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PPARs and molecular mechanisms of transrepression

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Abstract

In the last few years, PPARs have emerged as key regulators of inflammatory and immune responses. However, the mechanistic basis of the anti-inflammatory effects of Peroxisome Proliferator-activated receptors (PPARs) remains poorly understood. Accumulating evidence suggests that these effects result from inhibition of signal-dependent transcription factors that mediate inflammatory programs of gene activation. Several mechanisms underlying negative regulation of gene expression by PPARs have been described. Recent studies, using siRNA, microarray analysis and macrophage-specific knockout mice, have highlighted PPARs molecular transrepression mechanism in macrophages. Identification of their mechanism of action should help promote the understanding of the physiologic roles that PPARs play in immunity and contribute to the development of new therapeutic agents.

Keywords

peroxisome proliferator-activated receptors; inflammation; macrophage; transrepression; coactivators; corepressors

1. Introduction

PPARs are members of the nuclear receptor family of ligand-dependent transcription factors that regulate diverse aspects of energy homeostasis, lipid and lipoprotein metabolism, and glucose homeostasis (reviewed in [1,2]). In the last few years, PPARs have also emerged as key regulators of inflammatory and immune responses, opening a new area for the development of therapeutic drugs useful in the treatment of chronic inflammatory diseases such as atherosclerosis, obesity-induced insulin resistance, and neurodegenerative diseases (review in [3,4]).

There are three PPAR subtypes: α (NR1C1), β/δ (NRC2), and γ (NRC3), which exhibit distinct tissue distributions reflecting their biological functions [5,6]. PPARs are activated by fatty acids and naturally occurring fatty acid-derived molecules. It has been difficult to definitively establish the exact molecular species of fatty acids and/or their metabolites that bind to the various PPARs *in vivo*. However, considerable circumstantial evidence suggests that PPARs function as sensors of a variety of molecules that are derived either from extracellular or

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intracellular fatty acid metabolism (exemplified for PPAR γ in Fig. 1). In addition, PPARs can be regulated by several synthetic compounds. Fibrates, which include clofibrate, fenofibrate, bezafibrate, and gemfibrozil are PPAR α ligands widely used clinically to treat hypertriglyceridemia [7,8]. Thiazolidinediones (TZD), such as rosiglitazone and pioglitazone, are PPAR γ ligands used to treat type 2 diabetes [9,10].

PPARs activate gene expression by binding to specific DNA response elements in target genes as heterodimers with the retinoid X receptors (RXRs) [11,12] (Fig. 1 and 2). This activity enables PPARs to positively regulate gene networks involved in the control of lipid metabolism and glucose homeostasis in several tissues including adipose tissue, muscle and liver, ultimately influencing circulating lipid and glucose levels. Because saturated fatty acids have been shown to exert proinflammatory effects in several cell types [13], effects of PPAR agonists on circulating levels of these fatty acids could potentially affect inflammation indirectly. In addition, PPARs also act directly to negatively regulate gene expression of proinflammatory genes in a ligand-dependent manner by antagonizing the activities of other transcription factors such as members of the nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1) families [14-19] (Fig. 2 and 3). A major mechanism that underlies the ability of PPARs to interfere with the activities of these transcription factors has been termed transrepression. However despite the large amount of studies performed, the mechanisms whereby PPARs inhibit inflammatory gene expression are not completely understood. Recent studies using microarray analysis have shown that rosiglitazone inhibits only a subset of NF- κ B target genes [20,21]. The observation that PPAR γ inhibits only a subset of inflammatory response genes implies promoter-specificity in the mechanisms underlying transrepression. Here, we will review recent studies that describe anti-inflammatory actions of PPARs in different cell types and provide new insights into molecular mechanisms that may account for gene-specific transrepression by PPAR agonists.

2. PPARs and inflammatory/immune responses

In addition to the roles that PPARs play in lipid and glucose homeostasis, the three PPAR isoforms can participate in the regulation of inflammatory responses [3,4]. PPARs are expressed in vascular and immunological cell types such as monocyte/macrophages, endothelial, smooth muscle, lymphocytes, and dendritic cells. The three PPARs have been shown to inhibit the production of many inflammatory mediators and cytokines.

