PPARadigms and PPARadoxes: expanding roles for PPARγ in the control of lipid metabolism

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Abstract The nuclear receptor PPARγ is a central regulator of adipose tissue development and an important modulator of gene expression in a number of specialized cell types including adipocytes, epithelial cells, and macrophages. PPARγ signaling pathways impact both cellular and systemic lipid metabolism and have links to obesity, diabetes, and cardiovascular disease. The ability to activate this receptor with small molecule ligands has made PPARγ an attractive target for intervention in human metabolic disease. As our understanding of PPARγ biology has expanded, so has the therapeutic potential of PPARγ ligands. Recent studies have provided insight into the paradoxical relationship between PPARγ and metabolic disease and established new paradigms for the control of lipid metabolism. This review focuses on recent advances in PPARγ biology in the areas of adipocyte differentiation, insulin resistance, and atherosclerosis.—Walczak, R., and P. Tontonoz. PPARadigms and PPARadoxes: expanding roles for PPARγ in the control of lipid metabolism. J. Lipid. Res. 2002. 43: 177–186.

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The past 10 years have seen a new paradigm emerge for the transcriptional regulation of metabolic pathways with the discovery of the peroxisome proliferator-activated receptors (PPARα, PPARγ, and PPARδ), a trio of nuclear receptors activated by lipids. Characterization of PPARs led to the realization that certain nuclear receptors have evolved to recognize specific metabolic intermediates in the pathways that they control. Unlike the steroid receptors, which bind a single high affinity ligand, PPARs have the ability to recognize a range of structurally diverse molecules. The importance of this property became clear when it was discovered that the physiologic activators of these receptors are likely to be native and modified polyunsaturated fatty acids. Thus, the PPARs are transcription factors that regulate expression of genes involved in lipid metabolism, and the physiologic ligands for these receptors are lipids themselves.

PPARγ was originally identified as a central regulator of gene expression and differentiation in adipose cells (1). It has subsequently been shown to regulate differentiation-linked gene expression in several other tissues as well, including breast, colon, prostate, and macrophages. PPARγ signaling pathways are now recognized to be involved in the control of lipid uptake, transport, storage, and disposal. PPARγ binds to DNA as an obligate heterodimer with the retinoid X receptor (RXR). Naturally occurring ligands for PPARγ include native and oxidized polyunsaturated fatty acids and prostanoids such as 15-deoxy-Δ12,14-prostaglandin J2 (2–4). The thiazolidinedione (TZD) antidiabetic drugs have also been shown to be potent and selective ligands for PPARγ, linking PPARγ transcriptional activity to insulin sensitivity and glucose homeostasis (2, 5). Two glitazones, rosiglitazone (Avandia) and pioglitazone (Actos), are widely used for the treatment of type 2 diabetes.

PPARγ AND ADIPOCYTE DIFFERENTIATION

A dominant regulator of adipocyte differentiation

Advances in our understanding of lipid metabolism have identified the adipocyte as a central player in the control of energy balance and whole body lipid homeostasis. Storage and release of fatty acids and glycerol from the adipocyte impact overall lipid homeostasis as well as hepatic and peripheral glucose metabolism. Adipocytes also perform an important endocrine function by secreting numerous cytokines, bioactive peptides, and complement factors. Upon secretion into the bloodstream, adipocyte-derived signaling molecules act at distant sites to regulate energy homeostasis. PPARγ functions as a key modulator of lipid homeostasis, both through its ability to promote

Abbreviations: BAT, brown adipose tissue; FATP, fatty acid transport proteins; FIAF, fasting induced adipose factor; LXR, liver X receptor; NIDDM, non-insulin-dependent diabetes mellitus; oxLDL, oxidized LDL; PDK4, pyruvate dehydrogenase kinase 4; PGAR, PPARγ angiopoietin related; TZD, thiazolidinedione; RXR, retinoid X receptor; SHR, spontaneously hypertensive rat; WAT, white adipose tissue.

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adipocyte differentiation, and its ability to influence the production of secreted mediators.

