Decoding Transcriptional Programs Regulated by PPARs and LXRs in the Macrophage: Effects on Lipid Homeostasis, Inflammation, and Atherosclerosis

Mercedes Ricote, Annabel F. Valledor, and Christopher K. Glass

Abstract—Macrophages play essential roles in immunity and homeostasis. As professional scavengers, macrophages phagocytose microbes and apoptotic and necrotic cells and take up modified lipoprotein particles. These functions require tightly regulated mechanisms for the processing and disposal of cellular lipids. Under pathological conditions, arterial wall macrophages become foam cells by accumulating large amounts of cholesterol, contributing to the development of atherosclerosis. Peroxisome proliferator–activated receptors (PPARs) and liver X receptors (LXRs) are members of the nuclear receptor superfamily of transcription factors that have emerged as key regulators of macrophage homeostasis. PPARs and LXRs control transcriptional programs involved in processes of lipid uptake and efflux, lipogenesis, and lipoprotein metabolism. In addition, PPARs and LXRs negatively regulate transcriptional programs involved in the development of inflammatory responses. This review summarizes recent efforts to decode the differential and overlapping roles of PPARs and LXRs in the context of macrophage lipid homeostasis and the control of inflammation. (Arterioscler Thromb Vasc Biol. 2004;24:1-11.)

Key Words: peroxisome proliferator–activated receptor ■ liver X receptor ■ macrophage ■ lipid homeostasis ■ inflammation ■ atherosclerosis

Nuclear receptors are ligand-dependent transcription factors that regulate gene networks involved in controlling growth, morphogenesis, cellular differentiation, and homeostasis.1–3 On ligand binding, nuclear receptors undergo a conformational change that mediates exchange of corepressor and coactivator proteins to enable transcriptional activation or repression.4 A rapidly evolving line of investigation has recently linked peroxisome proliferator–activated receptors (PPARs) and liver X receptors (LXRs) to the regulation of both lipid homeostasis and inflammatory responses in macrophages. PPARs function as receptors for fatty acids and their metabolites,5,6 while LXRs are receptors for certain derivatives of cholesterol.7–9 PPARs and LXRs activate gene expression by binding to specific DNA response elements in target genes as heterodimers with retinoid X receptors (RXRs),10–12 which are themselves members of the nuclear receptor superfamily of transcription factors that have emerged as key regulators of macrophage homeostasis. PPARs and LXRs control transcriptional programs involved in processes of lipid uptake and efflux, lipogenesis, and lipoprotein metabolism. In addition, PPARs and LXRs negatively regulate transcriptional programs involved in the development of inflammatory responses. This review summarizes recent efforts to decode the differential and overlapping roles of PPARs and LXRs in the context of macrophage lipid homeostasis and the control of inflammation.

PPAR Subfamily

As a class, PPAR/RXR heterodimers bind to DNA response elements that generally consist of a direct repeat of hexameric core recognition elements spaced by one base pair (DR1).18,19 There are three PPAR subtypes: α (NR1C1), δ (NR1C2), and γ (NR1C3), which exhibit distinct tissue distribution.5,6 PPARα is highly expressed in liver, kidney, heart, and muscle and regulates the production of enzymes involved in the β-oxidation of fatty acids and lipoprotein metabolism. PPARγ is the molecular target of fibrates, such as gemfibrozil, that are used clinically to treat hypertriglyceridemia.20,21 PPARγ is most highly expressed in adipose tissue and has been demonstrated to be essential for adipocyte differentiation and normal glucose metabolism.22,23 PPARγ is activated...
by the thiazolidinedione (TZD) drug class, exemplified by rosiglitazone, which act as insulin sensitizers and are used in the treatment of type 2 diabetes mellitus. PPARs are ubiquitously expressed, and its biological roles are less established than those of PPAR α and γ. However, recent studies suggest roles in lipid metabolism, and energy homeostasis.