The first implication that PPARs played a role in inflammation was demonstrated in PPAR α -null mice. Mice lacking PPAR α have prolonged response to inflammatory stimuli such as leukotrienes and arachidonic acid [14]. Since these first studies, several observations have confirmed the important anti-inflammatory roles of PPAR α . PPAR α inhibits the production of inflammatory markers such as vascular cell adhesion molecule-1 (VCAM-1), interleukin (IL)-6, endothelin-1 (ET-1) and tissue factor (TF), in endothelial cells, smooth muscle cells and macrophages [22-26]. Similarly, in human aortic smooth muscle cells PPAR α activation by fibrates inhibits IL-1 induced secretion of IL-6 and induction of cyclooxygenase-2 (COX-2) [18]. Furthermore, Delerive et al have demonstrated that PPAR α -null mice aortae have an exacerbated response to lipopolysaccharide (LPS) demonstrating that the anti-inflammatory activity of these agonists requires PPAR α expression *in vivo* [27].

In addition to anti-inflammatory actions in the vascular wall, PPAR α ligands also control hepatic inflammation. Fibrates have been shown to be negative regulators of acute-phase proteins such as fibrinogen and C-reactive protein (CRP) [28]. Additional evidence supporting the role of PPAR α ligands in anti-inflammatory control comes from clinical trials. Interestingly, fenofibrate treatment of hyperlipidemic and atherosclerosis patients decreases the plasma concentrations of fibrinogen, IL-6, CRP, IFN- γ and TNF- α [18,29].

Ligand-induced activation of PPAR α has been shown to inhibit the production of IL-2 and IFN- γ in T cells [30-33]. In vivo treatment with the PPAR α ligand WY14,643 inhibits splenocyte cytokine production of IFN- γ , IL-6, and TNF- α [34]. Further investigation revealed that these effects are PPAR α -independent. In contrast, Poynter et al have shown that splenocytes from PPAR α -null mice produce higher levels of IL-6 and IL-12, supporting PPAR α -dependent anti-inflammatory effects [35].

In addition to the effects of PPAR α on lymphocytes, Lovett-Racke and colleagues have shown that PPAR α agonists inhibited MCP-1, NO, IL-1 β , TNF- α , IL-6 and IL-12 production in microglia cells, providing a potential mechanism by which PPAR α agonists may exert anti-inflammatory effects in the central nervous system [33,36]. Consistent with this, PPAR α agonists, gemfibrozil and fenofibrate, were shown to reduce severity of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) [33].

Recent studies have demonstrated protective roles of PPAR α in a number of other inflammation-related diseases such as atherosclerosis, inflammatory bowel diseases, liver fibrosis, and skin wound healing [34,37-42].

PPAR γ ligands have been shown to inhibit the production of many inflammatory mediators and cytokines in various cell types, including monocytes/macrophages, epithelial cells, smooth muscle cells, endothelial cells, dendritic cells and lymphocytes (reviewed in [3,4]). In addition, PPAR γ ligands have been shown to have anti-inflammatory effects in several disease models including atherosclerosis, obesity-induced insulin resistance, allergic encephalomyelitis, Parkinson, Alzheimer, psoriasis, inflammatory bowel diseases, and arthritis [42-54]. Recent clinical studies also suggest that negative regulation of gene expression may be the basis for some of the insulin-sensitizing effects of rosiglitazone observed in diabetic patients. Treatment of patients with type 2 diabetes treated with rosiglitazone reduced circulating inflammatory markers such as CRP, metalloproteinase (MMP)-9/gelatinase B, and TNF- α [55]. Genetic evidence for the anti-inflammatory effects of PPAR γ in disease remain limited, although a recent report showed that mice heterozygous for a null PPAR γ allele are more susceptible to experimentally induced arthritis and inflammatory bowel disease [44,51].

