Coordination of inflammation and metabolism by PPAR and LXR nuclear receptors

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Abstract

Biological systems are integrated networks constantly responding to internal and external stimulators. Understanding the intrinsic response to an imbalanced system provides the opportunity to develop therapeutic approaches to reinstate the natural balanced state. Increasing evidence suggests that members of the nuclear receptor superfamily integrate both inflammatory and metabolic signals to maintain homeostasis in immune cells such as macrophages and lymphocytes. PPAR and LXR are nuclear receptors activated by fatty acid and cholesterol derivatives respectively that control the expression of an array of genes involved in lipid metabolism and inflammation. Recent studies have uncovered distinct mechanisms for transcriptional regulation of metabolic and inflammatory target genes by PPAR and LXR and have expanded the biology of these receptors to include roles in alternative macrophage activation and adaptive immunity.

Introduction

PPAR and LXR: lipid-activated nuclear receptors

Nuclear receptors are a family of ligand-activated transcription factors consisting of 48 members. Most receptors share a similar structure that includes an amino terminal activation domain (AF-1), a DNA binding domain, a ligand-binding domain, and a second carboxy terminal activation domain (AF-2) [1]. Upon ligand binding these receptors are known to undergo a conformation change followed by the release of corepressors and the active recruitment of coactivators. Nuclear receptors have been demonstrated to affect transcription through multiple different modes of action, including direct activation of genes, ligand-independent repression, ligand-dependent repression, and transrepression [2].

Several members of the nuclear receptor family, including LXRs and PPARs, have emerged as important regulators of metabolic and inflammatory signaling, particularly in the context of metabolic disease and immunity [3]. PPARs and LXRs are activated by free fatty acid and cholesterol metabolites respectively, and control expression of a range of metabolic and inflammatory genes. The ability of these receptors to link metabolism to inflammatory signaling makes them potentially attractive targets for treatment of metabolic diseases, such as atherosclerosis and diabetes, and the modulation of inflammation and immune responses.

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Here we review recent advances in our understanding of the role of PPAR and LXR as transcriptional integrators of metabolic and inflammatory gene expression.

Peroxisome Proliferator-Activated Receptors (PPARs)

The founding member of the peroxisome proliferator-activated receptor (PPAR) subfamily is PPAR α , first identified as the target of fibrates and other compounds that induce peroxisome proliferation in rodents [4]. Subsequently, two other family members were discovered, PPAR δ/β and PPAR γ [5,6]. Natural ligands for the PPARs are believed to include native and modified polyunsaturated fatty acids and eicosanoids. Additionally, the PPARs have a large ligand binding pocket that can accommodate a diverse range of synthetic ligands [7]. Similar to LXRs, the PPARs form heterodimers with RXR and bind to DNA in a sequence-specific manner. The response element for PPAR (PPRE) is a direct repeat (AGGTCA) separated by one base pair (DR-1) [8].

The biological roles of the PPARs as regulators of fatty acid metabolism have been extensively characterized described and characterized [9]. PPAR α can be detected in variety of tissues involved in fatty acid oxidation, such as the liver, kidney, heart, skeletal muscle and brown fat. It is also expressed in endothelial cells and vascular smooth muscle cells. PPAR δ is expressed ubiquitously and plays an important role in energy homeostasis, thermogenesis and β -oxidation of fatty acids. PPAR γ is most highly expressed in adipose tissue but is also expressed in macrophages, colon, and a number of other cell types at lower levels. PPAR γ serves as a master regulator of adipocyte differentiation and is an important determinant of insulin sensitivity [10,11]. Since their discovery, a number of synthetic ligands for these receptors have been identified, including fibrates, GW501516 and thiazolidinediones, for PPAR α , PPAR δ and PPAR γ , respectively [12,13].