Unlike receptors for steroid hormones, which bind their respective ligands with high affinity and specificity, PPARs bind a broad range of fatty acids and their metabolites with relatively low affinity (e.g., 10⁻⁶–10⁻⁵ M). While there is some preference for specific fatty acids by each PPAR, many fatty acids are capable of activating all three PPAR isoforms when presented to cells at sufficiently high concentrations. It has therefore been difficult to ascertain the physiological ligands for PPARs using conventional methods that depend on high affinity and specificity of binding. The PPARγ crystal structure reveals a large ligand-binding pocket of >1300 Å, which may explain the diversity of ligands for this receptor. The concept has emerged that the relative lack of specificity is built into the receptors to enable them to sense a broad range of fatty acids and their metabolites that can be present in cells at relatively high concentrations. Recent reports have shown that PPARγ is altered in a ligand-specific way, resulting in distinct interactions between PPARγ and coactivators. Insights into physiological ligands have recently emerged from studies of enzymes involved in lipid and lipoprotein metabolism that are described in more detail below.

**LXR Subfamily**

LXR/RXR heterodimers generally bind to DNA response elements that consist of a direct repeat of hexameric core recognition elements spaced by four base pairs (DR4). Two distinct genes encode LXRα (NR1H3) and LXRβ (NR1H2). While LXRβ is ubiquitously expressed, LXRα is distributed in a tissue-specific fashion, being more abundant in liver and other tissues involved in lipid metabolism. LXRα is distributed in a tissue-specific fashion, being more abundant in liver and other tissues involved in lipid metabolism. LXRβ is activated by specific oxidized forms of cholesterol or oxysterols, such as 24(S)-hydroxycholesterol and 22(R)-hydroxycholesterol, or by certain intermediates of the cholesterol biosynthetic pathway like 24(S), 25-epoxycholesterol. Analysis of LXRα-deficient mice has revealed a broad role for these nuclear receptors in the regulation of genes involved in lipid homeostasis in different tissues.

It is important to remark that most of the studies that evaluate the implications of LXRs in lipid metabolism have been performed using murine models and we must take into consideration that some of these processes may be regulated differently in humans. In rodents, LXRs regulate the expression of cholesterol 7α-hydroxylase (Cyp7a1), the rate-limiting enzyme in the conversion of cholesterol to bile acids. Wild-type mice fed a high cholesterol diet show a marked increase in the hepatic levels of this enzyme. In contrast, LXRα knockout mice fail to upregulate Cyp7a1 expression in response to a high cholesterol diet, which results in the accumulation of large amounts of cholesterol in the liver. This phenotype is more exacerbated in LXRα/β double knockout mice; however, LXRβ-deficient mice do not exhibit changes in hepatic cholesterol and bile acid metabolism in response to a high cholesterol diet. In contrast to the scenario depicted in the murine system, human Cyp7a1 lacks an LXR inducible element. Dietary cholesterol fails to stimulate the human cholesterol 7α-hydroxylase gene (CYP7A1) in transgenic mice, and its expression is reduced in response to cholesterol-enriched diets. Mice expressing the human CYP7A1 gene in the mouse CYP7A1 knockout background lack induction of CYP7A1 expression by cholesterol feeding and have increased hypercholesterolemia when fed a high fat diet. Another example of the involvement of LXR in cholesterol homeostasis is the fact that administration of a synthetic LXR agonist to wild-type mice results in decreased cholesterol absorption in the intestine. This is mediated by increased intestinal expression of members of the family of ATP binding cassette (ABC) transporters, mainly ABCG5 and ABCG8, which function to efflux cholesterol, thus limiting its absorption by intestinal cells. LXRs are activated by specific oxidized forms of cholesterol or oxysterols, such as 24(S)-hydroxycholesterol and 22(R)-hydroxycholesterol, or by certain intermediates of the cholesterol biosynthetic pathway like 24(S), 25-epoxycholesterol. LXRα/β double knockout mice do not undergo changes in cholesterol absorption on administration of LXRs ligands. Apart from their role in cholesterol homeostasis, LXRs regulate the expression of a number of genes involved in fatty acid biosynthesis and esterification, which will be discussed later in this review.

