hydrolase inhibitors activate PPARα and suppress PDGF-induced VSMC proliferation through negative regulation of cyclin D1 expression (261). Finally, HO-1, in addition to antiinflammatory signaling, also has a role in VSMC antiproliferation (193) (Fig. 10). PPARα also has been shown to regulate VSMC migration. Integrins are critical for VSMC migration in atherosclerosis. PPARα may interact with Smad4 and inhibit TGF-β–induced beta5 integrin expression in VSMCs (187) (Fig. 10). In addition, docosahexaenoic acid may

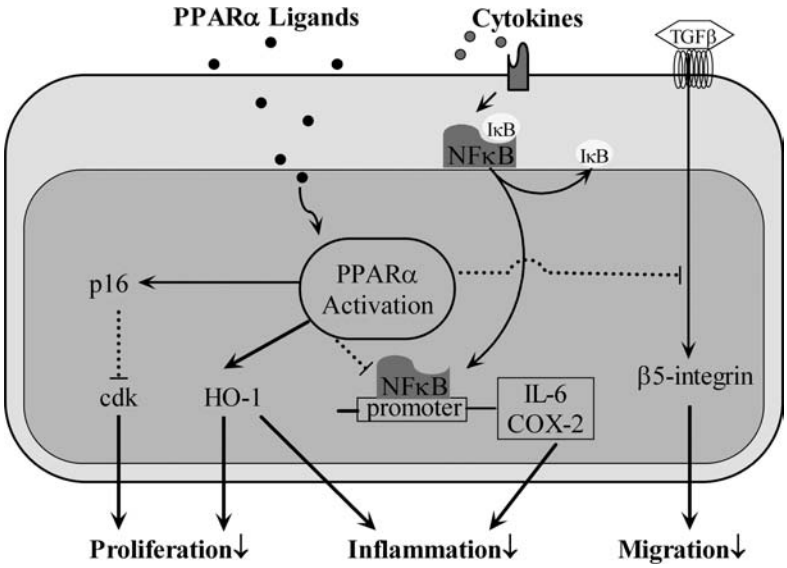

FIG. 10. Schematic view of PPARα activation in VSMCs. PPARα activation in VSMCs inhibits proliferation and migration by interfering with cdk and β5-integrin signaling pathways. PPARα activation also exerts anti-inflammatory roles *via* inhibiting NF-κB mediated–inflammatory factor release.

regulate VSMC apoptosis through PPARα-dependent p38 MAPK signaling (89).

D. PPARα and monocytes/macrophages

PPARα is expressed in differentiated human macrophages (64) and atherosclerotic lesion macrophages (63). This is important because differentiated macrophages play an important role in inflammation and plaque formation. The first evidence for a role of PPARα in inflammatory control demonstrated that PPARα-null mice display a prolonged response to inflammatory stimuli. Leukotriene B4 (LTB4) binding to PPARα results in activation of fatty acid oxidation (FAO) enzymes that degrade fatty acid and disrupt inflammatory signaling (86).

Further evidence that PPARα plays a protective role against the inflammatory response is shown from experiments using RAW 264.7 mouse macrophages, whereby Wy14,643 reduces nitrate accumulation in association with decreased iNOS and elevated HO-1 (Fig. 11). Interestingly, natural PPARα ligands, such as LTB4 and 8(S)-HETE, increase nitrate accumulation, an indication of proinflammatory activity. This difference may be due to variable selectivity to PPARα (74). Other studies in monocytes/macrophages provide evidence of PPARα-dependent antiinflammatory signaling. Fenofibrate suppresses LPS-induced MMP-9 secretion in monocytes (330) (Fig. 11). PPARα also has been shown to downregulate the platelet-activating factor (PAF) receptor, possibly regulating monocyte and macrophage inflammatory responses and cellular apoptosis (156).

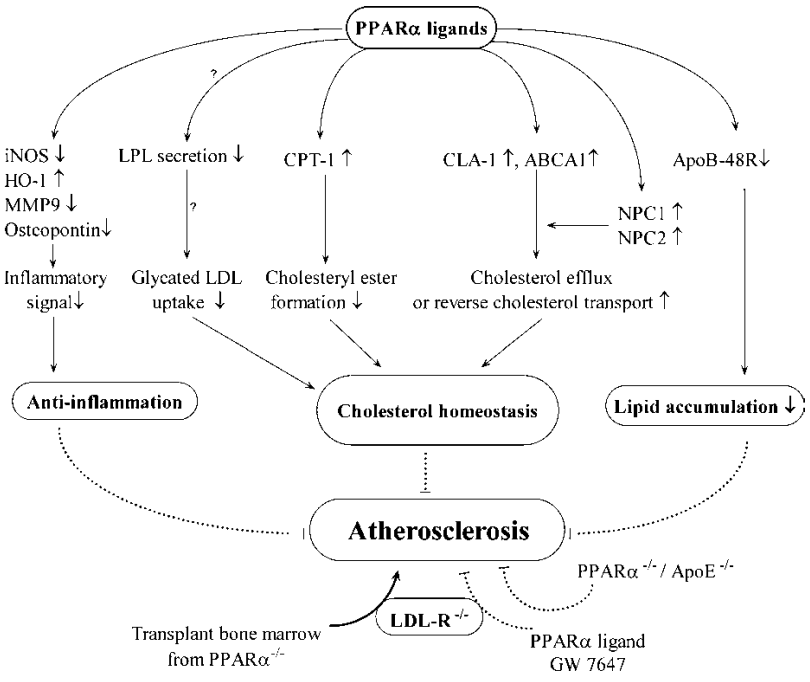

FIG. 11. Schematic view of PPARα ligand roles in macrophages and atherosclerosis. PPARα ligands may prevent atherosclerosis by improving cholesterol homeostasis, decreasing lipid accumulation, and participating in antiinflammatory signaling in macrophages. LDL-R$^{-/-}$ mice transplanted with bone marrow from PPARα$^{-/-}$ mice have increased atherosclerosis, whereas GW7647 decreases lesion development in LDL-R$^{-/-}$ mice. However, PPARα$^{-/-}$/apoE$^{-/-}$ mice are protected against the development of atherosclerosis.