PPARs and inflammation

The immune system like other biological system is a complex network designed to maintain homeostasis by responding to both acute and chronic perturbations. Macrophages play a crucial role in ensuring that balance is maintained through a diversity of contrasting mechanisms including but not limited to cell debris clearance and cell-to-cell interactions with other immune cells. In addition to PPARs' widely accepted role in metabolic pathways, PPARs have also been shown to modulate gene expression in macrophages. Numerous studies have shown that PPARs repress NF- κ B, NFAT, STAT, and AP-1 target genes in response to a variety of inflammatory stimuli, including cytokines and TLR ligands [14–16]. The mechanisms involved in the various repressive effects of each of the PPARs are still being elucidated, and some of these will be discussed in detail below. However, it is worth emphasizing that signal-, cell type-, even promoter-specific mechanisms may exist for PPAR family members. In addition, the fact that many synthetic activators of PPARs may exert receptor-independent effects underscores the need for caution when evaluating the biological activities of such compounds in inflammatory assays.

Each of the PPARs has also been linked to the development and potential therapy of inflammatory disorders including atherosclerosis. Aortic lesion formation begins with the activation of endothelial cells leading to the increased of vascular cell adhesion molecule-1 (VCAM-1). In response, leukocytes and monocytes accumulate in the arterial walls and drive the plaque formation. Ligand activation of PPAR α in endothelial cells is able to repress this cytokine-induced expression of the VCAM-1 thereby protecting against lesion formation [17,18]. Additionally, in macrophages, ligand activated PPAR γ promotes scavenging of oxidized LDL through induction of the scavenger receptor CD36 as well as enhances cholesterol efflux through induction of LXR α [19,20].

The role of PPARs in atherosclerosis is supported by a number of *in vivo* studies. LDLR^{-/-} mice reconstituted with PPAR γ ^{-/-} bone marrow showed an increase in lesion formation, whereas mice treated with either PPAR γ ligand or PPAR α ligand showed a reduction in atherosclerosis [21,22]. Bone marrow transplant studies reconstituting LDLR^{-/-} mice with PPAR δ ^{-/-} macrophages have reported a decrease in atherogenesis and inflammation [23]. Other studies using PPAR δ ligand have shown a reduction of inflammatory gene expression but not a decrease in atherosclerosis in LDLR^{-/-} mice challenged with hypercholesterolemic diet [22]. Recently, Takata et al. reported a reduction in atherosclerosis by PPAR δ ligand in an angiotensin II accelerated LDLR^{-/-} model [24].

Alternative Activation of Macrophages

Differentiated macrophages can acquire distinct phenotypic characteristics, including the so-called classically activated (M1) phenotype and the alternatively activated (M2) phenotype [25]. M1 activation is triggered by stimuli such as LPS and is associated with the production of proinflammatory cytokines including IFN- γ and IL-12 and the mediation of Th1 responses. In contrast, M2 activation is triggered by IL-4 and IL-13 and linked to Th2 responses, tissue remodeling and repair. Recent studies have suggested an important role for members of the PPAR subfamily in regulating macrophage phenotypic activation. Early studies by Glass and colleagues reported induction of PPAR γ in macrophages by IL-4, suggesting a potential role in alternative activation [26]. Recently, studies of mice lacking PPAR γ expression specifically in macrophages revealed that PPAR γ is important for the effective maturation of alternatively activated macrophages [27]. Additionally, reduced M2 macrophage differentiation in the absence of PPAR γ was associated with decreased insulin sensitivity. In corollary studies of human macrophages, Bouhrel et al. described an enhanced M2 macrophage phenotype in response to PPAR γ activation [28].

Further exploration into the metabolic regulation of macrophages has unveiled a role for PPAR δ in alternative activation as well. Both PPAR γ and PPAR δ regulate expression of the arginase I gene, a key marker of the M2 phenotype [25,27,29]. Odegaard et al. reported that PPAR δ is required for alternative activation of liver macrophages (Kupffer cells) by IL-4 and a yet to be identified fatty acid [30]. In addition, mice lacking PPAR δ in bone marrow exhibited decreased glucose tolerance and insulin sensitivity, suggesting that the alternative activation of Kupffer cells through PPAR δ affects systemic metabolic programs. In a highly related study, Kang et al. also presented findings suggesting that IL-13 produced by adipocytes biases macrophages towards the M2 phenotype in a PPAR δ -dependent manner [31]. They also reported that macrophage-specific PPAR δ knockout models exhibited a reduction in insulin sensitivity. Collectively, this recent work highlights intriguing connections between PPAR signaling pathways, macrophage phenotypic development and metabolic disease.

