

MINIREVIEW

Nuclear Receptors and Inflammatory Diseases

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It is well known that the steroid hormone glucocorticoid and its nuclear receptor regulate the inflammatory process, a crucial component in the pathophysiological process related to human diseases that include atherosclerosis, obesity and type II diabetes, inflammatory bowel disease, Alzheimer's disease, multiple sclerosis, and liver tumors. Growing evidence demonstrates that orphan and adopted orphan nuclear receptors, such as peroxisome proliferator-activated receptors, liver x receptors, the farnesoid x receptor, NR4As, retinoid x receptors, and the pregnane x receptor, regulate the inflammatory and metabolic profiles in a ligand-dependent or -independent manner in human and animal models. This review summarizes the regulatory roles of these nuclear receptors in the inflammatory process and the underlying mechanisms. *Exp Biol Med* 233:496–506, 2008

Key words: nuclear receptor; peroxisome proliferator-activated receptors; liver x receptors; farnesoid x receptor; NR4As; retinoid x receptors; steroid xenobiotic receptor/pregnane x receptor; inflammation; liver

Introduction

Nuclear receptors are a class of intracellular transcription factors activated by ligands. One of the unique characteristics of nuclear receptors is that they can directly interact with DNA and control transcription, distinguishing

them from other classes of receptors. Consequently, nuclear receptors play key roles in reproduction, development, and homeostasis of organisms (1–4).

According to their ligand-binding and DNA-binding properties, nuclear receptors are classified into three families. The first is the classic and most extensively characterized group, steroid- and thyroid-hormone receptors (1). Among these hormone receptors, glucocorticoid receptor (GR) is a ubiquitous receptor that switches off multiple inflammatory genes encoding cytokines, adhesion molecules, and inflammatory receptors. The second class is the orphan nuclear receptors, which are structurally related to nuclear hormone receptors but lack known physiological ligands. In this group, nerve growth factor-induced clone B (Nur77), nuclear receptor related-1 (Nurr1), and neuron-derived orphan receptor-1 (NOR1) are involved in the inflammatory process (5). The third class of nuclear receptors includes adopted orphan nuclear receptors, which function as heterodimers with retinoid x receptor (RXR). These orphan receptors are considered adopted, as studies show that they can bind physiological ligands and display physiological effects. Members of this group participating in the regulation of inflammatory process include receptors for fatty acids (peroxisome proliferator activated receptors [PPARs]: PPAR α , β/δ , and γ), oxysterols (liver x receptors [LXRs]: LXR α , and β), bile acids (farnesoid x receptor [FXR]), xenobiotics (steroid and xenobiotic receptor/pregnane x receptor [SXR/PXR] and constitutive androstane receptor [CAR]) (6).

Chronic inflammation is one of the key players in the common pathophysiological process related to atherosclerosis, obesity, and type II diabetes. A constellation of symptoms in early metabolic syndrome, such as weight gain, insulin resistance, hypertension, hypertriglyceridemia, and low levels of high-density lipoprotein, are closely related with the above diseases. Inflammation also contributes to

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other chronic inflammatory diseases, such as inflammatory bowel disease (IBD), Alzheimer's disease (AD), multiple sclerosis (MS), and arthritis. Many inflammatory cells are part of the overall group of immune cells that participate in chronic inflammation. Upon stimuli, these cells release multiple inflammatory mediators that interact with and activate structural cells at the site of inflammation. Although inflammatory cells and mediators differ among chronic inflammation-induced diseases, they are characterized by increased expressions of multiple inflammatory genes and proteins, some of which are common to all inflammatory diseases, with others more specific to a particular disease. In this review, we focus on the regulatory effects and the possible molecular mechanisms of class two (orphan) and class three (adopted orphan) nuclear receptors on the pathogenesis of chronic inflammatory diseases that include atherosclerosis, metabolic syndrome, IBD, AD, and MS (7–14).