In macrophages/monocytes, PPAR γ ligands suppressed the upregulation of inducible nitric oxide synthase (iNOS), TNF- α , IL-1 β , IL-12, and MMP-9 [15,16,20]. PPAR γ has also been shown to inhibit MMP-9 expression and activity in smooth muscle cells [56]. More recently, PPAR γ has been shown to inhibit monocyte chemo-attractant protein-1 (MCP-1), IFN- γ , IFN-inducible protein of 10 KDa (IP-10) and monokine induced by IFN- γ (Mig) in endothelial cells [57,58]. Recent studies have demonstrated that PPAR γ agonists inhibit LPS/IFN- γ induced production of TNF- α and iNOS in microglia cells [59]. However, at least part of this anti-inflammatory action may be PPAR γ -independent [60].

Furthermore, PPAR γ agonists regulate T lymphocyte proliferation and immune activation [3]. PPAR γ has been shown to inhibit IL-2 and IFN- γ after T-cell activation [61,62]. Similarly, PPAR γ ligands inhibit the production of IP-10, Rantes, macrophage inflammatory protein (MIP)-1 α and IL-12 in dendritic cells [58,63]. These findings suggest that PPAR activation might have a profound impact on the local immune response with consequences affecting the progression of chronic inflammatory diseases. Conversely, cytokines regulate PPAR γ expression in macrophages, and other immune cells. For example, the Th2 cytokine IL-4 strongly upregulates, while IFN- γ strongly downregulates PPAR γ expression in macrophages [64,65] (Fig. 1). These observations suggest that PPAR γ may mediate some of the anti-inflammatory activities of IL-4, and that full pro-inflammatory activities require down-regulation of PPAR γ .

Despite the large number of studies, the role of PPAR γ in inflammation was controversial for some time because several synthetic and natural PPAR γ agonists were found to be capable of inducing anti-inflammatory responses through PPAR γ -independent mechanisms. For example, the PPAR γ agonist 15dPGJ2 can directly inhibit NF- κ B signalling by inhibiting I κ B kinase (IKK) and the DNA-binding activity of NF- κ B [66-68]. Furthermore, the doses of TZDs that exert maximal inhibitory effects on LPS-inducible genes are significantly higher than the concentrations at which these compounds bind efficiently to PPAR γ and very high doses of TZDs were found to inhibit some NF- κ B target genes, such as IL-1 β , in PPAR γ -null macrophages [69,70].

More recent studies using microarray analysis and PPAR γ knockout macrophages demonstrated that the inhibitory effects of rosiglitazone on LPS and IFN γ responses are PPAR γ -dependent when the drug is used at concentrations close to their binding activity [20]. However, at higher concentrations the inhibitory effects are PPAR γ -independent, probably due at least in part to activation of PPAR δ . These observations underscore the importance of clearly establishing receptor-dependence by using PPAR-specific drugs and/or PPAR knockout/knockdown models.

Compared to PPAR α and PPAR γ , relatively little is known on the role of PPAR δ in the regulation of inflammatory responses. Welch et al demonstrated that a PPAR δ agonist inhibited LPS-inducible genes, such as iNOS and COX-2, in murine peritoneal macrophages [20]. It has also been shown that PPAR δ ligands inhibited LPS-induced TNF- α production from cardiomyocytes [71]. In addition, a recent report has suggested that PPAR δ represses inflammatory genes such as MCP-1, IL-1 β and MMP-9 by an unconventional ligand-dependent transcriptional mechanism involving the binding to PPAR δ to transcriptional repressors [19, 53].

3. Transcriptional activities of PPARs

PPARs can regulate transcription by several distinct mechanisms, including ligand-dependent transactivation, ligand-independent repression and ligand-dependent transrepression (Fig. 2). The prototypic activity of PPAR is to activate transcription in a ligand-dependent manner following direct binding to DNA response elements in the promoter or enhancer regions of target genes (so called DR-1 elements or PPAR Response Elements (PPREs)) (*ligand-dependent transactivation*) (Fig. 2a). Ligand-dependent transactivation is linked to the recruitment of coactivator complexes that modify chromatin structure and facilitate assembly of general transcriptional machinery at the promoter [72-74]. A large number of coactivator complexes have been identified, and it is hypothesized that combinatorial usage of these complexes provides the basis for cell type-specific, gene-specific, and signal-specific transcriptional responses.