Studies over the past 7 years have identified PPARy as a dominant regulator of adipogenesis (1, 6). PPARy cooperates with other transcription factor families including the C/EBPs and SREBPs, to regulate adipocyte differentiation. Together, these transcription factors effect the complex changes in gene expression necessary for the development of the functional adipocyte. The interplay of transcription factor families in the regulation of adipose tissue differentiation has been the subject of recent comprehensive reviews (1, 7–9).

Much of our understanding of the transcriptional regulation of adipose tissue development has evolved from experiments with cultured cell lines. PPARy is induced during the conversion of preadipocytes to adipocytes, and is highly expressed in both white and brown adipose tissue (10). Ectopic expression of the nuclear receptor PPARy in fibroblasts results in expression of adipose specific genes and intracellular accumulation of lipid droplets, features that are specific for mature white adipocytes (11). These early observations have been supported by recent studies showing that PPARy mutants with dominant negative activity inhibit adipogenesis in cultured preadipocytes (12, 13).

Since homozygous inactivation of the PPARy gene in mice results in placental insufficiency and embryonic lethality (14), genetic proof of the importance of PPARy function for adipose tissue development has required some creative approaches. Barak and colleagues utilized a tetraploid-rescue approach to generate a single PPARy null pup that survived to term. This PPARy null pup completely lacked both white and brown adipose tissue and showed profound hepatic steatosis, consistent with other models of lipoatrophy (14). In addition, several laboratories have shown that embryonic fibroblasts derived from PPARy−/− fetuses fail to differentiate into adipocytes in vitro (14, 15). Rosen et al. demonstrated that mice chimeric for wild-type and PPARy null cells show little or no contribution of null cells to adipose tissue, despite the ability of these cells to contribute to the formation of other tissues (16). Finally, results obtained from murine models have also been supported by limited human studies. Several groups have identified gain of function mutations in PPARy that appear to correlate with severe obesity and/or hyperlipidaemia in different populations (17–19).

PPARy, PGC-1, and brown adipose tissue function

Although PPARy has been most extensively studied in models of white adipose tissue (WAT) differentiation, this same nuclear receptor is also important for brown adipose tissue (BAT) development and function. While the function of white adipocytes is to store energy in the form of triglycerides, brown adipocytes are specialized to dissipate energy in the form of heat. The thermogenic properties of brown adipocytes are conferred by the tissue-specific protein UCP-1, a mitochondrial proton transporter that uncouples respiration from oxidative phosphorylation. PPARy is abundantly expressed in both embryonic and adult BAT (10, 14). Treatment of CD-1 rats with the PPARy selective ligand rosiglitazone results in marked increases in the mass of interscapular BAT (20). In vitro, the same ligand induces terminal differentiation of the brown preadipocyte cell line HIB-1B as well as expression of UCP-1 and other adipocyte-specific genes. Sears and colleagues have identified a PPARy response element in the enhancer region of UCP-1 promoter that appears to be important to its tissue-specific regulation (21).

An interesting feature of UCP-1 regulation by PPARy is a requirement for a specific coactivator protein, called PGC-1 (22). PGC-1 mRNA expression is dramatically elevated upon cold exposure of mice in brown fat and skeletal muscle, key thermogenic tissues. Ectopic expression of PGC-1 in white adipocytes stimulates expression of UCP-1 and mitochondrial enzymes of the respiratory chain, increases oxygen consumption, and increases the cellular content of mitochondrial DNA (23). Treatment of cultured human primary preadipocytes with rosiglitazone has also been reported to stimulate UCP-1 expression, presumably because there are brown adipocytes in these cultures (24). Together these data demonstrate that PPARy and its transcriptional cofactors are important not only for the storage of excess energy in WAT but also for energy dissipation in BAT.