PPARs

The PPAR family is comprised of three closely related isotypes (PPAR α , β/δ , and γ), which have been identified in various species and are structurally homologous. PPAR α and PPAR γ are found predominantly in liver and adipose tissue, respectively, and PPAR β/δ is ubiquitously expressed. PPARs can be activated by fatty acids, fatty acid derivatives, and synthetic compounds. PPARs heterodimerize with RXRs and bind to peroxisome proliferator response elements (PPREs) located in the promoter region of their target genes. Each member of the PPAR family plays a distinct role in lipid metabolism. PPAR α enhances fatty acid combustion in liver by inducing genes that encode enzymes involved in β -oxidation (15, 16). In contrast, PPAR γ serves as an essential regulator for adipocyte differentiation and lipid storage in mature adipocytes by increasing the expression of several essential genes in this pathway (16–18). PPAR β/δ participates in epidermal maturation and skin wound healing as well as in lipid metabolism (19, 20).

PPARs are expressed in macrophages, in T and B cells, and in endothelial cells that collectively participate in inflammation and immunity. Activated PPARs are most effective in reducing chronic inflammatory processes having less effect in acute inflammation. The anti-inflammatory effects of PPARs have been reviewed recently (21–27). One of the molecular mechanisms by which PPARs exert anti-inflammatory effects is their physical interactions with transcription factors, such as nuclear factor- κ B (NF- κ B), signal transducers and activators of transcription (STATs), nuclear factor of activated T cells (NF-AT), CAAT-enhancer binding protein (C/EBP), and activator protein 1 (AP-1). These interactions inhibit the expression of the majority of pro-inflammatory cytokines, chemokines, and enzymes. The second mechanism by which PPARs exert anti-inflammatory effects is sequestration of the common co-activators or co-repressors for transcription factors. For

instance, PPAR α and C/EBP β compete for the co-activator glucocorticoid receptor-interacting protein-1/transcriptional intermediary factor (GRIP-1/TIF) and repress inflammatory gene expression (21–27).

The first PPAR identified, PPAR α , is activated by natural lipophilic ligands, like fatty acids and their derivatives, certain leukotriene products, and synthetic ligands, such as fibrates. PPAR α regulates lipid metabolism and transport, fatty acid oxidation, and glucose homeostasis. In addition, PPAR α exerts anti-inflammatory effects. The anti-inflammatory effects by PPAR α are conducted through inhibiting the induction of pro-inflammatory cytokines, adhesion molecules, and extra-cellular matrix proteins or by stimulating the production of anti-inflammatory molecules. In general, PPAR α reduces the production of pro-inflammatory cytokines, limiting vascular inflammatory responses and atherosclerosis. Most evidence suggests that PPAR α -mediated pathways inhibit the initiation and progression of atherosclerosis, especially the atherosclerosis-associated inflammatory response. Activated PPAR α represses the early atherogenic gene vascular cell adhesion molecular1 (VCAM-1) expression (28, 29). This leads to a reduction of leukocyte adhesion to endothelial cells of the arterial vessel wall and an inhibition of subsequent trans-endothelial leukocyte migration. PPAR α activators fenofibrate or Wy14,643 inhibit tumor necrosis factor- α (TNF- α)-induced VCAM-1 gene expression and significantly reduce adhesion of U937 cells (human leukemic monocyte lymphoma cell line) to cultured human endothelial cells (ECs) (30). PPAR α activation also decreases expression of inflammatory cytokines, such as interferon- γ (IFN- γ), TNF- α , and interleukin (IL)-2 by Th1 cells (31, 32). In addition, PPAR α inhibits the induction of cyclooxygenase-2 (COX-2) expression stimulated by IL-1 β in smooth muscle cells (SMCs) (33). Aside from modulating the initiation stage of atherosclerosis, PPAR α inhibits the formation of macrophage foam cells during later stages of atherosclerosis and reduces the production of additional inflammatory cytokines, growth factors, and matrix metalloproteinases (MMPs) and enzymes. These effects are produced through limiting low density lipoprotein (LDL) oxidation and its uptake and inducing reverse cholesterol transport, such as CLA-1/scavenger receptor class B type I (SR-BI) and ATP-binding cassette transporter A1 (ABCA1) (34, 35). Furthermore, PPAR α may increase the stability of the atherosclerotic plaque and may limit plaque thrombogenicity. Repression of MMP-9 (36, 37), tissue factor (TF) (38, 39), and plasminogen activator inhibitor-1 (PAI-1) (40, 41) by activation of PPAR α may also partly account for these effects. In addition, activated PPAR α binds to PPREs or interacts with Sp1 at the promoter region of tumor suppressor p16 (p16) gene and enhances p16 gene expression. The up-regulated p16 inhibits the G1/S transition in SMCs and, subsequently, the cell-cycle progression and proliferation of the cells (42). The anti-inflammatory effect of PPAR α has not only been demonstrated in animal