PPARs can also negatively regulate gene expression in a ligand-dependent manner by inhibiting the activities of other transcription factors, such as members of NF- κ B and AP-1 families (*ligand-dependent transrepression*) (Fig. 2b). In contrast to transcriptional activation and repression, which usually involves the binding of PPAR to specific response elements in the promoter or enhancer regions of target genes, transrepression does not involve binding to typical receptor-specific response elements [75,76]. Several mechanisms have been suggested to account for this activity, but despite intensive investigation, unifying principles remain to be elucidated.

In addition, PPARs repress the transcription of direct target genes in the absence of ligands (*ligand-independent repression*) (Fig. 2c). This activity has been linked to the recruitment of corepressor complexes that function to antagonize the actions of coactivator complexes [77, 78]. The most extensively characterized nuclear-receptor binding co-repressors are NCoR

(nuclear-receptor corepressor) and the related silencing mediator of retinoic-acid and thyroid-hormone receptors (SMRT) [79,80]. NCoR and SMRT are components of co-repressor complexes containing HDAC3, transducin beta-like protein-1 (TBL1) and TBL1-related protein (TBLR1) that interact with a subset of unliganded nuclear receptors that mediate transcriptional repression [81,82]. The switch from repression to activation involves a ligand-induced allosteric change in the C-terminal region of the ligand-binding domain that reduces affinity for corepressors and increases affinity for coactivators by establishing a 'charge clamp' for LXXLL-containing motifs in nuclear receptor coactivators [83-86]. In addition to allosteric changes in the ligand binding domain, recent studies suggest that an active, ubiquitylation-dependent step is required to clear NCoR complexes from promoters of nuclear receptor target genes upon agonist binding [87]. In the case of retinoic acid receptors, this clearance mechanism is dependent on activation of the ubiquitin E3 ligase activity of TBLR1, which in turn functions to recruit the ubiquitin E2 ligase UbcH5 and proteasome machinery required for NCoR clearance.

Although initially identified as corepressors of nuclear receptors, subsequent studies demonstrated that NCoR and SMRT function as corepressors required for active repression of genes under transcriptional control of numerous additional signal-dependent transcription factors, including AP-1 and NF- κ B factors [88-90]. Active, signal-dependent removal of these complexes was found to be required for transcriptional activation of AP-1 and NF- κ B target genes [87-90]. As in the case of activation of retinoic acid responsive genes, clearance of NCoR complexes from inflammatory gene promoters required Tblr1 ubiquitin E3 ligase and Ubc H5 ubiquitin E2 ligase activities (Fig. 3e). Recent studies indicate that NCoR/SMRT complexes are required for PPAR γ -dependent transrepression, as described in further detail below [90].

4. Molecular mechanisms of transrepression

Previous studies have provided evidence that PPARs can inhibit inflammatory gene expression by several mechanisms, including competition for a limiting pool of coactivators, direct interaction with p65 and p50 subunits and c-Jun, modulation of p38 mitogen-activated protein kinase (MAPK) activity, and partitioning the corepressor B-cells lymphoma 6 (BCL-6) (Fig. 3) [19,23,91,92]. These findings have led to a number of different models, but some of these studies have been performed using 15-dPGJ2, which has been shown to have PPAR γ -independents effects. It is probable that at least some of the described mechanisms operate in a cell-type and in a PPAR isoform-specific manner. Consistent with this possibility, studies in macrophages indicate that PPAR γ agonists do not inhibit nuclear entry of NF- κ B or its binding to genes that are subject to transrepression and microarray analysis supports the conclusion that PPAR specifically regulates only a subset of LPS-induced genes in this cell type [20,21, 90]. These observations indicate promoter-specificity in the mechanisms underlying transrepression in this cell type and are thus inconsistent with models in which NF- κ B function is inhibited at a global level.