Treatment with Wy-14,643 and bezafibrate inhibits osteopontin expression in human macrophages through AP-1 inhibition (Fig. 11). Moreover, osteopontin expression is not suppressed in macrophages lacking PPARα expression (255). Another antiinflammatory mechanism points to simvastatin inhibiting PKC-induced phosphorylation of PPARα that may result in reduced iNOS and IL-6 expression in macrophages (288). PPARα ligands inhibit IFNγ, TNF-α, and IL-2 proinflammatory cytokine expression in human T cells (236). Conversely, ligand-activated PPARα can increase ROS production in mouse and human macrophages (352).

ApoB-48R is involved in macrophage lipid accumulation. Wy-14,643 attenuates apoB-48R expression in both monocytes and macrophages (147) (Fig. 11). Lipoprotein lipase (LPL) hydrolyzes the lipids of lipoproteins and is generally considered to be expressed in cells of atherosclerotic plaques, including macrophage-derived foam cells (266). Although several studies demonstrated that PPARα activators increase LPL mRNA in macrophages (120, 216, 412), conflicting evidence exists regarding LPL secretion. Decreased LPL secretion due to PPARα activators may reduce glycated LDL uptake witnessed in macrophages (120) (Fig. 11). Conversely, increased LPL secretion could stimulate PPARα target gene expression in macrophages or provide an antiinflammatory role by reducing VCAM-1 expression in endothelial cells (412). PPARα ligands are involved in intracellular cholesterol homeostasis and have been shown to reduce cholesteryl ester formation in human macrophages and foam cells, possibly through upregulation of carnitine palmitoyltransferase type 1 (CPT-1), an enzyme involved in fatty acid degradation (66) (Fig. 11). PPARα ligands can also regulate reverse cholesterol transport or cholesterol efflux. PPARα ligands increase CLA-1 expression in differentiated human macrophages (63) (Fig. 11). Furthermore, Wy-14,643 was found to elevate ABCA1 expression in macrophages to facilitate apoAI-induced reverse cholesterol transport (65) (Fig. 11). Niemann-Pick type C1 and C2 (NPC1 and NPC2) proteins control intracellular cholesterol mobilization to the plasma membrane for extracellular transport. PPARα agonists were found to upregulate NPC1 and NPC2 expression in human macrophages (Fig. 11). In addition, NPC1 and NPC2 inhibition has been shown to prevent ABCA1-mediated extracellular cholesterol transport (62) (Fig. 11). Overall, these studies suggest that PPARα ligands are actively involved in macrophage cholesterol efflux (Fig. 11). Furthermore, PPARα ligands have been demonstrated to be regulators of cholesterol homeostasis in both normal and atherosclerotic lesion macrophages (Fig. 11).

E. PPARα and atherosclerosis

A role for PPARα has been identified in atherosclerotic lesion formation involving several cell types. As mentioned earlier, PPARα ligands are critical in controlling macrophage cholesterol homeostasis, and PPARα has been shown to inhibit VSMC proliferation and migration, important steps in the prevention of atherosclerosis. Wy-14,643 induces SR-B1 expression in atherosclerotic lesions (63). PPARα also may play a role in atherosclerotic thrombosis by inhibiting tissue factor (TF) mRNA and activity in human monocytes and macrophages (238, 260).

Although much evidence suggests that PPARα ligands protect against atherosclerosis, murine animal models have yielded conflicting results. The loss of PPARα is shown to protect against atherosclerosis in apoE$^{-/-}$ mice (359) (Fig. 11). Conversely, fenofibrate attenuates the development of atherosclerotic lesions, with a more pronounced decrease observed in apoE$^{-/-}$ mice that express the human apoA-I transgene (99). Another study showed that GW7647 decreases lesion formation in LDL-R$^{-/-}$ mice (214) (Fig. 11). Furthermore, lesion size is deceased in human apoE2 knockin mice administered fenofibrate (152). Finally, male and female LDL-R$^{-/-}$ mice transplanted with bone marrow from PPARα$^{-/-}$ mice display increased aortic atherosclerosis (Fig. 11), along with decreased peritoneal macrophage cholesterol efflux (17). Thus, from these studies, the role of PPARα in atherosclerotic lesion formation is controversial; however, much of the data tends to suggest an atheroprotective effect of PPARα.

Possible explanations for decreased atherosclerotic development witnessed with the removal of PPARα in apoE$^{-/-}$ mice may involve systemic or vessel wall effects. Systemic effects may include decreased glucose levels and insulin resistance, lower blood pressure, and the loss of liver PPARα target genes that lead to atherosclerotic development. Furthermore, the absence of PPARα may attenuate LPL activity in the subendothelial space of the vessel wall and decrease atherosclerosis. Systemic effects can alter gene expression in vessel walls, making it difficult to confirm the role of vascular wall PPARα in atherosclerosis (359).

F. PPARα and the heart

The use of both gain- and loss-of-function techniques has proven useful in evaluating PPARα and its effects on cardiac energy metabolism. Cultured myocyte treatment with PPARα ligands or adenoviral overexpression of PPARα induces several genes involved in fatty acid metabolism (23, 124, 161). However, the effects of PPARα ligands on myocardial target genes *in vivo* have been disappointing (75). PPARα ligands decrease cardiac FAO rates in diabetic mice (1, 2). PPARα, similar to fatty acid metabolism, may also display direct effects on the heart by inhibiting inflammation and collagen deposition resulting from AngII-induced hypertension. Clinically, PPARα activation may provide a cardioprotective effect against hypertension and hyperlipidemia. Furthermore, fenofibrate activation of PPARα may decrease hypertension-induced changes in mechanical overload that lead to ventricular hypertrophy (103).

PPARα ligands are known to have direct effects on mitochondrial function (180, 181). PPARα activators can differentially inhibit cardiac mitochondrial respiration. The attenuation of cardiac mitochondrial respiratory function is greater with the administration of fenofibrate compared with Wy-14,643 (413). This suggests a possible PPARα-independent effect because the Wy-14,643 compound has a higher PPARα affinity than does fenofibrate.