**PPARs and LXRs in Macrophage Lipid Homeostasis and Atherosclerosis**

A key function of macrophages is the phagocytosis of pathogens and apoptotic or necrotic cells. This uptake process involves pattern recognition receptors that include the scavenger receptor A, CD36, and others. Scavenger receptors also contribute to the development of macrophage foam cells that are the major cellular elements of early atherosclerotic lesions due to their ability to bind and internalize modified lipoproteins, exemplified by oxidized LDL (oxLDL). The uptake of apoptotic/necrotic cells and modified lipoproteins imposes special demands on lipid homeostasis that cannot be met by negative feedback regulation of the expression of sterol regulatory element binding protein (SREBP) target genes involved in cholesterol biosynthesis and uptake. Recent studies suggest that LXRs and PPARs play critical roles in feed-forward mechanisms that regulate cholesterol and fatty acid homeostasis in macrophages in response to rapid changes in cellular lipids.

The role of PPARs in regulating lipid metabolism in macrophages was initially suggested by the discovery of the scavenger receptor CD36 as a PPARγ target gene (Figure 1). CD36 is a member of the scavenger receptor family that mediates uptake of oxLDL and results in massive lipid accumulation and foam cell formation. Nagy et al. found that oxidized lipids present in oxLDL, such as 9-HODE and 13-HODE, had the capability to activate PPARγ and stimulate CD36 expression. These findings suggested the existence of a positive feedback loop that would potentially lead to increased foam cell formation. Studies using PPARγ-null embryonic stem cells, as well as macrophages derived from mice homozygous for conditional PPARγ alleles, confirmed that CD36 is a direct PPARγ target gene. How-
ever, despite increased CD36 expression, TZDs do not induce significant cellular cholesterol accumulation in either wild-type or PPARγ-deficient mouse macrophages or human monocyte-derived macrophages.55,57

Direct evidence for an anti-atherogenic role of PPARγ has been provided by a number of studies using two different murine models of atherosclerosis.58–61 In agreement, reconstitution of the hematopoietic system of LDL receptor (LDLR)−/− mice with PPARγ+/− bone marrow progenitor cells resulted in increased atherosclerosis compared with LDLR−/− mice reconstituted with wild-type progenitor cells.62 PPARγ agonists reduce carotid artery wall thickening in diabetic patients, consistent with overall anti-atherogenic effects.63,64 Clinical trials evaluating the effects of PPARγ agonists on endpoints, including myocardial infarction, are in progress. A clinical trial examining effects of the PPARγ agonist gemfibrozil in men with a history of coronary heart disease and low HDL levels demonstrated a significant reduction in incidence of fatal and nonfatal myocardial infarction.65 These effects could only be partially explained by increased levels of HDL66 and are consistent with actions in peripheral tissues, including macrophages.

Substantial progress has been made in recent years in the understanding of cholesterol efflux pathways in macrophages and other cell types. In particular, the discovery that mutations in ABCA1 cause Tangier disease, characterized by a severe HDL deficiency and accumulation of cholesterol in tissue macrophages, provided a new insight into mechanisms regulating cholesterol homeostasis.67–70 ABCA1 functions in the efflux of phospholipids and cholesterol from peripheral cells to exogenous apolipoprotein acceptors, such as apoAI.71 Tangier disease patients are more susceptible to developing atherosclerosis, suggesting that upregulation of ABCA1 may exert protective effects by clearing excess cholesterol from macrophages in the arterial wall. An important connection between nuclear receptor action and reverse cholesterol transport was provided by the finding that ABCA1 was a direct target gene for LXR in human and murine cells42,72,73 (Figure 1). The induction of ABCA1 by oxysterols was completely abolished in primary macrophages deficient for LXR.52 Stimulation of macrophages with LXR agonists resulted in an increase in cholesterol efflux to extracellular apoAI acceptors.74 These observations suggested that by inducing the expression of a key gene in reverse cholesterol transport, LXR activation played a critical role in the prevention of foam cell formation. Subsequent studies confirmed this hypothesis by demonstrating that LXR agonists were able to inhibit the development of atherosclerosis in mice.75–77 Another member of the ATP binding cassette family, ABCG1, which has been reportedly involved in lipid flux, was also shown to undergo LXR-mediated regulation in macrophages.78 However, the exact relevance of this regulation in reverse cholesterol transport or general lipid homeostasis is not clear. Recently, two independent reports have suggested a point of crosstalk in the regulation of cholesterol homeostasis by PPARs and LXRs.57,62 PPARγ and PPARγ induced the expression of ABCA1 and stimulated cholesterol efflux in human primary and THP-1 macrophages through a transcriptional cascade mediated by LXRγ.57,62 The ability of TZDs to stimulate cholesterol efflux was completely abolished in PPARγ-null embryonic stem cells.62 Consistent with these findings, Akiyama et al56 found that basal cholesterol efflux from cholesterol-loaded