atherogenic, dermatitis, and paw edema models (33, 43–45) but also in human patients (46). The chemotactic mediators and adhesion molecules are essential for recruitment of monocytes/macrophages, T cells, or neutrophils into the inflamed tissues. PPAR α agonists reduce the production of chemotactic mediators and adhesion molecules, such as monocyte chemoattractant protein-1 (MCP-1) (47), and its receptor chemokine (C-C motif) receptor-2 (CCR-2), IL-8 (48), and intercellular adhesion molecule-1 (ICAM-1) (49). PPAR α activation also induces the expression of anti-inflammatory mediator IL-10 (50) and cytochrome P450 4A (CYP4A), which degrades inflammatory fatty acids and leukotriene B₄ (LB₄), a potent chemotactic factor for neutrophils (51–53). In addition, PPAR α triggers monocyte/macrophage apoptosis (54); this, too, contributes to its anti-inflammatory effects *in vivo*.

The ubiquitously expressed PPAR β/δ is the last identified member of the PPAR family (55). The highest PPAR β/δ levels are found in small intestine, colon, heart, adipose tissues, and brain. Although little is known about the role of PPAR β/δ in comparison with that of PPAR α and γ , PPAR β/δ participates in epidermal maturation (19, 20, 56, 57). Recent studies have identified PPAR β/δ as an important regulator of atherosclerosis, lipid, glucose, and energy homeostasis (58–61).

One role of PPAR β/δ that has been elucidated is its involvement in the development of atherosclerosis. PPAR β/δ acts as a molecular switch between pro-atherogenic and anti-atherogenic activities. When atherosclerosis-prone LDL receptor-null mice are transplanted with PPAR β/δ -deficient bone marrow followed by consumption of an atherogenic diet, lesions and serum cholesterol profiles are reduced in the recipient mice (62, 63). Moreover, PPAR β/δ -/- macrophages display reduced inflammatory markers, such as MCP-1, IL-1 β , and MMP-9, suggesting that PPAR β/δ is pro-atherogenic (63). On the other hand, synthetic PPAR β/δ ligands suppress inflammation in wild-type macrophages, which is consistent with the reduced inflammation found in PPAR β/δ -null cells. This discrepancy has been interpreted in the following manner: PPAR β/δ binds to transcriptional repressors, such as B cell CLL/lymphoma 6 (BCL-6), in the absence of agonists, and is unable to inhibit expression of inflammatory genes, such as MCP-1 expression, but, in the presence of the agonists, BCL-6 is released and represses MCP-1 expression. Hence, genetic deletion of PPAR β/δ or activation of PPAR β/δ by the agonists leads to the dissociation of BCL-6 from PPAR β/δ and, consequently, represses the expression of MCP-1, MCP-3, and IL-1 β genes. The culmination of this series of activities produces anti-inflammatory effects (63).

PPAR β/δ participates in fat metabolism and prevents obesity. The PPAR β/δ agonist GW501516 produces remarkable changes in fat metabolic profiles in obese monkeys (64). GW501516 stimulates fatty acid β -oxidation by 50% in 3T3-L1 pre-adipocytes over-expressed with VP16-PPAR β/δ . GW501516 also increases fatty acid

metabolism and uncoupling in C2C12 skeletal muscle cells (58). In leptin-receptor deficient (db/db) obese mice, the PPAR β/δ -specific agonist L165041 induces high-density lipoprotein (HDL)-cholesterol levels without affecting blood glucose or triglyceride levels (65). Activation of PPAR β/δ in adipose can reverse the obesity phenotype of db/db obese mice. PPAR β/δ transgenic mice, generated by expressing VP16-PPAR β/δ in adipose tissue, have decreased lipid content in both serum and adipose tissue. In addition, the PPAR β/δ transgenic mice are completely resistant to high-fat diet-induced obesity (66).