PPARα is regulated by hypoxia, as shown by the reduction in PPARα-dependent transcriptional activity of muscle carnitine palmitoyltransferase I, an enzyme involved in mitochondrial FAO. The DNA-binding activity of the PPARα:RXR heterodimer is reduced in hypoxic cardiomyocytes (161). Furthermore, myocardial hypoxia can decrease PPARα-dependent gene expression in two *in vivo* rat models (299). The level of PPARα mRNA, along with its target gene,

medium-chain acyl-CoA dehydrogenase, is decreased after 7 days in a model of hypoxia-induced right ventricular hypertrophy. However, these levels are upregulated at day 14, suggesting a compensatory response by the heart due to increased load. It is likely that part of the transcriptional response to hypoxia-induced right ventricular hypertrophy involves the regulation of PPARα by hypoxia in the early stages and, in the later stages, by increased load (323).

PPARα cardiac-specific transgenic mice were developed to discern between PPARα-induced cardiac effects and ligand-induced systemic effects (107, 108, 149, 284, 316). PPARα overexpression induces genes involved in cardiac fatty acid metabolism and utilization (108) while suppressing genes known to participate in glucose uptake and utilization (108, 284). Of great interest, these abnormalities are more prominent in mice that are insulin resistant or fed a high-fat diet (107), both of which are capable of elevating circulating lipids. It is likely that increased reliance of fatty acid utilization, along with the concomitant decrease in glucose utilization by the heart, may aggressively promote remodeling, leading to eventual cardiomyopathy. However, the mechanisms whereby altered fatty acid and glucose utilization result in cardiac remodeling are still unclear.

Although a cardiac-specific PPARα-knockout mouse model has yet to be characterized, murine models with generalized PPARα-ablated gene expression have been developed and are often used in examining PPARα function in cardiac energy metabolism and utilization (53, 93, 183, 205, 211, 229, 281, 381). Malonyl-CoA decarboxylase is an important regulator of cardiac fatty acid oxidation (77), and PPARα knockout mice have decreased malonyl-CoA decarboxylase gene expression (53). PPARα-null mice show decreased fatty acid oxidation rates (53, 93, 211, 381) along with increased glucose metabolism and oxidation (53, 281). As a result, it is possible that the alterations pertaining to the dependence on each fuel source in PPARα-deficient mice make it difficult for the heart to adapt to increase workloads (53, 229). Furthermore, increased ventricular afterload is improved in PPARα-knockout mice with GLUT1 overexpression (229), suggesting that glucose ATP production in PPARα-null mice may not be sufficient to meet the demands of greater cardiac workload. Moreover, because chronic pressure overload deactivates PPARα (134, 208), this model may be suitable for studies in cardiac metabolic dysfunction. PPARα activation can reduce cardiomyocyte hypertrophy, as fenofibrate decreases ET-1–induced neonatal rat cardiomyocyte enlargement (171, 220). A recent investigation with PPARα-knockout mice demonstrated greater cardiac hypertrophy after pressure overload in association with enhanced inflammatory marker expression (335), and the follow-up study asserts that PPARα and PPARδ inhibit inflammation and cardiac hypertrophy by suppressing NF-κB signaling (334).

XV. PPARδ

PPARδ is distributed ubiquitously in almost all tissues, including liver, fat, skeletal muscle, and skin, and differs from the other two PPAR isotypes. Several studies show that PPARδ has important roles in cell growth, differentiation, placenta growth, colon tumorigenesis, and wound healing (20, 289, 350). Recent studies focused on the effects of PPARδ regarding lipid metabolism and insulin sensitivity. PPARδ is expressed in the vascular system and displays essential regulatory roles in vascular biology.

PPARs, liver X receptors (LXRs), farnesoid X receptor (FXR), and krüpple-like factor (KLF) are transcription factors controlling lipid and glucose metabolism, as well as the inflammatory response. These transcription factors interact with each other and synergistically regulate gene expression. PPARδ overexpression influences the activity of PPARα and PPARγ in 3T3 fibroblasts and nontransformed monkey kidney CV-1 cells (329). PPARδ inhibits PPARγ activity by interfering with PPARγ DNA-binding activity and not PPARγ gene expression in colon cancer cells, which is identified by PPARδ knockout and gain-of-function approaches (414). LXR can bind to all three PPAR subtypes, and PPAR ligands can regulate LXR/PPAR interaction, as studied by SPR technology (402). LXR induces fatty acid synthesis, whereas PPARδ induces fatty acid oxidation. Moreover, the diverging effects of PPARδ and LXR on metabolic gene regulation are apparent because PPARδ represses the expression of the LXR target gene angpt13, and L-165041 enhances the inhibitory effect. The likely mechanism is that PPARδ competes with LXR for binding to RXR, and L-165041 increases the affinity between PPARδ and RXR (243). KLF5, a member of the KLF superfamily, is critical for regulation of adipocyte differentiation and energy metabolism (274). KLF5$^{+/-}$ heterozygous mice are not prone to high-fat diet–induced obesity, insulin resistance, and hypercholesterolemia. Under basal conditions, SUMOylated KLF5, unliganded PPARδ, and co-repressors form a transcription-repressor complex. Once PPARδ agonists activate PPARδ, KLF5 is deSUMOylated and associates with the transcription activation complex composed of liganded PPARδ and the CREB binding protein (273).