Figure 1.PPARs and LXRs regulate the expression of genes involved in macrophage lipid homeostasis. PPAR target genes are indicated in green while LXR target genes are shown in blue. ACAT, acetyl-coenzyme A acetyltransferase; FFAs, free fatty acids; PGs, prostaglandins; LTs, leukotriens; PLA2, phospholipase A2; SRs, scavenger receptors.
macrophages to HDL was significantly reduced after disruption of the PPARγ gene. In addition, Chinteti et al.79 showed that PPARα reduces cholesterol esterification in macrophages, resulting in an enhanced availability of free cholesterol for efflux through the ABCA1 pathway. PPARα has also been suggested to stimulate cholesterol efflux from macrophage-derived foam cells by upregulation of CLA-1/ scavenger receptor class B type I (SR-BI).80 However, studies in vitro show that PPARα and PPARγ have the potential to downregulate the expression of macrophage cholesteryl ester hydrolase,79,81 an enzyme responsible for hydrolysis of stored cholesterol esters in macrophage foam cells and release of free cholesterol for HDL-mediated efflux.

One study has demonstrated that PPARδ can stimulate ABCA1 expression and cholesterol efflux in macrophages.26 However, PPARδ activation has also been shown to promote cholesterol accumulation in macrophages by upregulation of genes implicated in cholesterol uptake, including CD36 and SR-A, and downregulation of genes involved in lipid metabolism and efflux, such as cholesterol 27-hydroxylase (Cyp27) and apoE.82 The basis for these reported differences is not clear. In addition, recent studies demonstrated that hydrolysis and uptake of triglycerides present in VLDLs can activate PPARα and PPARδ in macrophages.83,84 Treatment of macrophages with VLDL results in triglyceride accumulation and in the induction of adipose differentiation-related protein in a PPARδ-dependent manner.83 Thus, the overall action of PPARδ on macrophase lipid and cholesterol metabolism remains unclear, and future studies in mouse models and PPARδ knockout mice are needed to clarify the role of this receptor in atherosclerosis.

Microarray analysis of wild-type and PPARγ-deficient macrophages suggests that, in contrast to adipose tissue, relatively few genes are positively regulated by synthetic PPARγ ligands in these cells.85 Most of these genes have roles in lipid transport and metabolism such as CD36, ADRP, ABCG1, the peroxisomal enzymes Ech1 and Pex11a, α-mannosidase II, and carnitine palmitoyl transferase (Cpt1). Rosiglitazone had little or no effect on ABCA1 or LXRα expression in these studies, consistent with the work of other groups.56,61 The basis for this discrepancy is not clear, but may be due to different experimental conditions or phenotypic differences in macrophages derived from different sources. Interestingly, some of the target genes for PPARγ were also induced by PPARδ ligands, suggesting that these two isoforms have overlapping transactivator functions in macrophages.85