In vitro studies show that activation of PPAR β/δ by GW0742 inhibits lipopolysaccharide (LPS)-induced expression of inducible nitric oxide synthase (iNOS), myeloperoxidase (MPO) activity, and epithelial inflammation (67). PPAR β/δ ligand L165041 reduces TNF α -induced up-regulation of VCAM-1 and MCP-1 expression as well as NF- κ B translocation in EAhy 926 human endothelial cell line (30, 36). Additionally, carrageenan-induced paw edema is reduced by PPAR β/δ ligand L783483 in rodents (68, 69). PPAR β/δ and PPAR γ may play redundant roles in inflammatory regulation (67). PPAR β/δ and γ agonists exhibit a similar profile of promoter specificity for inhibition of LPS target genes. At a low concentration (1 μ M), inhibition of iNOS and IL-12 p40 gene expression is PPAR γ -dependent; at a high concentration (50 μ M), this expression pattern is PPAR β/δ -dependent (67).

PPAR β/δ also functions in skin homeostasis and keratinocyte differentiation under normal and inflammatory conditions. Expression of PPAR β/δ is undetectable in healthy rodent skin; however, immediately following injury, elevated PPAR β/δ expression is observed in keratinocytes at the edges of skin wounds. This elevation continues throughout the entire healing process. In parallel, the production of PPAR β/δ endogenous ligand is induced and activates the newly synthesized PPAR β/δ . The enhanced PPAR β/δ activity increases the resistance of keratinocytes to apoptotic signaling. In addition, more pronounced inflammatory skin responses are observed in PPAR β/δ -deficient mice. Thus, the cytokine-induced PPAR β/δ expression is crucial for wound healing, and its anti-apoptotic role ensures sufficient viable keratinocytes for wound re-epithelialization (56, 57).

In 1993, PPAR γ was discovered in mammals. The expression of PPAR γ is detected in vascular tissues, including ECs and vascular smooth muscle cells (VSMCs), and in monocytes/macrophages. PPAR γ ligands have various impacts on the above cells with a net effect of proven anti-atherosclerosis. In a variety of atherosclerogenic mouse models and balloon injury models, PPAR γ ligands attenuate atherosclerotic lesion formation and intimal hyperplasia. Results of studies show that PPAR γ is up-regulated in differentiated macrophages and atherosclerosis lesions. These results also indicate that multiple PPAR γ agonists consistently repress inflammation and reduce atherosclerosis in mice (62, 70–73). Thiazolidinediones

(TZDs), synthetic PPAR γ ligands, reverse the induction of CD36, a scavenger receptor, in obese and atherosclerotic mouse models. This finding suggests that PPAR γ agonists reduce CD36 expression, resulting in decreased uptake of modified lipoproteins and inhibition of atherosclerosis (74). Furthermore, TZDs-activated PPAR γ suppresses monocytes/macrophages with reduced expression of inflammatory cytokines, including adhesion molecules, TNF- α , IL-1 β , iNOS, and gelatinase B. In addition, PPAR γ induces LXR α and, therefore, stimulates ABCA1-dependent cholesterol efflux from macrophages (35, 74). This induction is important in contributing to the anti-atherogenic effects of PPAR γ ligands. In human studies, TZDs decrease circulating inflammatory markers, including TNF- α , MMP-9, MCP-1, matrix soluble CD40 ligand (sCD40L), C-reactive protein, and white blood cell count (75–77). These findings demonstrate that PPAR γ inhibits macrophage activation and that synthetic PPAR γ ligands have anti-inflammatory and anti-atherogenic effects.