A. PPARδ ligands

PPARδ, on activation by ligands, regulates gene expression. For several years, highly selective PPARδ ligands were not known, and as a result, the progress in PPARδ research was hampered. Natural ligands, such as unsaturated fatty acids, eicosanoid derivatives, and prostaglandins, have binding affinity for PPARδ, although natural ligand selectivity tends to be low (389). cPGI activates both PPARδ and PPARα (221), whereas retinoid acid activates both RAR and PPARδ without activating PPARα and PPARγ (324). As a result, synthetic ligands were developed to widen this research scope. L-796449, L-165461, and L-783483 have high affinity for PPARδ, but also to PPARγ, whereas L-165041 has a high affinity for only PPARδ (30). Both GW501516 and GW0742 are widely used and are 1,000 times more selective for PPARδ compared with PPARα and PPARγ. The EC_{50} of PPARδ transactivation is $1 \sim 2\,nM$ (345). PPARδ and RXR form an obligatory heterodimer and recruit co-repressors such as BCL-6 and SMART to form a transcription complex that binds to the gene-promoter PPRE. Once ligand activated, co-repressors dissociate from the complex, and coactivators such as p300 and SRC-1 bind to the complex, transactivating target gene expression. Recently, Shearer *et al.* (326) identified GSK0660 as a potent antagonist of PPARδ with a binding assay IC_{50} of $\sim 160\,nM$. However, GSK0660 is inactive on PPARα and PPARγ, with IC_{50} levels above $\sim 10\,\mu M$. This antagonist will be useful for elucidating the biologic roles of PPARδ (326).

B. PPARδ and endothelial cells

Endothelial dysfunction is characterized by endothelial proinflammatory, procoagulant, and profibrotic states. Impaired endothelial cell permeability, together with the previous clinical entities, is a marker of early-stage atherosclerosis. Endothelial activation is induced by several risk factors, including LDL/oxLDL, hypercholesterolemia, hyperglycemia, and cytokines (TNF-α, IL-1β), which promote increased adhesion molecule expression and ensuing leukocyte–endothelial adhesion. L-165041 inhibits TNF-α–induced MCP-1 secretion and VCAM-1 expression in the EAhy926 cell line (311). Both GW0742 and GW501516 have potent antiinflammatory effects in endothelial cells (Fig. 12), inhibiting inflammatory cytokine (TNF-α and IL-1β)-induced adhesion molecule expression and ensuing leukocyte–endothelial adhesion in primary HUVECs. The mechanisms of PPARδ antiinflammatory effects involve the attenuation of oxidative stress through the upregulation of antioxidant genes catalase, CuZn superoxide dismutase, and thioredoxin, as well as control of BCL-6 co-repressor translocation to proinflammatory genes (105).

In endothelial cells, ligand activation of PPARδ increases human endothelial cell proliferation and angiogenesis *via* upregulating VEGF expression and release (290). Next, PPARδ activation by either PGI2 or L-165041 inhibits H_2O_2-induced EC apoptosis *via* upregulation of 14-3-3 epsilon (226). L-165041 and GW501516 activate the 14-3-3 gene YWHAE promoter, increasing 14-3-3 expression in a C/EBP-dependent manner, and not in a PPRE-dependent fashion. PPARδ regulates expression of C/EBP and forms a transcriptional complex with C/EBP in ECs (45). PPARδ activation stimulates proliferation and attenuates apoptosis in EPCs through phosphorylated Akt-dependent signaling. These effects promote enhanced vasculogenesis and may be therapeutically beneficial in the treatment of ischemic cardiovascular disease (144).

C. PPARδ and VSMCs

PDGF, a neointimal stimulator, induces PPARδ expression *via* the PI3-kinase/Akt pathway in VSMCs (410). *In vivo* data show that PPARδ is upregulated during the development of vascular lesion formation (410). Overexpression of PPARδ in VSMCs increases post-confluent cell proliferation (Fig. 12) by modulating cell-cycle checkpoint genes including cyclin A, cdk2, and p57(Kip2) (410). The suppression of PPARδ expression may mediate the inhibitory effects of prostacyclin synthase on neointimal formation (166). However, the role of PPARδ in VSMCs is not yet agreed on. Recently, Lim *et al.* (222) reported that L-165041 suppresses rat VSMC proliferation by inhibiting phosphorylation of the retinoblastoma protein and cell-cycle progression. *In vivo* data show that L-165041 attenuates neointima formation in the carotid artery balloon injury model. GW501516 also dose-dependently suppresses TNF-α–induced VSMC proliferation (184). PPARδ receptors and agonists may play different roles in VSMC proliferation, accounting for the seemingly inconsistent results. TGF-β1, known as a potent regulator in the pathogenesis of atherosclerosis and restenosis, is upregulated by PPARδ in VSMCs as a target gene. GW501516 inhibits IL-1β–induced MCP-1 expression, which is mediated by TGF-β1 and its effector, Smad3. The expression of TGF-β1 is upregulated, and proinflammatory genes are suppressed in the thoracic aorta prepared from GW501516-treated mice. Thus, it is apparent the PPARδ/TGF-β/MCP-1 pathway stimulates PPARδ antiinflammatory signaling mechanisms (184).