Macrophages contribute to lipoprotein metabolism by secreting apolipoproteins and enzymes involved in lipoprotein modification. Treatment of macrophages with LXR or PPARγ agonists results in upregulation of apoE expression.56,86,87 ApoE is a component of chylomicron remnants, VLDLs and IDLs, and plays critical protective roles in atherosclerosis (reviewed in Reference 88). First, recognition of apoE by LDL receptors facilitates hepatic uptake of lipoprotein remnants. Second, apoE secreted by macrophages plays a role in promoting cholesterol efflux, thus preventing and/or reducing cholesterol ester accumulation in arterial wall macrophages,89–93 although the relative importance of this apoE-dependent cholesterol efflux as compared with the ABCA1/apoAI-dependent lipid efflux is currently unknown. Third, apoE directly modifies both macrophage- and T lymphocyte-mediated immune responses that contribute to the development of the atherosclerotic lesion.

Interestingly, in both human and murine macrophages, LXR activation leads to the coordinate upregulation of other apolipoproteins that form a gene cluster with apoE. These include apoC-I, apoC-IV, and apoC-II.87 ApoC-II is the obligate cofactor for lipoprotein lipase (LPL) and is required for the LPL-dependent hydrolysis of triglycerides present in chylomicrons, VLDLs, and HDLs.94 Deficiency of apoC-II results in hypertriglyceridemia.95 However, transgenic mice expressing human apoC-II are also hypertriglyceridemic, suggesting that apoC-II may have other unknown functions in addition to acting as the obligate cofactor of LPL.96 ApoC-I, like apoC-II, is associated with triglyceride-rich chylomicrons and VLDLs.97 ApoC-I has been reported to inhibit cholesterol ester transfer protein, to activate the enzyme lecithin-cholesterol acyltransferase, and to inhibit lipoprotein binding to the LDL receptor-related protein (reviewed in Reference 98). The physiological role of apoC-IV remains to be established. However, some studies suggest that apoC-IV may function to inhibit the hydrolysis of triglycerides contained within VLDL particles.99 The fact that LXRs control the expression of the whole apoC-I/apoC-II/apoC-IV cluster may contribute to the ability of LXR agonists to inhibit atherosclerosis in an apoE-deficient setting.77

LXR agonists, as well as PPARα and γ ligands, modulate the expression and production of lipoprotein-modifying enzymes by macrophages. One example is the upregulation of LPL expression,56,100,101 which catalyzes the hydrolysis of lipoprotein triglycerides, thus promoting the remodeling of triglyceride-rich chylomicrons and VLDL into chylomicron remnants and cholesterol-rich lipoproteins such as LDL. However, despite an effect in gene expression, PPAR activation results in reduced LPL secretion and enzyme activity.101 The exact implications of LPL upregulation are not clear since this enzyme has been suggested to have both pro- and anti-atherogenic properties.102 Overexpression of LPL in macrophages accelerates atherosclerosis in both apoE- and LDLR-deficient mice.103,104 In contrast, when overproduction of human LPL is induced systemically, LPL appears to protect against atherosclerosis.105,106 However, overexpression may not reflect the physiological role of this enzyme in the arterial wall. Macrophages efficiently take up cholesterol-rich lipoproteins, and their cholesterol esters can be converted to oxysterols and free cholesterol that can be mobilized to the liver by reverse cholesterol transport. Strauss et al.107 showed that adenoviral-mediated expression of LPL in Lpl-deficient mice is necessary and sufficient to promote maturation of HDL. Moreover, phospholipid transfer protein (PLTP), another modulator of HDL metabolism with a potential role in reverse cholesterol transport,108 is also a direct target gene for LXR.109–111 PLTP acts in coordination with LPL in the formation of pre-β-HDL particles; the lipolysis of VLDL mediated by LPL generates phospholipids and apolipoproteins that are subsequently transferred to pre-β-HDL particles by the action of PLTP. Expression of
human PLTP in mice increases the generation of pre-β-HDL particles and enhances hepatic uptake and clearance of cholesterol esters. Therefore, the coordinated action of LXR on both LPL synthesis and mechanisms for cholesterol efflux and reverse cholesterol transport may facilitate clearance of cholesterol-rich lipoproteins from the serum and the arterial wall.