PPAR γ is highly expressed in the colon. The potential link between PPAR γ and intestinal diseases was first reported in 1998 (78–80). Regulation of colon inflammation by PPAR γ has been demonstrated in both experimental models of colitis as well as in ulcerative colitis patients. There is now emerging interest in the roles of PPAR γ in the regulation of gut homeostasis and chronic IBD (81, 82). PPAR γ expression in colon epithelial cells is associated with intestinal microorganisms. LPS, *Saccharomyces boulardii*, and *Helicobacter pylori* increase PPAR γ expression in colon epithelial cells (HT-29 and Caco-2) and gastric cells (KatoIII) (83–85). Extremely low levels of PPAR γ have been reported in mouse colon that has nonfunctional Toll-like receptor 4 (TLR4) (86). Thus, LPS recognition of TLR4 likely is involved in the enhancement of PPAR γ expression by microorganisms. These results indicate the pivotal role of bacteria in the regulation of PPAR γ expression in epithelial cells. This may account for the PPAR γ expression pattern observed in the colon compared with other parts of the digestive tract. Taken together, PPAR γ is highly expressed in the colon and is a key receptor in the regulation of intestinal inflammation induced by bacteria. Results from other studies also indicate a role of PPAR γ in tumor suppression, especially in colon cancer.

Alzheimer's disease is characterized by a major inflammatory component associated with amyloidosis and neurodegeneration (87). In the AD model, amyloid β -peptide (A β) is formed by cleavage of APP (amyloid precursor protein) through β -secretase1 (BACE1). PPAR γ agonists reduce inflammatory cytokine-induced A β production. Moreover, PPAR γ -dependent suppression of the BACE1 promoter accounts for inhibition of pro-inflammatory cytokine-induced gene expression by non-steroidal anti-inflammatory drugs (NSAIDs). *In vivo* data show that BACE1 transcription and expression are reduced in APP transgenic mice upon oral pioglitazone (a PPAR γ agonist) treatment (88, 89). Recent results show that PPAR γ

activation increases the uptake and clearance of A β from medium in glia and neuron cell culture models through unknown mechanisms (90). In addition, PPAR γ activation suppresses the expression of iNOS and COX-2, inhibits nitric oxide production, and prevents neuronal and microglial cell death *in vitro* and *in vivo* (12, 91).

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system with the characterized pathological process of multiple areas of white matter inflammation, demyelination, and glial sclerosis. Pro-inflammatory cytokines have been recognized as crucial factors in the pathogenesis of MS (12, 92). PPAR γ ligands, troglitazone and pioglitazone, significantly decrease the mRNA levels of CCL5/RANTES (regulated on activation, normal T cell expressed and secreted) and CCL3/macrophage inflammatory protein-1 (MIP-1) in experimental allergic encephalitis (EAE), an established animal model for MS (93). The anti-inflammatory effects of PPAR γ agonists in EAE mice may be due to PPAR γ agonist-mediated down-regulation of adhesion molecule expression (94), an important factor for EAE development.

In animal stroke and ischemic models, robust inflammatory responses exacerbate tissue damage. Some PPAR γ agonists repress inflammatory responses, reduce infarct volumes, and improve sensorimotor function (12, 95). Utilizing a middle cerebral artery occlusion (MCAO) model in the rat, neuroprotective effects, characterized by reduced infarct size and improved neurological scores, have been reported after the administration of the synthetic PPAR γ agonist L796449 (96, 97). Both types of PPAR γ agonists, TZDs and non-TZDs, exert neuronprotective effects on experimental stroke models. PPAR γ activators repress MCAO-induced iNOS and MMP-9 expression, induce the cytoprotective stress protein heme oxygenase-1 (HO-1) in brain, and, thus, exert neuroprotective effects. Other studies have also validated the neuroprotective effects of PPAR γ (98–100).

The majority of studies demonstrate an anti-inflammatory role for PPAR γ activation; however, no anti-inflammatory activity or pro-inflammatory response of PPAR γ activation has been reported. Furthermore, anti-inflammatory effects of PPAR γ ligands still remain in PPAR γ knockout mice, questioning the anti-inflammatory actions of PPAR γ . Nevertheless, anti-inflammatory effects do exist for all members of the PPAR family, which at least partly explains their anti-inflammatory activities. Clearly, PPAR-independent anti-inflammatory effects cannot be excluded.