PPARy as an adipocyte transcription factor

To date, only a limited number of genes are known to be direct targets of PPARy in adipose tissue. The majority of these encode proteins with direct links to lipid metabolism, including the adipocyte specific fatty acid binding protein aP2, lipoprotein lipase, the fatty acid transport proteins (FATP) and CD36, adipophilin, long chain acyl-CoA synthase, phosphoenolpyruvate carboxykinase, and liver X receptor α (LXRα) (1, 25). However, target gene searches have also identified a number of novel molecules, including the secreted molecules fasting induced adipose factor (FIAF)/PPARγ-interacting protein (26, 27), and resistin (28–30). Recently, IRS-2 gene expression was also reported to be induced in 3T3-L1 adipocytes and human primary adipocytes in response to TZDs (31). Whether or not these newly identified PPARy-regulated genes are direct targets is still under investigation.

PPARy AND INSULIN RESISTANCE

PPARy ligands regulate systemic lipid and glucose homeostasis

Insulin resistance is a common feature of obesity, non-insulin-dependent diabetes mellitus (NIDDM), and lipodystrophy. Although the role of PPARy in adipocyte development suggested a possible connection between PPARγ activity and insulin sensitivity, the discovery that PPARy is the biologic target for the thiazolidinediones class of antidiabetic drugs provided the first definitive link (2, 5, 32, 33). The discovery that TZDs are PPARγ ligands presented a paradox because of the correlation of obesity and insulin resistance. These drugs stimulate adipocyte differentiation in vitro and in vivo, yet lower glucose and improve
lipid profiles in type 2 diabetics. Further evidence for a connection between PPARγ and insulin sensitivity has come from studies of human populations. PPARγ polymorphisms and dominant negative mutations have been associated with metabolic syndrome features such as hyperlipidemia, obesity, severe insulin resistance, diabetes mellitus, and hypertension (18, 19, 34).

Many labs have been working to decipher the mechanism by which PPARγ ligands modulate systemic lipid metabolism and insulin sensitivity. One plausible model for the role of adipose tissue in systemic insulin resistance postulates a critical role for FFA. According to this model, insulin resistance is caused, at least in part, by alterations in partitioning of FFA between the adipose tissue, skeletal muscle, and liver (35). This imbalance results in intracellular accumulation of triglycerides and fatty acid metabolites in muscle and liver. A number of studies support the concept that TZDs reduce circulating FFA levels and improve insulin sensitivity in muscle and liver due to promotion of adipocyte differentiation and FFA uptake. Identification of the fatty acid transporters FATP and CD36 as PPARγ targets provided a straightforward mechanism by which PPARγ ligands may promote selective FFA uptake into adipose tissue (36–38). In fact, the CD36 gene was independently identified as a determinant of insulin resistance in the spontaneously hypertensive rat (SHR) model (39).

Comprehensive gene profiling studies have provided additional insight into the mechanism of action of PPARγ agonists. Administration of a highly potent and selective PPARγ agonist (GW1929) to rats revealed increased expression of genes involved in lipogenesis, fatty acid transport, lipid storage, and oxidation in both WAT and BAT (40). By contrast, a marked decrease was observed in the expression of a number of genes involved in fatty acid transport and oxidation in skeletal muscle, even though some of these genes are established PPAR targets in other tissues. These findings are consistent with the hypothesis that PPARγ can improve insulin action by stimulating adipogenesis as well as the uptake and oxidation of fatty acids by adipose tissue. Interestingly, Way and colleagues also observed a marked decrease in expression of pyruvate dehydrogenase kinase 4 (PDK4) in GW1929 treated animals (40). PDK4 is a potent repressor of oxidative glucose metabolism in muscle, and its activity leads to TG accumulation. These authors speculate that the effects of GW1929 on the expression of PDK4 and other genes in muscle are likely to be secondary to changes in circulating FFA concentrations. The fact that no genes were induced in muscle in response to GW1929 in these studies, the fact that PPARγ is not a transcriptional repressor, and the low level of PPARγ expression in skeletal muscle collectively suggest that changes in muscle gene expression are secondary to direct effects in other tissues. A definitive test of this hypothesis is likely to require a tissue-specific PPARγ knockout.