Apart from their role in reverse cholesterol transport, LXR agonists have also been shown to positively regulate fatty acid and triglyceride biosynthesis. In many tissues, including macrophages, LXRs induce the expression of the transcription factor SREBP-1c, which in turn triggers the expression of enzymes involved in fatty acid synthesis and triglyceride formation, such as fatty acid synthase (FAS) and stearoyl coenzyme A desaturase (SCD). LXRs can directly bind and activate the expression of at least FAS. The positive regulation of fatty acid biosynthesis in macrophages may reflect an adaptive mechanism provided by LXRs as cholesterol sensors. Excess free cholesterol is toxic and its esterification to fatty acids represents an important mechanism for buffering free cholesterol levels. On the other hand, fatty acid synthesis and its subsequent desaturation may provide the cell with ligands for other nuclear receptors, including PPARs. Indeed, evidence for a role for SREBP1 in the production of endogenous ligands for PPARγ has been provided in adipocytes.

The fact that lipogenesis is so strongly activated by available synthetic LXR agonists limits the potential use of these compounds as anti-atherogenic drugs. However, by analogy to the development of selective modulators of other nuclear receptors, it may be possible to develop LXRs ligands that differentially regulate programs of gene expression involved in cholesterol efflux and fatty acid biosynthesis. Genetic and biochemical studies suggest that unliganded LXR/RXR heterodimers actively repress target genes by binding nuclear receptor corepressors such as NCoR and SMRT. Treatment with synthetic LXR agonists results in dissociation of NCoR and recruitment of transcriptional coactivators. Intriguingly, NCoR is not recruited to LXR target genes in LXR-deficient macrophages, which is sufficient to allow increased expression of the ABCA1 gene and enhanced cholesterol efflux, but does not result in derepression of SREBP1c or increased fatty acid biosynthesis. Therefore, the generation of selective LXRs modulators that disrupt the binding of LXR to corepressors without leading to coactivator recruitment may have the potential to selectively increase ABCA1 expression in macrophages and thus be used for anti-atherogenic purposes without having a side effect on lipogenesis.

PPARs and LXRs in Macrophage Mediated Inflammation

In addition to the regulation of lipid metabolism, PPARs and LXRs play roles in influencing inflammatory and immune responses. PPARs can be activated by eicosanoids, which are produced by metabolism of arachidonic acids and other long-chain PUFAs during inflammatory responses. For example, ligands for PPARα are leukotriene LTB4 and 8(S)-hydroxyeicosatetraenoic acid (HETE), whereas 15deoxy-prostaglandin J2 (15d-PGJ2), 15-HETE, and 13-hydroxyoctadecadienoic acid (NODE) act as ligands for PPARγ. Interestingly, the expression of PPARs is differentially regulated by factors that control the development of immune responses. PPARγ expression is dramatically upregulated in macrophages and T cells during the inflammatory response and can be induced in vitro by interleukin (IL)-4 and other immunoregulatory molecules. In contrast, interferon (IFN)γ and lipopolysaccharide (LPS) repress the expression of PPARγ. PPARγ is highly expressed in elicited peritoneal macrophages, while low levels of PPARα are present. The opposite pattern is observed in primary human monocytes.

PPARα and PPARγ have been shown to inhibit the expression of proinflammatory genes, suggesting that they might inhibit inflammatory responses in vivo. Activation of PPARα resulted in the induction of genes involved in fatty acid oxidation with the subsequent degradation of fatty acids and fatty acid derivatives like LTB4. In addition, the response to LTB4 and arachidonic acid was prolonged in mice lacking the PPARα gene as compared with wild-type mice. However, some in vivo studies show proinflammatory effects for PPARα ligands, such as an increase in the plasma levels of TNFα during endotoxemia and in the production of monocyte chemotactic protein (MCP-1) by endothelial cells.