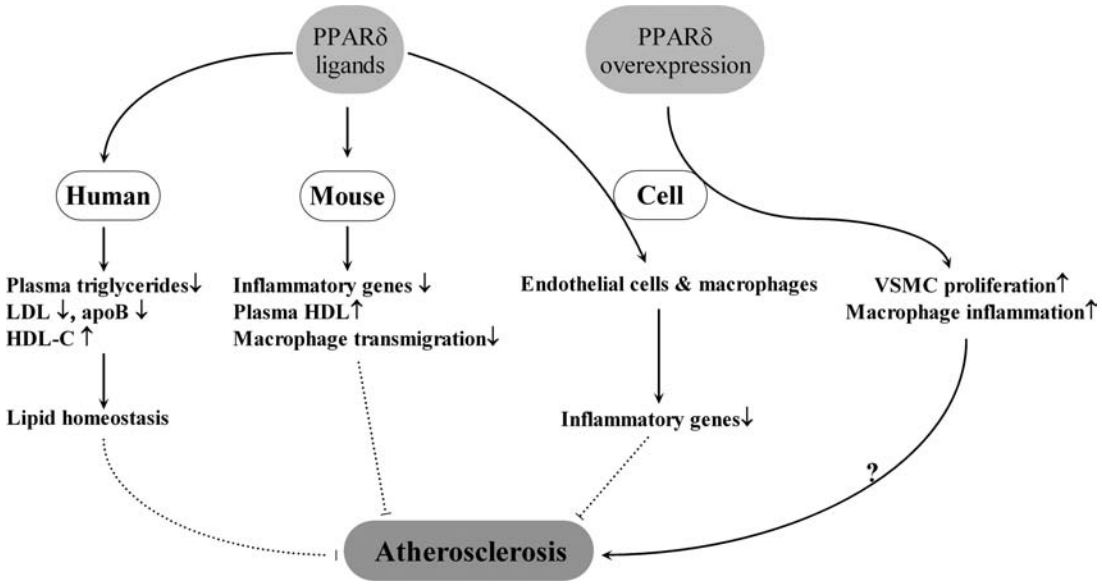

FIG. 12. Schematic view of PPARδ roles in atherosclerosis. PPARδ ligands are beneficial against the development of atherosclerosis by regulating lipid homeostasis in humans. PPARδ ligands attenuate the development of atherosclerosis in mice by decreasing inflammatory gene expression and macrophage migration while increasing plasma HDL. Inhibition of EC and macrophage inflammatory gene expression by PPARδ ligands prevents the development of atherosclerosis. However, PPARδ overexpression stimulates VSMC proliferation and macrophage release of inflammatory factors, which may promote atherosclerotic development.

D. PPARδ and monocytes/macrophages

Macrophage inflammation and lipid dysfunction are involved in the pathogenesis of atherosclerosis. PPARδ regulates lipid metabolism in macrophages. VLDL activates expression of genes involved in β-oxidation, thermogenesis, lipid mobilization, and carnitine biosynthesis through PPARδ-dependent signaling. Knocking out PPARδ has the same effect as PPARδ agonists on fatty acid utilization in macrophages, indicating that the endogenous unliganded PPARδ receptor has an inhibitory effect on lipid oxidation (202). GW501516 increases ABCA1 expression and induces apolipoprotein A1–specific cholesterol efflux in macrophages (276). However, different results are achieved in primary human macrophages and THP-1 human monocytes with compound F. Compound F upregulates genes related to lipid accumulation and downregulates genes involved in lipid efflux and metabolism. Both compound F and PPARδ overexpression promote lipid accumulation in macrophages (371). Alternatively, activated macrophages are believed to improve the metabolic syndrome although the mechanism of modulating alternative activation of tissue macrophages is still unclear. Adipocyte-derived Th2 cytokines IL-13 and IL-4 induce macrophage PPARδ expression. Both adipose tissue and liver-resident macrophages are activated to the alternative phenotype by PPARδ, and this switch is beneficial for fatty acid metabolism and improves insulin sensitivity (177, 268).

The removal of PPARδ leads to downregulation of MCP-1 and IL-1β expression, attenuating macrophage proinflammatory responses. Overexpression of PPARδ enhances the inflammatory response, suggesting that endogenous PPARδ has a proinflammatory effect in macrophages (Fig. 12). However, similar to endothelial cells, PPARδ agonists have a potent inhibitory effect on macrophage inflammation (Fig. 12). GW0742 inhibits LPS-induced expression of inflammatory genes *iNOS* and *COX-2* in macrophages (382). Ligand-activated PPARδ regulates the translocation of nuclear repressor BCL-6 to inflammatory genes and controls the inflammatory switch in a ligand-dependent manner (201). Graham *et al.* (141) reported that GW0742X decreases TNF-α expression in peritoneal macrophages and adipose tissue.

Foam cell and subsequent fatty-streak formation play critical roles in atherogenesis. LDL/oxLDL induces macrophage differentiation into foam cells, in which many genes likely modulate the transformation process. One such example may include the regulation of scavenger-receptor expression by the PPAR family. Both compound F administration and overexpression of PPARδ stimulate PMA-induced macrophage differentiation (370).

E. PPARδ and atherosclerosis

A deteriorated plasma lipoprotein profile directly affects vascular function. Elevated plasma levels of low-density lipoproteins (LDLs) increase the risk of atherosclerosis. Conversely, the increase of HDLs has a cardiovascular protective effect. Very low density lipoproteins (VLDLs) and their triglyceride components regulate gene expression *via* activation of PPARδ in macrophages (58). Accumulating evidence demonstrates that PPARδ regulates lipid metabolism in metabolically active tissues. Adipose tissue–specific activated PPARδ protects against obesity and induces expression of genes required for fatty acid oxidation and energy uncoupling. Adipose-specific PPARδ transgenic mice also show improved overall lipid profiles and reduced plasma triglyceride levels (379), demonstrating a possible atheroprotective effect. GW501516 increases HDL levels and decreases small dense LDL, triglycerides, and insulin in insulin-resistant middle-aged obese rhesus monkeys (276). In St. Kitts vervet atherosclerotic primate models, GW501516 increases plasma HDL-C, apoA-I, and apoA-II concentrations, demonstrating protective effects of PPARδ on the cardiovascular system (375). However, considerably less is known about the function of PPARδ on lipid homeostasis in humans.

In vivo results also were observed in human subjects. A clinical study performed in healthy white normolipidemic male subjects showed that plasma triglyceride and LDL levels significantly decline, whereas HDL-C levels are enhanced after 2 weeks of GW501516 administration (339) (Fig. 12). Consistently, Riserus *et al.* (310) reported that GW501516 treatment significantly reduces plasma triglycerides, apoB, and LDL cholesterol in healthy moderately overweight subjects (Fig. 12). Presently, laboratory and clinical studies indicate that lowering lipid levels can be achieved by administering PPARδ agonists, resulting in improved lipid homeostasis (Fig. 12). With regard to its genetic basis, the lipid-regulating function of PPARδ is associated with gene polymorphisms (333). Plasma HDL-C levels are elevated in the PPARδ exon 4 + 15 C/C and exon 7 + 65 G/G genotypes of healthy white subjects with exposure to endurance training compared with those with other genotypes (150).