4.1. Direct interactions between PPARs and other transcription factors

Several reports have suggested that PPARs inhibit the expression of proinflammatory genes by interference with signal-dependent activation of NF- κ B, AP-1, C/EBP, STAT and NF-AT. In the direct interaction model, PPARs and these transcription factors bind each other via protein-protein interactions and prevent binding to their response elements.

Ligand-activated PPAR α has been shown to interfere with DNA binding of both AP-1 and NF- κ B activity in IL-1 α stimulated IL-6 induction in smooth muscle cells. PPAR α inhibits the vascular inflammatory response by direct protein-protein interaction with p65 and c-Jun (Fig. 3a) [23]. In a similar manner, PPAR α ligands interfere with the activator protein-1 signaling pathway, which mediates thrombin-activation of ET-1 gene expression in endothelial cells

[63]. Fenofibrate, a PPAR α agonist, down-regulates IL-6-induced acute phase response (APR) gene expression in vivo. This suppression is due to the down-regulation of the IL-6 receptor components gp80 and gp130 in the liver, thereby reducing the phosphorylation and activation of STAT3 and c-Jun; and to the reduction of the basal expression of the transcription factors CCAAT enhancer-binding protein- α , β , and δ (C/EBP α , β , and δ) [93].

In addition, PPAR α ligands, in smooth muscle cells and hepatocytes, induce the expression of the inhibitory protein inhibitor of kappa B (I κ B) α , which sequesters the NF- κ B subunits in the cytoplasm and consequently reduces their DNA binding activity (Fig. 3b) [27,94]. Similarly, fibrates down regulate IL-1 β -induced CRP expression in a PPAR α -dependent manner, via reduction of the formation of the nuclear p50/C/EBP β complex due to an increase in I κ B α expression and to a decrease in the hepatic p50 and C/EBP β protein levels [95,96].

PPAR γ also negatively modulates the AP-1 and NF- κ B pro-inflammatory pathways. In human vascular endothelial cells PPAR γ has been shown to alter c-Jun binding to the human ET-1 promoter, as reported above for PPAR α [63]. Similarly, PPAR γ inhibits LPS-stimulated production of IL-12 in macrophages by direct interaction with p65/p50 [97]. In addition, Zingarelli et al demonstrated that PPAR γ inhibits activation of AP-1 and JNK activity and reduces activity of IKK and consequent degradation of I κ B α in the lungs, resulting in reduced activation of NF- κ B [98].

In activated T lymphocytes, Yang and colleagues have shown a direct protein-protein interaction between the nuclear factor of activated T cells (NFAT) and PPAR γ , which might explain the inhibition of IL-2 and IL-12 secretion by PPAR γ ligands [62,97]. Cunard et al have shown that PPAR γ acts on the IFN γ promoter by interfering with c-Jun activation in T cells [61]. Recently, Kelly and colleagues have described a novel anti-inflammatory mechanism in the gut, by which commensal anaerobic bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR γ and RelA [92]. The pharmacological relevance of this mechanism needs to be demonstrated.

4.2. Regulation of kinase activity

The mitogen-activated protein (MAP) kinase (MAPK) pathway is also regulated by PPARs at different levels. Activation of PPAR γ reduces c-Jun N-terminal kinase (JNK) MAPK and p38 activation in the colon, leading to down regulation of pro-inflammatory gene expression (fig. 3c) [44]. Similarly, Goetze et al have shown that the PPAR γ ligands, rosiglitazone and troglitazone, inhibit vascular smooth muscle cell migration pathways downstream of the extracellular signal-regulated kinase (ERK)/MAPK pathway [99-101]. In addition, they have shown that PPAR α and PPAR γ ligands inhibit endothelial cell migration by inhibition of VEGF-induced Akt phosphorylation [102]. In a recent study, Akaike et al have proposed a role of ERK5 in flow-mediated anti-inflammatory effects of PPAR γ in endothelial cells [103].

Jones and colleagues have shown that unliganded PPAR α suppresses the phosphorylation of p38 MAPK after T-cell stimulation. Ligand activation releases this inhibition and promotes the expression of the transcription factor of T cells (T-bet) [104]. Recently it has been shown that the anti-inflammatory effects of PPAR α in macrophages involve the inhibition of the Protein kinase C signaling pathway [105,106]. However, in general very little is known about the molecular mechanisms by which PPARs and their ligands modulate kinase activities. In addition, the PPAR-dependence of these mechanisms needs to be addressed using PPAR knockout animals.