LXRs

LXRs (α and β) are important transcriptional factors controlling lipid and glucose metabolism as well as the inflammatory response (21, 101). LXRs heterodimerize with RXRs and regulate gene expression by binding to LXREs (LXR responsive elements) of target genes. LXRs are activated by physiologic levels of cholesterol metabolites,

including 25-hydroxycholesterol and 24, 25-epoxycholesterol (102–104). LXR α is highly expressed in the liver; lower levels of LXR α are found in macrophages, adrenal glands, the intestine, adipose tissue, the lung, and the kidney. In contrast, LXR β is ubiquitously expressed (103).

The mechanism of anti-inflammatory effects by LXR is poorly understood. Because LXR response motifs have not been identified in the proximal promoters of repressed genes, an indirect mechanism, such as competition for co-activators, is predicted (105).

Studies show that LXR agonists induce cholesterol efflux and reverse cholesterol transport, inhibit macrophage-derived inflammation, and suppress the proliferation of VSMCs. By regulating the expression of multiple genes involved in these pathways, LXR agonists prevent the development and progression of atherosclerosis (101, 106, 107). Activation of LXRs protects against lesion development and causes regression of established lesions. An approximately 50% reduction of lesion size has been observed in atherosclerosis-prone ApoE $^{-/-}$ and LDLR $^{-/-}$ mice upon LXR ligand treatment (108). LXR agonists also reduce the size of pre-existing lesions in LDLR $^{-/-}$ mice, and such reduction is dependent on macrophage LXR activity (109). Moreover, transplantation of bone marrow from LXR α , β $^{-/-}$ mice into ApoE $^{-/-}$ and LDLR $^{-/-}$ mice produces a macrophage-specific loss of LXRs resulting in a marked increase in lesion size and accelerated atherosclerosis (110).

Studies have demonstrated that activated LXRs regulate whole-body lipid homeostasis by decreasing intestinal cholesterol absorption and inducing cholesterol efflux. LXRs also regulate the conversion of cholesterol to bile acids and lipogenesis. In macrophages, LXR activators induce cholesterol efflux transporters ABCA1, ABCG1, and ABCG4. LXR α , β double-knockout mice exhibit increased cholesterol accumulation in vascular macrophages on a normal chow diet. Genetic deletion of the individual LXRs alone does not display this phenotype (109). The functions of LXRs in inflammation have been recently reviewed (101, 106, 111, 112).

Considerable evidence indicates that LXRs reciprocally repress a set of inflammatory genes upon bacterial, LPS, TNF- α , or IL-1 β stimulation (105). LXR ligands GW3965 and T1317 repress inflammatory genes (iNOS, COX-2, IL-6, IL-1 β , MCP-1, MCP-3, MMP-9, TF, and osteopontin) in macrophages derived from wild-type and LXR α or β single knockout mice (105, 112–115); however, such repression is diminished in macrophages that are derived from LXR α and β double knockout mice, indicating that both isoforms possess anti-inflammatory activity.

The beneficial outcomes of anti-inflammatory effects by LXR activators also are observed in neurodegenerative diseases, like AD. Inflammatory processes and altered cholesterol metabolism are risk factors for AD. The LXR agonist GW3695 significantly attenuates LPS-induced iNOS mRNA, nitrate secretion, iNOS, and COX-2 protein

in murine microglial BV2 cells. Furthermore, in primary mixed glial cultures, GW3965 accelerates the clearance of inflammatory fibrillar A β (fA β) by phagocytes. Consistent with these findings, genetic loss of LXR signaling in APP/PS1 transgenic mice results in increased senile plaque accumulation (116, 117).

Notably, members of both the LXR and PPAR subfamilies are expressed in macrophages and in other cell types that are involved in the metabolism of fat and cholesterol as well as in the regulation of inflammation. They can influence the development of inflammatory responses in a ligand-dependent manner. Their combined effects on peripheral metabolism, foam cell formation, and vascular wall inflammation have made LXR and PPAR major targets in the treatment of cardiovascular diseases, obesity, and diabetes.