The role of PPARδ in atherosclerosis has been identified in an atherosclerotic animal model. PPARδ$^{-/-}$ bone marrow transplanted into γ-irradiated LDL-R$^{-/-}$ mice significantly reduced atherosclerosis lesions, likely as a result of the attenuated inflammatory status of macrophages (201). Li *et al.* (214) reported that PPARδ agonist GW0742 has no effect on atherosclerotic lesions, whereas PPARα and PPARγ agonists strongly inhibit atherosclerosis in hypercholesterolemic diet–fed LDL-R$^{-/-}$ mice. However, PPARδ agonists inhibit inflammatory gene expression (Fig. 12), including IFN-γ, TNF-α, MCP-1, VCAM-1, and ICAM-1 in atherosclerotic lesions (214). It is likely that the antiinflammatory effect of PPARδ may not reverse the proatherogenic impact of extreme hypercholesterolemia in this animal model. Treatment with GW0742X reduces atherosclerotic lesions in LDL-R–null mice and decreases MCP-1 and ICAM-1 expression in the aorta (141). In the apoE$^{-/-}$ mouse atherosclerotic model, treatment with GW501516 attenuates atherosclerotic lesion formation through multiple pathways, which may include increases in plasma HDL levels, potent antiinflammatory effects, and suppression of macrophage transmigration (Fig. 12). PPARδ inhibits the chemokines-receptor signaling pathway by increasing the expression of regulator of G-protein signaling (RGS) genes (25). In the AngII-accelerated atherosclerotic model, GW0742 attenuates AngII-induced atherosclerotic lesion formation. GW0742 increases the expression of BCL-6, RGS4, and RGS5 in the vascular wall, which inhibits inflammatory and atherogenic gene expression (348). In agreement with several *in vitro* studies, these *in vivo* data support an atheroprotective role of PPARδ agonists (Fig. 12).

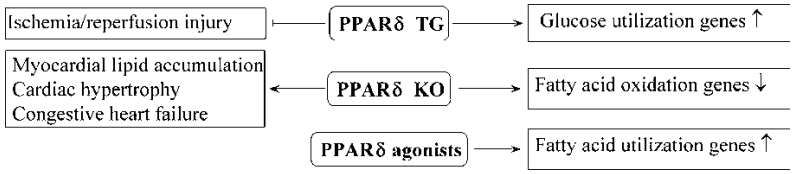

FIG. 13. Schematic view of PPARδ roles in the heart. PPARδ ligands increase myocardial fatty acid utilization genes. Cardiac-specific PPARδ-knockout mice have decreased myocardial expression of fatty acid oxidation genes along with increased myocardial lipid accumulation, cardiac hypertrophy, and congestive heart failure. Myocardial PPARδ overexpression in mice increases expression of genes involved in glucose utilization, which may prevent further injury after ischemia/reperfusion.

F. PPARδ and the heart

PPARδ activation by GW0742 increases palmitate oxidation in neonatal and adult cardiomyocytes, meanwhile upregulating the expression of fatty acid oxidation genes (61) (Fig. 13). Consistently, the expression of key fatty acid oxidation genes (mCPT1, ACOX1, UCP3) and also basal myocardial FAO rates decrease in cardiomyocyte-specific PPARδ-knockout mice (60) (Fig. 13). Cardiac-specific overexpression of PPARδ increases the expression of GLUT4 and phosphofructokinase, a glycolytic gene, promoting myocardial glucose utilization, which may contribute to reduced myocardial injury after ischemia/reperfusion (46) (Fig. 13). GW610742X increases fatty acid oxidation after myocardial infarction in both left and right ventricles, along with the upregulation of PPARδ metabolic target gene expression, such as CD36, CPT1, and UCP3 (176). These studies suggest PPARδ increases fatty acid oxidation and related gene expression, providing a physiological benefit for metabolic-related heart disease.

Inflammatory responses are involved in the pathophysiologic processes of ischemia/reperfusion, hypertrophy, and fibrosis. Much evidence suggests that PPARα and PPARγ suppress myocardial inflammatory responses. PPARδ attenuates LPS-induced expression of TNF-α through inhibition of NF-κB in cultured cardiomyocytes (90). PPARδ interacts with the p65 NF-κB subunit, inhibiting the LPS-induced NF-κB signaling pathway and decreasing MCP-1 expression in rat cardiomyocytes (293). Furthermore, GW0742 reduces cardiac expression of IL-6, IL-8, MCP-1, and ICAM-1, which are induced by ischemia/reperfusion (403).

Progressive myocardial lipid accumulation and hypertrophy occur in cardiomyocyte-specific PPARδ-knockout mice (Fig. 13). The function of the PPARδ-null heart is impaired, characterized by a decrease in rates of contraction and relaxation, decreased cardiac output, and increased left ventricular end-diastolic pressure (60) (Fig. 13). GW0742X reduces right ventricle hypertrophy and lung congestion (176). Furthermore, PPARδ activation by L-165041 inhibits phenylephrine-induced protein synthesis and increases carnitine palmitoyltransferase and pyruvate dehydrogenase kinase 4 expression in cultured rat cardiomyocytes (293).

GW501516 inhibits proliferation of cardiac fibroblasts and myofibroblasts and also suppresses differentiation of fibroblasts into myofibroblasts (354). Collagen accumulation is involved in myocardial fibrosis, and GW501516 attenuates AngII-stimulated collagen synthesis in cardiac fibroblasts (354, 408).