Liver X Receptors (LXRs)

The Liver X Receptors, LXR α and LXR β are now recognized to be central regulators of cholesterol metabolism in mammals [32]. Both LXRs activate target genes by binding to response elements located in their promoter regions as heterodimers with the Retinoid X Receptor (RXR). LXR response elements are comprised of two direct repeats (DRs) of the hexamer sequence, AGGTCA, separated by four base pairs (DR-4). Oxysterols and intermediates of the biosynthetic cholesterol pathway have been identified as the natural ligands for LXR, specifically 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 27-hydroxycholesterol, 24(S)-epoxycholesterol, 25-epoxycholesterol and desmosterol [33,34]. Synthetic agonists such as T0901317 and GW3965 have also been described that have aided in the characterization of LXR function. LXRs share 77% structural identity, but their expression patterns vary greatly. LXR β is found ubiquitously, while LXR α is expressed primarily in the liver, intestine, kidney, adrenal glands, adipose and macrophages [32].

Considerable evidence suggests that the targets for the two LXRs are highly overlapping and that the receptors functionally compensate for one another in most physiological contexts [35].

Numerous studies have established that LXRs regulate gene expression linked to cholesterol metabolism in a tissue-specific manner. For example, LXR activation in rodent liver upregulates Cyp7a1, a member of the cytochrome P450 family that is critical for bile acid synthesis [36]. In the intestine, LXR controls the reabsorption of cholesterol via the expression of ABCG5 and ABCG8 [37]. In peripheral cells such as macrophages, LXRs regulates the expression of a panel of genes involved in reverse cholesterol transport. In response to macrophage cholesterol overload, LXRs induce expression of the cholesterol efflux transporters ABCA1 and ABCG1, the apolipoproteins apoE and apoCs, and the lipoprotein-remodeling enzyme PLTP [32,35]. As a result of these effects, systemic activation of LXRs thus initiates a series of tissue-specific transcriptional programs that regulate whole body cholesterol content. Pharmacologic activation of these receptors *in vivo* results in increased HDL levels, net whole body cholesterol loss, and reduced atherosclerosis [38,39].

LXRs in Innate Immunity

In addition to their key role in cholesterol homeostasis, LXRs have emerged as important regulators of inflammatory gene expression and innate immunity. We and others have found that ligand-activated LXR blunts the induction of classical inflammatory genes such as iNOS, COX-2, MMP-9 and various chemokines in response to LPS, TNF- α and IL-1 β stimuli [16, 40,41]. LXRs also have been shown to positively regulate expression of arginase II, a gene that may have anti-inflammatory effects through antagonism of NO signaling [42]. Importantly, all of these effects of LXR agonists are not observed in macrophages lacking LXR α and LXR β expression. Studies have also shown that activation of TLR3 and 4 by bacterial and viral components inhibits LXR signaling via the transcription factor IRF-3, suggesting that LXR functions to regulate crosstalk between inflammatory and metabolic pathways [43]. Finally, LXR ligands have proven effective in the amelioration of inflammation in a number of *in vivo* assays, including models of contact dermatitis and atherosclerosis [41, 44,45].

In an effort to understand the relevance of LXR signaling for innate immune responses, Joseph et al. challenged mice lacking LXRs with *Listeria monocytogenes* [46]. Remarkably, LXR $\alpha^{-/-}$ and LXR $\alpha\beta^{-/-}$ mice showed increased susceptibility to infection. This effect was shown to be due to defective macrophage function and to correlate with decreased expression of the macrophage survival factor AIM/Sp α , an LXR target gene. Valledor et al. documented a similar role for LXR and AIM/Sp α in macrophage survival in the setting of additional *E. coli* and *Salmonella typhimurium* infection [47].