**PPARγ ligands regulate secretion of adipocyte-derived signaling molecules**

Another potential mechanism by which PPARγ agonists may affect lipid and glucose metabolism is through alterations in the endocrine functions of adipose tissue. Adipocytes secrete a number of signaling molecules that have been termed adipocytokines. These endocrine factors have the potential to modulate gene expression and metabolism in other organs such as skeletal muscle, liver, and brain. TNFα is a potent inhibitor of adipocyte differentiation and has been suggested to act as an autocrine or paracrine regulator that limits adipose tissue expansion. Elevated TNFα levels are observed in several rodent models of obesity and NIDDM (1). Recent studies utilizing gene disruptions in mice knockouts confirmed that absence of TNFα or its receptor results in significantly improved insulin sensitivity (41, 42). PPARγ ligands appear to antagonize TNFα-mediated inhibition on insulin signaling at several different levels. First, TZD treatment has been shown to decrease circulating TNFα levels in rodents (43, 44). Second, TZDs antagonize the inhibitory effect of TNFα on the insulin receptor and its substrate IRS-1 (45, 46). Third, TZD increase expression of IRS-2 and the p85 subunit of the PI3-kinase in adipocytes (31, 47). The paradigm of TNFα as a mediator of insulin resistance is based primarily on animal data and has not yet been thoroughly explored in humans. For example, Peiffer et al. have reported increased plasma levels of TNFα in male but not in female patients with NIDDM (48).

Leptin, the protein product of the ob gene is an adipocyte-derived hormone that controls body weight by modulating food intake and energy expenditure (49). Leptin’s principal site of action is the hypothalamus where it binds to a tissue-specific variant of the leptin receptor (Ob-Rb) (50). Leptin expression is regulated by both hormonal and nutritional signals; it is decreased by fasting and catecholamines and increased by overfeeding, high fat diet, insulin, and glucocorticoids. A majority of obese humans exhibit elevated circulating leptin levels and have been postulated to be leptin resistant. Ob gene expression is dramatically repressed in 3T3-L1 adipocytes within a few hours after rosiglitazone treatment (51, 52). In rats, administration of pioglitazone increases food intake and adipose tissue weight while reducing ob mRNA (53). Adiponectin was independently identified by several laboratories as a protein specifically and highly expressed in human adipose tissue (54, 55). A mouse homolog was designated AdipoQ (56) and ACRP30 (57). Adiponectin mRNA and protein are significantly reduced in obese mice, primates, and humans (56, 58, 59). By contrast, expression of adiponectin in mice is markedly enhanced by PPARγ ligands, although it does not seem to be a direct target gene. Maeda and colleagues found that adiponectin levels were significantly reduced by TNFα, and this effect was antagonized by TZDs (60). Very recently, Yamauchi and colleagues reported that decreased expression levels of adiponectin coincide with insulin resistance in murine models and that physiological doses of adiponectin improve insulin resistance (61). Consistent with these results, Fruebis et al. have shown that a proteolytic product of the ACRP30 protein increases fatty acid oxidation in muscle and causes significant weight loss in mice (62).
Resistin gene expression is induced during adipocyte differentiation in culture and is restricted to WAT and to BAT in vivo (29). Its expression in adipose tissue and plasma levels is low during fasting and highly increased when animals are refed (29, 30). Steppan et al. found that administration of resistin impairs glucose tolerance and insulin action in mice. This same group also reported that circulating resistin was markedly increased in both genetic and diet-induced obesity. However, another group has reported that adipose tissue mRNA for resistin is significantly decreased in several models of obesity and diabetes (28). At present, there is no agreement as to whether resistin is positively or negatively regulated by TZDs (28, 29, 63).