Natural and synthetic PPARγ ligands exert anti-inflammatory effects in several models of inflammation (Table 1). The investigation of potential anti-inflammatory effects of PPARγ agonists in these settings was based on earlier work performed in macrophages and other cell types. In those studies, PPARγ agonists were shown to inhibit the induction of inflammatory genes by LPS, IL-1β, and IFN-γ. However, subsequent research has provided different perspectives to the interpretation of these results.

First, 15d-PGJ2 inhibits NFκB-dependent transcription through a PPARγ-independent mechanism. Second, the doses of TZDs that exert maximal inhibitory effects on LPS-inducible genes are significantly higher than their binding affinity to PPARγ. Furthermore, two different reports have shown that deletion of the PPARγ gene in stem-cell-derived macrophages does not alter basal or stimulated cytokine production. In addition, these studies showed that high concentrations of PPARγ ligands still inhibit cytokine responses to LPS stimulation in these cells. More recent studies in wild-type and PPARγ knockout macrophages demonstrated that the inhibitory effects of rosiglitazone on LPS responses are PPARγ-dependent when the drug is used at concentrations close to the EC50, but become PPARγ-independent at higher concentrations. Several lines of evidence suggest that PPARγ-independent effects of rosiglitazone are due to activation of PPARδ. Intriguingly, PPARγ-specific effects of rosiglitazone resulted in inhibition of only a subset of the genes induced by LPS, indicating promotor-specificity in the mechanism underlying transrepression.

The subset of LPS responsive genes that are inhibited by PPARγ includes mediators of both the native and acquired immune responses, such as interferon inducible protein (IP)-10, monokine induced by IFNγ, and IL-12p40, which is an important positive regulator of IFNγ production by T helper,
Evidence for Protective Roles of PPARs and LXR s in Murine Inflammatory Disease Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Experiment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis in ApoE−/− mice</td>
<td>Transplantation of LXRα/β−/− bone marrow</td>
<td>77</td>
</tr>
<tr>
<td>Western diet; males</td>
<td>Treatment with fenofibrate</td>
<td>132</td>
</tr>
<tr>
<td>Western diet; males and females</td>
<td>Treatment with troglitazone, rosiglitazone</td>
<td>60, 61</td>
</tr>
<tr>
<td>Atherosclerosis in LDLR−/− mice</td>
<td>Transplantation of PPARγ−/− bone marrow</td>
<td>62</td>
</tr>
<tr>
<td>Western diet; females</td>
<td>Treatment with T0901317</td>
<td>76</td>
</tr>
<tr>
<td>Western diet; males</td>
<td>Transplantation of LXRα/β−/− bone marrow</td>
<td>77</td>
</tr>
<tr>
<td>Western diet; males and females</td>
<td>Treatment with rosiglitazone, GW7845, GW3965</td>
<td>58, 59, 75</td>
</tr>
<tr>
<td>DSS-induced colitis</td>
<td>Treatment with troglitazone</td>
<td>133</td>
</tr>
<tr>
<td>TNBS-induced colitis</td>
<td>Treatment with rosiglitazone</td>
<td>134</td>
</tr>
<tr>
<td>Experimental autoimmune encephalomyelitis (EAE)</td>
<td>Treatment with troglitazone, pioglitazone, 15d-PGJ2, ciglitazone</td>
<td>135–138</td>
</tr>
<tr>
<td>Antigen-induced arthritis</td>
<td>PPARγ−/− mice</td>
<td>128</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Treatment with rosiglitazone, tetradecylthioacetic acid, troglitazone</td>
<td>139, 140</td>
</tr>
<tr>
<td>TPA-induced contact dermatitis</td>
<td>Treatment with T0901317, GW3965</td>
<td>17</td>
</tr>
</tbody>
</table>