FXR

FXR plays essential roles in maintaining bile acid, cholesterol, and glucose homeostasis. FXR is highly expressed in tissues exposed to high concentrations of bile acids, including the liver, intestine, and kidney. More recently, FXR has been detected in white adipose tissue, atherosclerotic lesions, and VSMCs. The hydrophobic bile acid chenodeoxycholic acid (CDCA) is the most effective activator of FXR. Ligand-activated FXR binds to FXR response elements (FXREs) either as a heterodimer or as a monomer (118–120).

Recent studies indicate that FXR influences endothelial function and atherosclerosis; thus, FXR plays a regulatory role in the cardiovascular diseases and in metabolic syndrome (121). Guo and other researchers demonstrated that disruption of the FXR gene could attenuate atherosclerosis development, most likely resulting from reduced oxLDL-C uptake by macrophages (122, 123).

Hepatic inflammation can be observed in the hydrophobic bile acid-induced cholestasis rodent model (124) or after feeding a bile acid-supplemented diet (125). The pro-inflammatory effects of bile acids are proposed to act as FXR ligands and to induce ICAM-1. Additionally, bile acid-activated kinase pathways, including protein kinase C, extracellular signal-regulated kinase (ERK), and JNK, contribute to hepatic inflammation (126–128). In hepatocytes, bile acid induces ICAM-1 expression through an FXRE located within the promoter region (125). In primary human endothelial cells, bile acid levels at a high concentration (100 μ M) induce ICAM-1, VCAM-1, and E-selectin expression through stimulation of NF- κ B and p38 MAPK signaling pathways. Moreover, bile acid-induced ICAM-1 and VCAM-1 proteins are sufficient to enhance the adhesion of human acute monocytic leukemia (THP-1) cells to human umbilical vein endothelial cells. This would suggest a potential pathological role of bile acids in the vasculature under conditions in which serum bile acid levels become elevated (129).

Inflammation is known to promote liver tumorigenesis (130–132). An intriguing link between FXR and hepatocarcinogenesis has been identified. FXR knockout mice display prominent liver injury and inflammation from 9 to 12 months of age. When the FXR knockout mice are 15 months old, hepatocellular adenoma and carcinoma, but not other tumor types, are developed spontaneously with an elevated expression of inflammatory genes (INF- γ , TNF- α , and IL-6). In contrast, no liver tumors are observed in wild-type mice of the same age (133). Diet enriched with bile acid strongly promotes N-nitrosodiethylamine-initiated liver tumorigenesis, whereas lowering the bile acid pool in FXR knockout mice significantly reduces the malignant lesions. These results suggest that the increased expression of pro-inflammatory genes in aging FXR knockout mice may eventually contribute to liver carcinogenesis (133).

NR4As

The NR4A subfamily includes three members: Nur77, Nurr1, and NOR1. Nur77 was documented first as an early response gene in nerve growth factor-stimulated rat pheochromocytoma cell line PC12 cells (134). Subsequently, Nurr1 and NOR1 were identified (135, 136). Nur77, Nurr1, and NOR1 are expressed in a wide variety of tissues, such as skeletal muscle, adipose, the heart, the kidney, T cells, the liver, and the brain. No classical ligands have been identified for Nur77, Nurr1, or NOR1. All three proteins can bind to NGFI-B response element (NBRE) as monomers (137) and with the palindromic Nur77 responsive element (NurRE) as homodimers and/or heterodimers (138, 139). Additionally, Nur77 and Nurr1 can heterodimerize with RXRs and mediate retinoid responses (140). NR4As are induced by multiple signaling molecules, such as hormones, growth factors, apoptotic stimuli, and inflammatory stimuli to regulate differentiation, proliferation, apoptosis, and survival of various cell types. The functional involvement of NR4As in regulating chronic inflammatory diseases like atherosclerosis has been investigated only recently (5).

NR4As are induced upon atherogenic stimuli to inhibit human foam cell formation and pro-inflammatory cytokine production. Over-expression of NR4As in human THP-1 macrophages results in down-regulation of IL-1 β , IL-6, IL-8, monocyte chemoattractant-1, MIP-1 α , and MIP-1 β . Moreover, ox-LDL is reduced by overexpression of NR4As (141). Knockdown of Nur77 or NOR-1 augments inflammatory responses and increases lipid loading. It has been demonstrated that NR4As reduce monocyte-to-macrophage differentiation thus limiting human macrophage foam cell formation and inflammatory responses (141). Moreover, Nur77 interacts with p65 inhibiting IL-2 and IL-8 promoter activity, which suggests that NR4As transrepress the NF- κ B signaling pathway (142).