Lessons from mouse models

Studies using mouse genetic models have also greatly advanced our understanding of the role of PPARγ signaling in insulin resistance (Fig. 1). Several groups have analyzed the actions of TZDs in lipoatrophic mice. Total lipoatrophy in the A-ZIP/F-1 mouse is associated with insulin resistance, hyperglycemia, and an increase in muscle and liver triglyceride content (64). Transplantation of wild-type adipose tissue reversed the hyperglycemia, lowered insulin levels, and improved insulin sensitivity in these mice, demonstrating that diabetes in A-ZIP/F-1 mice is caused by the lack of adipose tissue. Chao et al. found that TZDs failed to reduce glucose and insulin levels in this model system, suggesting that white adipose tissue is required for the antidiabetic effects of these ligands (65). However, these authors also found that TZDs were effective in lowering circulating TG and in increasing whole body FFA oxidation in A-ZIP/F-1 mice, indicating that target tissues other than fat must be involved in these effects (65). In contrast, Graves and colleagues found troglitazone effective in lowering glucose and insulin in a different lipoatrophic model, the aP2/DTA transgenic mouse (66). The basis for the difference between these models is not yet clear.

Important advances have also come from analysis of the influence of PPARγ gene dosage on lipid metabolism and insulin resistance in mice. Some of these studies are summarized in Fig. 2. In wild type mice, a high fat diet promotes adipocyte hypertrophy, obesity, triglyceride accumulation in skeletal muscle and liver, and insulin resistance (15). Kubota et al. have hypothesized that TZDs ameliorate insulin resistance in this model by stimulating de novo

Fig. 1. PPARγ ligands modulate lipid metabolism and insulin sensitivity: lessons from animal models. In mouse models of lipoatrophic diabetes such as the A-ZIP/F1 mouse, complete absence of adipose tissue is associated with severe insulin resistance and hyperglycemia (62, 63). Transplantation of wild type fat lowers basal glucose, prevents hyperinsulinemia, and significantly improves insulin sensitivity. However, the improvement in serum FFA and TG levels is very modest. On the other hand, thiazolidinedione (TZD) treatment does not reduce glucose or insulin levels, suggesting that white adipose tissue (WAT) is required for the antidiabetic effects of PPARγ ligands. TZDs are effective in lowering circulating TGs and increasing whole body fatty acid oxidation in this model, indicating that these effects occur via tissues other than WAT. In wild-type (wt) mice, a high fat diet induces adipocyte hypertrophy, obesity, and insulin resistance (15, 66). TZD administration is hypothesized to reverse these metabolic disturbances by stimulating de novo adipogenesis. This action of PPARγ ligands results in a redistribution of triglycerides from skeletal muscle and liver into the WAT. Blood glucose and insulin levels were normalized, and circulating FFA were decreased upon TZD treatment. In the ob/ob obese diabetic model, genetic absence of leptin results in increased food intake, obesity, and insulin resistance (1, 63). These animals are hyperinsulinemic, hyperglycemic, and have elevated FFA in the plasma, and increased TG levels in liver and skeletal muscle. TZD administration reduces basal insulin levels with a modest decrease in serum glucose and FFA.
adipogenesis, thus increasing the number of small insulin sensitive adipocytes and promoting TG redistribution from liver and muscle into the WAT. Unexpectedly, PPARγ+/− mice were found to have smaller adipocytes and to be more insulin sensitive than wild type controls (15, 67). Moreover, adipocyte hypertrophy in response to high fat diet was partially prevented in PPARγ+/− mice (15, 68). These observations suggest that reduced expression of PPARγ may prevent adipocyte hypertrophy and thereby improve insulin sensitivity. Consistent with this hypothesis, PPARγ+/− mice show reduced levels of factors associated with insulin resistance including FFA and TNFα, increased levels of leptin and adiponectin, and a significantly increased rate of fatty acid β-oxidation. Paradoxically, this favorable phenotype is largely reversed by TZD treatment (Fig. 2).