Interestingly, many of the LPS-inducible genes inhibited by rosiglitazone have been previously documented as targets for IFNγ. Rosiglitazone inhibited the responses of these genes to IFNγ in a PPARγ-dependent manner. Collectively, these findings support a physiological role of PPARγ in the negative regulation of both native and acquired immune responses (Figure 2). Consistent with this idea, administration of TZDs attenuated inflammation in murine models of atherosclerosis, inflammatory bowel disease, and autoimmune diseases such as allergic encephalomyelitis and psoriasis (Table 1). Genetic evidence for the anti-inflammatory effects of PPARγ in disease remains limited, but a recent report showed that mice heterozygous for a null PPARγ allele develop much more severe adjuvant-induced arthritis than wild-type mice. Negative regulation of gene expression may also be the basis for some of the insulin-sensitizing effects of rosiglitazone observed in diabetic patients. Rosiglitazone treatment has recently been shown to reduce circulating concentrations of inflammatory markers of cardiovascular disease in type 2 diabetic patients, such as C-reactive protein, the metalloproteinase MMP-9, and TNF-α.

Interestingly, LXR s may have overlapping functions with PPAR s in the negative control of the inflammatory response. LXR agonists have been shown to inhibit the macrophage response to bacterial pathogens and to antagonize a number of pro-inflammatory genes in macrophages. These include iNOS, COX-2, IL-1β and IL-6; MMP-9 and chemokines such as MCP-1 and –3; macrophage inflammatory protein (MIP)-1β; and IP-10. Similar to what has been described for PPARγ, LXR antagonizes the NFκB pathway through a mechanism that is not completely understood. LXR-deficient mice exhibited enhanced responses to inflammatory stimuli, and LXR ligands reduced inflammation in murine models of contact dermatitis and atherosclerosis (Table 1). These observations raise the idea that LXR and PPAR agonists may exert their anti-atherogenic effect not only by promoting cholesterol efflux but also by limiting the production of inflammatory mediators in the arterial wall (reviewed in Reference 131).

**Summary**

In the last few years, PPARs and LXR s have emerged as key regulators of macrophage biology. Clear evidence has been provided that these nuclear receptors control transcriptional programs involved in macrophage lipid homeostasis. In addition, PPARs and LXRs negatively regulate macrophage-mediated inflammation. However, several important issues need further exploration. For example, it is not clear whether anti-atherogenic effects of PPAR and LXR agonists result primarily from changes in known target genes or are mediated by effects on gene expression that remain to be identified.

Future studies using engineered mouse models and functional genomic approaches are needed to clearly establish the mechanisms by which these nuclear receptors exert their anti-atherogenic and anti-inflammatory actions. These findings should help guide the development of receptor–selective modulators that retain therapeutic actions but exhibit reduced side effects that would be useful in the prevention and treatment of human diseases such as hyperlipidemia, diabetes, and chronic inflammatory diseases, including atherosclerosis.

**Acknowledgments**

M.R. was supported by a beginning grant-in-aid from the American Heart Association Western Affiliate. A.F.V. was supported by a Biostar grant from the University of California. C.K.G. is an Established Investigator of the American Heart Association. These studies were also supported by NIH grants to C.K.G. We thank A. Zulueta for assistance with manuscript preparation.

**References**

Figure 2. Roles of PPARγ and LXRs in innate and acquired immunity. LPS and IFNγ induce the expression of genes involved in macrophage activation. PPARγ and LXRs exert negative regulation on a subset of these genes. Genes inhibited by PPARγ or LXRs are shown in blue or green, respectively. PPARγ expression is repressed by LPS and IFNγ. HETEs, hydroxyeicosatetraenoic acids; NFκB, nuclear factor κB; PGs, prostaglandins; PUFAs, polyunsaturated fatty acids; STAT1, signal transducer and activator of transcription 1; TLR4, toll-like receptor 4; Th, T helper cells.


104. Shachter NS. Apolipoproteins C-I and C-III as important modulators of lipoprotein lipase and apolipoprotein C-II. Curr Opin Lipidol. 1996;7:151–160.


Decoding Transcriptional Programs Regulated by PPARs and LXRs in the Macrophage: Effects on Lipid Homeostasis, Inflammation, and Atherosclerosis
Mercedes Ricote, Annabel F. Valledor and Christopher K. Glass

Arterioscler Thromb Vasc Biol. published online October 30, 2003;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2003/10/30/01.ATV.0000103951.67680.B1.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/