4.3. Interactions with Coregulators

PPARs and many of the transcription factors that drive inflammatory responses require an overlapping set of coactivator proteins. In the co-activator competition model, PPARs compete with NF- κ B and AP-1 for binding to the general coactivators CREB-binding protein (CBP) and p300, or other coregulators, which are present in the cell in limiting amounts (Fig. 3d) [107]. Li et al have shown a strong correlation among PPAR γ interaction with coactivators and iNOS promoter repression in response to ligand binding. This repression requires both the PPAR γ ligand-dependent transactivation domain 2 (AF2), shown to be essential for coactivator recruitment, and the DNA binding domain [91]. Similarly, in liver, fibrates down-regulate IL-6-stimulated fibrinogen expression via inhibition of CCAAT-box/enhancer-binding protein-beta (C/EBP β) activity by competing for the glucocorticoid receptor-interacting protein-1/transcription intermediary factor-2 (GRIP-1/TIF-2) [39]. Others have reported, however, that the PPAR-dependent repression of both AP-1 and NF- κ B-mediated gene expression is independent of the amount of CBP in the cell [23]. The basis for these differences is not clear, but in many cases, conclusions regarding roles of coregulators have been based on the use of transient reporter assays using artificial transcription units and overexpression of various cofactors that restore repressive effects of PPAR agonists. It is now clear that these assays do not accurately reflect the specificity of transrepression observed for endogenous genes and naturally occurring levels of coregulators. Therefore future efforts will require the use of experimental model systems that focus more specifically on the regulation of endogenous genes.

4.4. Corepressor-dependent model of transrepression

Recent studies have suggested two distinct models for corepressor-dependent transrepression by PPARs. In the case of PPAR δ , evidence has been presented in which PPAR δ controls the inflammatory status of macrophages based on its association with the transcriptional repressor BCL-6 [19]. In the absence of ligand, PPAR δ sequesters BCL-6 from inflammatory response genes, leading to increased levels of gene expression. In contrast, in the presence of ligand, PPAR δ releases the repressor, which now distributes to NF- κ B-dependent promoters and exerts anti-inflammatory effects by repressing transcription from these genes. This mechanism was shown to repress expression of MCP-1 and it will be of interest to determine the extent to which this mechanism operates to mediate repression of other inflammatory response genes.

In the second model, recent studies have proposed that PPAR γ mediates transrepression of a subset of inflammatory response genes in macrophages by preventing the signal-dependent clearance of corepressor complexes on inflammatory promoters downstream of LPS signaling (Fig. 3e) [90,108]. Chromatin immunoprecipitation (ChIP) assays and siRNA knockdown experiments showed that under basal conditions NCoR/HDAC3/TBL/TAB2 complexes are associated with the promoter of the gene encoding iNOS, and that the NCoR and HDAC3 components were cleared within 10 minutes following LPS stimulation. This clearance step required the ubiquitin E3 ligase activities of Tbl1/TblR1 and the Ubc H5 ubiquitin E2 ligase, as described above. Intriguingly, PPAR γ agonists caused PPAR γ to localize to NCoR complexes on the iNOS promoter and prevented their removal by a ubiquitylation-dependent mechanism. The targeting of PPAR γ to NCoR complexes was found to depend on its ligand-dependent SUMOylation by SUMO1, facilitated by the SUMO E3 ligase PIAS1. The protein inhibitor of activated STAT1 (PIAS1) was initially identified as a suppressor of interferon-dependent transcription [109] and is now known to belong to the SUMO E3 ligase family [110]. PPAR γ contains two SUMOylation sites (K77 and K365). The SUMOylation of K77 inhibited PPAR γ transactivation but did not affect transrepression [111]. However, the mutation of K365 eliminated PPAR γ recruitment to the iNOS promoter and its ability of repressing it. As a consequence of SUMOylation of K367 and PPAR γ binding to NCoR complexes, the ubiquitin-conjugating enzyme Ubc H5 is not recruited to the co-repressor