LXRs in Acquired Immunity

In addition to their importance in innate immune cells, recent studies have revealed unexpected links between sterol metabolism, LXR and adaptive immune responses. An important characteristic of adaptive immunity is the capacity of antigen-specific lymphocytes to undergo rapid and extensive proliferation in response to antigenic challenge. Bensinger et al. have found that the intracellular availability of sterols is dynamically regulated during lymphocyte cell activation, and that this is linked to transcriptional responses mediated by SREBP and LXR, as well as to cell cycle control [48]. Analysis of purified primary lymphoid cultures established that activation of LXR β by physiologic or pharmacologic ligands diminishes the proliferative capacity of B and T cells. Conversely, genetic loss of LXR β rescued cells from the inhibitory effect of LXR agonist and potentiated mitogen- and antigen-driven expansion. Furthermore, the ability of LXR to impact cell proliferation has a functional consequence for lymphoid

homeostasis and antigen-driven immune responses *in vivo*. Unexpectedly, the effects of LXR on cell proliferation are not due to transrepression of inflammatory signaling pathways, rather they are related to control of cellular cholesterol metabolism through the sterol transporter ABCG1.

Mechanisms of Transrepression - LXRs and PPARs

As outlined above, an important function of PPARs and LXRs is the negative regulation of gene expression. Both receptors have the ability to inhibit inflammatory gene expression in a signal-specific manner through a mechanism termed 'transrepression.' In contrast to target gene activation, transrepression does not depend on direct binding of PPAR/RXR or LXR/RXR heterodimers to the promoters being repressed [2]. Over the past several years, an important series of studies have shed light on the mechanism of ligand-dependent transrepression [49]. NF- κ B and AP-1 are key inflammatory transcription factors, and binding sites for these proteins have been described in many immediate inflammatory response genes. On inactive promoters, factors such as NF- κ B are bound to N-CoR corepressor complexes, maintaining basal repression. During transrepression, nuclear receptor activation by ligand prevents NCoR from being cleared from the promoters of inflammatory genes by ubiquitylation or other clearance processes.

Glass and colleagues have examined the exact molecular mechanisms by which PPAR and LXR confer transrepression in response to TLR3 or TLR4 activation. In a seminal study, they proposed that transrepression by PPAR γ is dependent on ligand-induced SUMOylation of the receptor by PIAS1 and SUMO1 [49]. Sumoylated PPAR was shown to be present in complexes bound to NF- κ B sites in inflammatory promoters and to block the ubiquitylation and removal of the NCoR complex resulting in gene repression. Further studies by Ghisletti et al. have outlined a parallel pathway which LXR effects transrepression. SUMOylation sites were identified in LXRs and shown to interact with HDAC4 E3 ligase and SUMO2/3 to prevent NCoR clearance and repress gene activation [50].

Conclusions

Although the nuclear receptors PPAR and LXR were initially characterized as regulators of metabolic diseases, recent studies have clearly demonstrated an important role for these nuclear receptors in inflammatory pathways and immunological regulation. These pioneering studies advocate continued exploration of the manner by which nuclear receptors execute control of metabolism and inflammation and integrate these pathways in complex biological systems. A better understanding of nuclear receptors crosstalk between metabolism and immunity may ultimately lead to the development of new therapeutics for metabolic diseases in which inflammation plays an important role.

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Figure 1.

Regulation of cholesterol and inflammatory signaling by LXR. Uptake of oxidized LDL by macrophages leads to increased intracellular levels of cholesterol and oxysterols and to LXR activation. LXR induces expression of cholesterol efflux transporters ABCA1 and ABCG1 through direct promoter activation. LXR activation also blunts the expression of inflammatory gene expression triggered by stimuli such as TLR ligands and cytokines. Inhibition of inflammation by LXR occurs via the mechanism of transrepression.

Figure 2.

A role for PPAR signaling in alternative (M2) macrophage activation. Recent studies suggest that cytokines such as IL-4 and IL-13 promote alternative macrophage activation through a pathway that requires PPAR γ and PPAR δ transcriptional activity. PPARs directly regulate expression of the M2 marker Arg I and promote mitochondrial biogenesis and oxidative metabolism to support the M2 phenotype. The balance between less inflammatory M2 cells and classically activated M1 macrophages is altered in mice lacking PPARs and has been proposed to be involved in the pathogenesis of insulin resistance.