PPARδ is critical for maintaining normal fatty acid oxidation and energy balance in the heart (60), suggesting that PPARδ and its ligands may be important for cardiac function, distribution of muscle fiber type, and endurance performance (60, 150). PPARδ overexpression or activation may be a contributing factor to increasing endurance and may mimic the effects of exercise on muscle metabolism (102, 119). PPARδ and its ligands have been shown to improve exercise performance and regulate physical endurance and training in skeletal muscle (380). Conversely, exercise has been shown to promote skeletal muscle PPARδ accumulation in murine animal models (230). The possibility exists whereby increased exercise may activate PPARδ by facilitating the internalization of certain fatty acids that act as ligands (380). Another possibility is that exercise increases PPARγ coactivator-1α (PGC-1α) expression (137), and PGC-1α binding to PPARδ can potently activate this transcription factor, irrespective of the presence of ligands (379). Furthermore, plasma HDL-C levels are higher in the PPARδ exon 4 + 15 C/C and exon 7 + 65 G/G healthy white genotypes with endurance training compared with other genotypes (150), and PPARδ agonist administration increases plasma HDL-C concentrations in various animal models (210, 276, 375). One explanation may be that increased availability of free fatty acids due to exercise activates PPARδ and promotes reverse cholesterol transport (150). Finally, a recent study demonstrated that GW501516 and exercise training work synergistically to increase running endurance (256). These studies have important cardiovascular significance because running performance in humans appears to be linked more to cardiovascular performance and not to muscle fiber–type distribution (304).

In summary, although all three PPAR isotypes are involved in the metabolic syndrome and cardiovascular disease, evidence suggests that PPARδ is different from the other two subtypes. The PPARδ receptor and agonists can sometimes show distinct modes of action. PPARδ can repress both PPARγ and PPARα target gene activity, and PPARδ repression is likely PPRE dependent (329). PPARδ improves the metabolic syndrome and cardiovascular activity through potent antiinflammatory effects and regulation of lipid and glucose metabolism. To date, several studies indicate that PPARδ is a potential therapeutic target for treatment of the metabolic syndrome and cardiovascular diseases, including atherosclerosis and cardiac hypertrophy. PPARδ appears to act as a "housekeeper" because of its near-ubiquitous expression. Therefore, it is critical for PPARδ to be further examined regarding its effects on metabolism and the various tissues related to metabolic function.

XVI. Perspective

PPARs have now been firmly entrenched as key players in the cardiovascular system. During the past decade, considerable evidence has been accumulated regarding the role of peroxisome proliferator–activated receptors in cardiovascular diseases and clinical complications related to cardiovascular

abnormalities. PPARs regulate several cell-signaling mechanisms related to cardiovascular health and disease. A continuing need exists for basic science and clinical investigations to understand fully the role of PPAR in the physiology and pathology of cardiovascular-related diseases. Thus, it is important to gain a better understanding of the regulatory role of PPARs in vascular cells and the heart.

TZDs and fibrates are pharmacologic agents that have pleiotropic effects, many of which are beneficial in alleviating cardiovascular abnormalities in animal models. However, this has not necessarily translated into markedly improved clinical cardiovascular outcomes. This may be because of differences in both uptake and effects on target pathways between various animal species and humans. In addition, increasing evidence shows that several beneficial PPAR agonist effects are not from direct participation of PPAR-signaling pathways. No definitive evidence indicates that activated PPARγ pathways are critical for the beneficial effects of TZDs in the cardiovascular system. Moreover, greater evidence exists that ligand-activated PPAR signaling may play a role in the witnessed pharmacologic side effects of TZDs.

Hence, dual PPAR agonists were generated to circumvent this problem and simultaneously to activate two PPAR isoforms. However, the administration of dual PPAR agonists in the clinical setting has been somewhat disappointing because of increased risks for cardiovascular events. Selective PPAR modulators (SPPARMs) were developed to find newer, safer, and more effective agonists and have been shown to improve the overall clinical profile. The possibility that cardiovascular diseases in patients may be the result of depleted endogenous PPAR ligand concentrations must also be considered. Furthermore, a need exists to conduct a greater number of studies on the role of PPAR antagonists in the cardiovascular system.

The development of animal model systems specifically for studying PPARs and PPAR agonists has led to greater increases in information regarding the mechanisms of these nuclear transcription factors in the cardiovascular system. Because global deletion of PPAR is embryo-lethal, the use of conditional knockout mice (*e.g.*, ECs, VSMCs, macrophages) has been critical to understanding the development of human cardiovascular diseases. Nonetheless, limitations are found in using the mouse model. Genetically modified mice often do not show characteristics evident of the human phenotype. Thus, we need more suitable animal models that may correct for many, if not all, of these characteristics. The use of genetically modified rabbits, pigs, or monkeys may be more appropriate for studying the effects of PPARs and their agonists in the cardiovascular system and for providing a clearer understanding of the pathophysiology of cardiovascular diseases (Fig. 14).

Finally, although previous studies have successfully targeted PPAR for deletion in cardiovascular cells, the possibility of PPAR cell–cell crosstalk should not be overlooked in the cardiovascular system. For example, does VSMC PPARγ affect function in PPARγ-null ECs and *vice versa*? The ability to gain a better understanding of PPARs and agonists in the cardiovascular system will enable us to address the controversy regarding the subsequent administration of pharmacologic agents that not only activate PPAR pathways, but may also have PPAR-independent effects.

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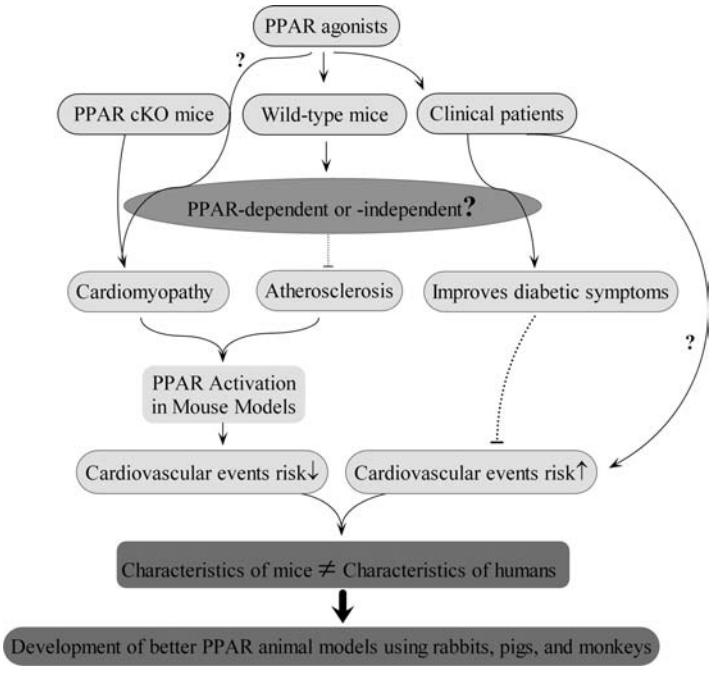