In conclusion, there appears to be an optimal amount of PPARγ activity in adipose tissue required for optimal whole body lipid metabolism. Too little PPARγ can lead to lipatrophy and too much can lead to adipocyte hypertrophy, both of which can cause insulin resistance. PPARγ agonists have opposite effects on adiposity and energy expenditure in PPARγ+/+ versus PPARγ+/− mice. Heterozygous PPARγ deficiency and TZD administration each prevent adipocyte hypertrophy and insulin resistance, although via different mechanisms. Heterozygous PPARγ+/− deficiency increases fatty acid combustion and energy dissipation, whereas TZD stimulate de novo adipogenesis, thereby increasing fatty acid flux from muscle and liver into WAT.

**PPARγ AND MACROPHAGE LIPID METABOLISM**

**Oxidized lipids and atherosclerosis**

The earliest events in atherogenesis include the recruitment of circulating monocytes to the artery wall, their differentiation into tissue macrophages, and their transformation into foam cells through the accumulation of LDL-derived cholesterol (69). Macrophage lipid uptake is mediated primarily by scavenger receptors including scavenger receptor A (SR-A), CD36, and CD68. Considerable evidence has emerged to suggest that oxidized lipids play a critical role in these early events (70, 71). LDL acquires a number of novel biological activities as a result of oxidative modification, including the ability to bind scavenger receptors, the ability to attract circulating monocytes to the sites of endothelial injury, and the ability to regulate macrophage gene expression.

Recent work suggests that nuclear receptors including PPARγ and the LXRs may mediate important effects of oxidized lipids on macrophages and other vascular cells. PPARγ is expressed at a low level in circulating monocytes, and its expression is significantly increased upon differentiation to macrophages. Moreover, PPARγ protein is present at high levels in the macrophage-derived foam cells of atherosclerotic lesions (38, 72). Treatment of macrophages with oxidized LDL (oxLDL) in vitro induces expression of both PPARγ and LXRα mRNAs (25, 38). Internalization of oxLDL by macrophages provides the cell with activators of PPARγ, such as oxidized fatty acids, as well as with activators of LXRs such as 27- and 25-hydroxycholesterol (3, 73, 74). PPARγ ligands can also be produced locally in atherosclerotic lesions through the oxidation of fatty acids by 12/15 lipoxygenase (75).

**PPARγ regulates lipid uptake and efflux**

Alterations in the rates of lipid uptake or efflux from the artery wall each have the potential to affect the development of atherosclerotic lesion. Work from a number of laboratories over the past 4 years have provided evidence supporting a role for PPARγ in pathways for both lipid uptake and lipid efflux in macrophages (Fig. 3). PPARγ was implicated in lipid uptake by the observation that the gene encoding the scavenger receptor CD36 is a direct target of PPARγ/RXR heterodimer...
A critical role for PPARγ in the regulation of this gene is supported by both gain of function and loss of function studies. Retroviral expression and activation of PPARγ in macrophages or fibroblasts induces expression of the CD36 gene. In addition, the ability of synthetic PPARγ ligands to induce CD36 expression is abolished in PPARγ null cells (76, 77). In NIH-3T3 fibroblasts (which lack scavenger receptors), expression of PPARγ endows these cells with the ability to take up oxLDL. However, in differentiated macrophages in vitro, loss of PPARγ expression does not significantly compromise oxLDL uptake, presumably due to compensation by other scavenger receptors (76, 77). In contrast to CD36, expression of SR-A is down regulated in response to PPARγ activation (77, 78). Although the contribution of PPARγ to lipid uptake in vivo is not yet clear, selective loss of CD36 in mice has been shown to decrease both macrophage lipid uptake and atherosclerosis (79, 80). It is important to note that CD36 expression is also regulated by PPARγ in adipose tissue (36). Its regulation in this context is likely to contribute to uptake of free fatty acids for esterification into triglycerides (79). Interestingly, the related protein SR-BI has also been identified as a PPAR-responsive gene in human macrophages (81).

**PPARγ and atherosclerosis**

The initial observation that PPARγ activation promotes CD36 expression raised concerns about the effects of the thiazolidinediones on cardiovascular disease risk in humans. Patients with NIDDM are already at increased risk of developing atherosclerosis. Fortunately, available data to this point suggest that on balance the effect of systemic administration of synthetic PPARγ ligands is antiatherogenic in both mice and humans. Although the mechanisms involved in this effect are not completely worked out, they are likely to include favorable alterations in plasma lipid profiles, amelioration of insulin resistance, and direct effects on cells of the artery wall.