complex, and the NCoR complex remains bound to the promoter and maintain it in an actively repressed state. Similar results were obtained for four additional endogenous LPS-target genes: Ccl3, Ccl7, Cxcl10 and Tgtp, indicating that this mechanism of transrepression is not specific for the iNOS promoter. In addition, because only a subset of LPS-target genes is repressed by NCoR complexes, this mechanism provides an explanation for the PPAR γ promoter-specific repression. In a very recent study, Ghisletti et al have proposed that Liver X Receptor transrepression of inflammatory target genes also utilizes a SUMOylation and NCoR-dependent pathway suggesting that this mechanism is a general molecular strategy for transrepression [108]. It will be very interesting to define the extent to which this pathway is used by other PPAR isoforms and other cell types. Ultimately, it will be important to address whether this pathway contributes to the anti-inflammatory effects of PPAR γ in inflammatory and metabolic diseases.

5. Conclusions

Since their characterization, it is now clear that PPARs are important in the control of inflammatory responses and immunity. However, the range of transcription factors affected and the molecular mechanism involved may be different for each PPAR isoform and cell type. Defining the molecular mechanisms by which PPARs negatively regulate inflammatory programs of gene expression will improve our understanding of the roles they play in immunity and will allow for us to exploit their potential in the therapeutic arena. Future studies using engineered mouse models and functional genomic approaches are needed to more clearly establish the mechanisms by which PPARs exert their anti-inflammatory actions.

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Fig 1.

PPARs functions as sensors of lipids that are derived either from the diet and intracellular fatty acid metabolism. PPAR γ expression is upregulated in macrophages and T cells during the inflammatory response, and can be induced by IL-4 and GM-CSF. In contrast, IFN- γ and LPS repress the expression of PPAR γ . IL-4, Interleukin-4; GM-CSF, granulocyte-macrophage-colony stimulation factor; IFN- γ , interferon- γ ; LPS, lipopolysaccharide.

Fig 2.

Transcriptional activities of the Peroxisome Proliferator Activated receptors. PPARs can both activate and inhibit gene expression. (a) Ligand-dependent transactivation. PPARs activate transcription in a ligand-dependent manner by binding directly to specific PPAR-response elements (PPRE) in target genes as heterodimers with RXR. Binding of agonists ligand leads to the recruitment of coactivator complexes that modify chromatin structure and facilitate assembly of the general transcriptional machinery to the promoter. (b) Ligand-dependent transrepression. PPARs repress transcription in a ligand-dependent manner by antagonizing the actions of other transcription factors, such as nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1). (c) Ligand-independent repression. PPARs bind to response elements in the absence of ligand and recruit corepressor complexes that mediate active repression. This complex antagonizes the actions of coactivators and maintains genes in a repressed state in the absence of ligand.

Fig 3.

Mechanisms of PPAR-mediated transrepression. (a) Direct interaction between PPAR and p65 subunit. (b) Induction of $I\kappa B\alpha$ expression. (c) Activation of PPAR inhibits c-Jun N-terminal kinase (JNK) MAPK activity. (d) Competition for a limiting pool of coactivators, such as CREB-binding protein. (e) Corepressor-dependent model of transrepression. PPAR γ can inhibit inflammatory responses by blocking the signal-dependent clearance of NCoR corepressor complexes. LPS stimulation promotes the ubiquitin-dependent proteosomal degradation of NCoR corepressor complexes. In the presence of ligand, PPAR γ is sumoylated and targeted to the NCoR corepressor complexes on gene promoters, preventing the clearance of these complexes. AP-1, activator protein-1; NCoR, nuclear-receptor co-repressor

complexes; HDAC3, histone deacetylase 3; TBL1, transducin- β -like 1, TBL1; TBL1-related protein, TBLR1; PIAS1, protein inhibitor of activated STAT1; Tab2, TAK1-binding proteins; K, SUMO target lysine within PPAR γ DNA-binding domain; Su, SUMO conjugate on target cystine.