FIG. 14. Perspective view of PPARs and PPAR ligands in the cardiovascular system. The use of mouse models has shown that PPAR ligands have many beneficial effects in the cardiovascular system. However, PPAR ligand administration (*e.g.*, rosiglitazone) in the clinical setting has not necessarily translated into markedly improved cardiovascular outcomes. Furthermore, some question exists as to whether the beneficial effects of PPAR agonists involve PPAR-dependent signaling. Although the development of animal model systems specifically for studying PPAR agonists and PPAR gain- and loss-of-function has elucidated important findings regarding the molecular mechanisms of cardiovascular disease, certain limitations pertain to the use of mouse models. In many cases, genetically altered murine models do not display characteristics similar to those of humans. Hence, a need exists for using genetically modified animals, such as rabbits, pigs, or monkeys, that have a closer phenotypic resemblance to humans and therefore may be more appropriate for studying PPARs and PPAR agonists in the cardiovascular system.

Abbreviations

4E-BP1, 4E-binding protein 1; 15d-PGJ_2, 15-deoxy-δ 12,14-prostaglandin J_2; ABC, ATP-binding cassette; AGP, 1-*O*-octadecenyl-2-hydroxy-*sn*-glycero-3-phosphate; AngII, angiotensin II; AP-1, activator protein-1; APC, angiogenic progenitor cell; $apoE^{-/-}$, apo E knockout; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; azPC, 1-*O*-hexadecyl-2-azelaoyl-*sn*-glycero-3-phosphocholine; BADGE, bisphenol A diglycidyl ether; bFGF, basic fibroblast growth factor; CARLA, coactivator-dependent receptor ligand assay; CBP, CREB-binding protein; CCR2, chemokine receptor 2; C/EBP, CCAAT/enhancer-binding protein; CPT-1, carnitine palmitoyltransferase type 1; CTGF, connective tissue growth factor; ECs, endothelial cells; Egr-1, early growth response-1; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; ERK 1/2, extracellular signal regulated kinase 1/2; ET-1, endothelin-1; FAO, fatty acid oxidation; FATP-1, fatty acid transport protein-1; FRET, fluorescence resonance energy transfer; FXR, farnesoid X receptor; FOXO, forkhead-box class O; GLUT1, glucose transporter 1; GLUT4, glucose transporter 4; GM-CSF, granulocyte–macrophage colony-stimulating factor; HASMCs, human aortic smooth muscle cells; HDAC-3, histone deacetylase-3; HDL, high-density lipoprotein; HETE, hydroxyeicosatetraenoic acid; HO-1, heme-oxygenase 1; HODE, hydroxyoctadecadienoic acid; HUVECs, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IFN-γ, interferon-gamma; IGF, insulin-like growth factor; IκBα, IkappaB-alpha; IKK, IkappaB kinase; IL, interleukin; IL-1β, interleukin-1beta; IL-1Ra, IL-1 receptor antagonist; iNOS, inducible nitric oxide synthase; IP-10, IFN-inducible protein of 10 kDa; IRF-1, interferon regulatory factor; I-TAC, IFN-inducible T-cell α-chemoattractant; KLF, krüpple-like factor; LDL, low-density lipoprotein; $LDL\text{-}R^{-/-}$, low-density lipoprotein receptor knockout; LNO_2, nitro-9,12-*cis*-octadecadienoic acid; LPA, lysophosphatidic acid; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LTB4, leukotriene B4; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; MCM, minichromosome maintenance protein; MCP-1, monocyte chemoattractant protein-1; MHC-II, major histocompatibility complex class II; Mig, monokine induced by IFN-γ; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; N-CoR, nuclear receptor co-repressor; NF-κB, nuclear factor-kappa B; NO, nitric oxide; NPC, Niemann-Pick, type C; OA-NO_2, nitro-9-*cis*-octadecenoic acid; OPG, osteoprotegrin; OPN, osteopontin; oxLDL, oxidized LDL; PAF, platelet-activating factor; PAI-1, plasminogen activator inhibitor type-1; PDGF, platelet-derived growth factor; PECAM-1, platelet–endothelial cell adhesion molecule; PGC-1α, PPARγ coactivator-1α; PKC, protein kinase C; PLA, phospholipase A2; PPAR, peroxisome proliferator-activated receptor; PPARα, PPARalpha; PPARβ/δ, PPARbeta/delta; PPARγ, PPARgamma; PPARγ E null, endothelial cell PPARgamma knockout; PPRE, peroxisome proliferator response element; PTEN, phosphatase and tensin homologue; Rb, retinoblastoma protein; RGS, regulator of G-protein signaling; RXR, retinoic X receptor; SHIP2, Src homology (SH) 2–containing inositol phosphatase 2; SHP-2, Src homology region 2–containing protein tyrosine phosphatase-2; SHRs, spontaneously hypertensive rats; SM-α-actin, smooth muscle alpha-actin; SM-MHC, smooth muscle myosin heavy chain; SPA, scintillation proximity assay; sPLA2-II2, secretory phospholipase A2; SPPARMs, selective PPAR modulators; SPR, surface plasmon resonance; SR-A, scavenger receptor A; SR-B, scavenger receptor B; STAT, signal transduction and activator of transcription; TERT, telomerase reverse transcriptase; TF, tissue factor; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; TZD, thiazolidinedione; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VLDLs, very low density lipoproteins; VSMCs, vascular smooth muscle cells.

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Address reprint requests to:
Y. Eugene Chen, M.D., Ph.D.
Cardiovascular Center
Department of Internal Medicine
University of Michigan Medical Center
1150 W. Medical Center Drive
Ann Arbor, MI 48109

E-mail: echenum@umich.edu

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