Crosstalk Between Nuclear Receptors and Cytokine Signaling Pathways During Inflammatory Processes

The crosstalk between nuclear receptors and other transcriptional factors regulates cytokine production or cytokine-mediated signaling transduction and cell responses. Several crosstalk mechanisms, including interactions between nuclear receptors and other transcriptional factors and modifications of nuclear receptors by kinases, have been demonstrated. For instance, GR and AP-1 physically interact on the target gene promoter containing the binding site for either of the two transcription factors. Thus, the interaction between GR and AP-1 prevents their binding to either the GR response element (GRE) site or the AP-1 site and antagonizes both regulators' activities. Most frequently, this crosstalk results in negative interference of both factors' transcriptional capacities if AP-1 is composed of c-jun/c-fos dimer. Such crosstalk is also observed in PPAR γ , sex steroids receptors, and vitamin D receptor (143, 144).

The expression and activity of nuclear receptors can be regulated by post-translational modifications, including phosphorylation, ubiquitylation, sumolation, and acetylation. Kinases associated with general transcription factors or ones that are activated in response to various signals (MAPK, Akt, PKA, and PKC) participate in this crosstalk. Such crosstalk often facilitates the recruitment of co-activators or components of the transcription machinery and, therefore, cooperates with the ligand to enhance transcriptional activation (143). For example, phosphorylation can alter all major domains of nuclear receptors and affect protein stability, nuclear localization, DNA binding, and protein-protein interactions, thereby affecting the overall transcriptional activity of the nuclear receptors.

Recent reports have investigated the link between inflammation-mediated cell signaling and regulation of nuclear receptors in the liver. Studies show that LPS signaling induces the rapid and significant reduction of the hepatic RXR α protein, but not of mRNA levels, and the redistribution of hepatic RXR α from nucleus to cytoplasm. It has been revealed that the LPS-induced release of IL-1 β from kupffer cells activates the JNK pathway, which phosphorylates RXR α at the Ser²⁶⁰ site, leading to further modification of RXR α (145). The alteration of RXR α triggers the rapid export of the receptor from nucleus to cytoplasm and the consequent degradation of the receptor and, therefore, the marked suppression of RXR α -targeted inflammatory gene expression (146). Crosstalk occurs between human PXR (hPXR)/RXR and NF- κ B signaling pathways as well. LPS or TNF- α activated NF- κ B represses SXR/RXR α -mediated gene expression through the direct interactions between the DNA binding domain of RXR α and p65. This interaction may prevent RXR α from binding to its consensus DNA sequences thus inhibiting PXR/RXR α -mediated transactivation (147). Moreover, reciprocal

inhibition between NF- κ B and hPXR has been reported (6, 148). Activated PXR inhibits the activity of NF- κ B and its target genes (IL-1 α , IL-1 β , IL-6, IL-15, COX-2, ICAM-1) in the liver and the intestine. In addition, the small bowel of PXR^{-/-} mice exhibits a prominent and increased chronic inflammatory infiltration. On the other hand, NF- κ B activation reciprocally inhibits PXR and its target genes, whereas inhibition of NF- κ B enhances PXR activity. These findings clearly demonstrate the interaction between nuclear receptor PXR and NF- κ B.

Conclusions

Current understanding of the nuclear receptor-mediated regulation of chronic inflammatory processes and diseases has increased. Moreover, inflammatory cytokines crucial in governing a specific disease state may be sensitive or resistant to a particular nuclear receptor ligand. Clarification of the sensitivity of sets of inflammatory genes to particular nuclear receptor ligands will help design treatment options for specific inflammatory diseases. The presence of crosstalk between nuclear receptors and other transcriptional factors is also recognized. However, fully understanding the mechanisms of nuclear receptor action in a well-defined model is still necessary. Increased understanding in these areas will potentially assist in designing novel prevention and treatment options for specific chronic inflammatory diseases.

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