Several studies have examined the effects of PPARγ ligands in murine models of atherosclerosis. Li et al. demonstrated that two unrelated agonists (rosiglitazone and GW7845) reduced atherosclerosis in LDLR−/− mouse fed a Western diet (82). Markedly fewer and smaller lesions were found in male mice despite a significant increase in the expression of CD36 in the vessel wall. Subsequent studies showed a similar beneficial effect of TZDs in the apolipoprotein E (apoE)−/− and LDLR−/− models (83, 84). Limited human studies also support an antiatherogenic effect of PPARγ ligands. For example, Minamikawa...
et al. found a significant decrease in carotid artery thickness in Type 2 diabetics treated with troglitazone (85).

The observation that the net effect of systemic PPARγ activation is antiatherogenic suggests that the potential of PPAR ligands to promote CD36 expression and lipid uptake is balanced by other systemic and/or local actions. One plausible explanation for this paradox involves the function of the nuclear receptor LXRα in macrophages. Recent data indicate that in differentiated macrophages, the PPARγ and LXR signaling pathways converge to mediate a key response to lipid loading: a pathway for cholesterol efflux. PPARγ and the LXRα cooperate to induce expression of the putative cholesterol/phospholipid transporter ABCA1 and apoE in macrophages (86, 87). The molecular basis for this cooperation is that the LXRα gene is itself a direct transcriptional target of PPARγ. Ligand activation of PPARγ leads to primary induction of LXRα expression and to coupled induction of the ABCA1 and apoE genes, which are both direct LXR targets (88–90). ABCA1 and apoE have both been implicated in the efflux of cholesterol and phospholipid to extracellular acceptors. As a consequence of this regulatory loop, PPARγ and LXR ligands additively promote cholesterol efflux from macrophages (86, 87). In PPARγ null macrophages, the ability of PPARγ ligands to increase expression of ABCA1 and stimulate efflux is abolished (86). Thus, PPARγ may be an important modifier of the reverse cholesterol transport pathway. This modulation may be particularly important in tissues where PPARγ is highly expressed, such as macrophages, adipocytes, and certain epithelial cells.

The realization that PPARγ could influence both lipid uptake and efflux raised the question of whether the net effect of PPARγ ligands on macrophages within an atherosclerotic lesion would be to promote or impede foam cell formation. Studies in which PPARγ ligands are administered to mice do not permit one to differentiate between systemic and local effects. Chawla et al. addressed this issue by examining atherosclerosis in LDLR null mice transplanted with wild type or PPARγ null bone marrow (86). Loss of bone marrow PPARγ expression led to a significant increase in atherosclerosis, suggesting that the PPARγ-LXR-ABCA1 efflux pathway dominates in vivo. Moreover, these observations support the hypothesis that direct effects of PPARγ ligands on cells of the artery wall are important for the antiatherogenic properties of these compounds.

Other local effects of PPARγ ligands are also likely to contribute to their antiatherogenic effects. PPARγ ligands inhibit macrophage production of inflammatory cytokines (78, 91), although some of this activity may be not be mediated by PPARγ (76, 77). Oxidized lipid activators of PPARγ have also been found to antagonize expression of CCR2 in monocytes, and thus may decrease monocyte recruitment into the vessel wall (92). Local effects on smooth muscle cells may also play a role. For example, TZDs have been shown to inhibit migration of smooth muscle cells in response to chemotactic signals and thus may limit their recruitment into lesions (93). Thus, systemic treatment with PPARγ ligands results in the simultaneous activation of many PPARγ regulatory pathways. As outlined above, PPARγ agonists have multiple effects on systemic lipid and glucose metabolism in addition to their effects in vascular cells. The net effect is likely to reflect a balance between local effects in the artery wall and systemic effects on lipid metabolism (84).

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