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Nuclear receptor signaling in macrophages

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Abstract

Macrophages play diverse roles in host defense and in maintenance of homeostasis. Based on their ability to promote inflammatory responses, inappropriate macrophage function also contributes to numerous pathological processes, including atherosclerosis, rheumatoid arthritis and inflammatory bowel disease. Members of the nuclear receptor superfamily of ligand-dependent transcriptions factors have emerged as key regulators of inflammation and lipid homeostasis in macrophages. These include the glucocorticoid receptor (GR), which inhibits inflammatory programs of gene expression in response to natural corticosteroids and synthetic anti-inflammatory ligands such as dexamethasone. Also, in response to endogenous eicosanoids and oxysterols, respectively, peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs) regulate transcriptional programs involved in inflammatory responses and lipid homeostasis. Identification of their mechanisms of action should help guide the development of new therapeutic agents useful in the treatment of diseases in which macrophages play critical pathogenic roles.

Keywords: Nuclear receptors; Macrophages; Lipid homeostasis; Inflammation; Differentiation

1. Introduction

Nuclear receptors (NR) are members of a superfamily of ligand-dependent transcription factors that regulate diverse aspects of reproduction, development, homeostasis and immune function [1–6]. The NR superfamily includes receptors for steroid hormones, such as the estrogen (ER) and glucocorticoid (GR) receptors, receptors for nonsteroidal ligands, such as the thyroid hormone (TR) and retinoic acid (RAR) receptors, as well as receptors that bind diverse products of lipid metabolism, such as peroxisome proliferator-activated (PPAR) and liver X receptors (LXR). The NR superfamily also includes a large number of orphan receptors for which ligands have not been identified [5,6]. Several members of the NR superfamily have been shown to play important physiologic roles in macrophages (Table 1). In this review, we will focus on these receptors and their role in macrophage biology.

Members of the NR superfamily share a common structure. There is a variable N-terminal region that contains a ligand-independent transactivation domain (AF1) and a highly conserved DNA binding domain (DBD), containing two zinc finger motifs that target the receptor to specific DNA sequences known as hormone response elements (HREs). NRs also contain a C-terminal region with the ligand binding domain (LBD), the dimerization interface, and a ligand-dependent activation function (AF-2). Most NRs activate transcription as dimers, either homodimers or heterodimers with the retinoid X receptor (RXR), although a subset can bind and stimulate transcription as monomers. Upon ligand binding, nuclear receptors undergo a conformational change that coordinately dissociates corepressors and facilitates recruitment of coactivator proteins, thereby promoting transcriptional activation [7–11].

Members of the NR family regulate transcription by several mechanisms and they can both activate and inhibit gene expression [12]. The prototypic activity of NRs is ligand-dependent activation of transcription by binding to specific HREs in target genes [11,12]. Several mechanisms of transcriptional inhibition have also been established. In the absence of ligand, a subset of NRs that heterodimerize with RXR, including TR, LXR and RAR, are capable of actively repressing target genes by binding to HREs [13–16]. In addition, several other NRs, including GR, LXR and PPAR are capable of inhibiting the activities of other transcription factors, such as the activator protein-1 (AP-1) and the nuclear factor (NF)-kB, in a ligand-dependent manner. This effect does not require DNA binding by the NR and is referred to as transrepression.

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Table 1
NR expression in macrophage populations

NR	Expression in macrophage populations	Ligands
ERα (NR3A1)	PM, BMDM, blood monocytes, osteoclasts, microglia, Kupffer cells, dendritic cells[a] [30,153,153–157]	17β-Estradiol, androstenedione, 3β,17β-androstenediol [37,158]
ERβ (NR3A2)	Osteoclasts [155]	
GRα (NR3C1)	PM, dendritic cells, microglia, osteoclasts, blood monocytes[a] [57,159–162]	Glucocorticoids [163]
GRβ (NR3C2)	Osteoclasts, alveolar macrophages [160,162]	
LXRα (NR1H3), LXRβ (NR1H2)	PM, BMDM, Kupffer cells [15,115,164]	22(*R*)-Hydroxycholesterol, 24(*S*)-hydroxycholesterol, 24(*S*),25-epoxycholesterol, 27-hydroxycholesterol [47,165]
PPARα (NR1C1)	Human blood monocytes, low levels in Kupffer cells [72,164]	LTB4, 8-HETE, Fas [166]
PPARγ (NR1C3)	PM, Kupffer cells, dendritic cells, microglia [19,153,164,167–169]	PUFAs, FAs, 15d-PGJ2, TZDs, 13-HODE, 9-HODE, 5-HETE [166]
PPARδ (NR1C2)	PM, BMDM, Kupffer cells, osteoclasts[a] [19,164,170]	FAs, carbaprostacyclin [166]
RARα (NR1B1)	Kupffer cells, dendritic cells, osteoclasts, blood monocytes [171–173]	ATRA, 9-*cis*-RA [174,175]
RARβ (NR1B2)	Kupffer cells, blood monocytes, dendritic cells [171,172]	
RARγ (NR1B3)	Microglia, Kupffer cells [171,176]	
RXRα (NR2B1)	PM, BMDM, blood monocytes, microglia, Kupffer cells, dendritic cells[a] [171,172,176]	9-*cis*-RA, FAs, methoprene acid, DHA [177,178]
RXRβ (NR2B2)	Kupffer cells, osteoclasts [171,173]	
RXRγ (NR2B3)	Kupffer cells [171]	
TRα (NR1A1), TRβ (NR1A2)	Osteoclasts [179]	Thyroid hormones [180]
VDR (NR1I1)	BMDM [181]	$1,25(OH)_2D_3$ [182]

The data represent documented expression of each nuclear receptor in macrophage populations. Most of the studies mentioned here are based on rodent models. However, we have to take into consideration that differences between species might exist. $1,25(OH)_2D_3$, 1α,25-dihydroxyvitamin D3; 9-*cis*-RA, 9-*cis*-retinoic acid; ATRA, all-*trans* retinoic acid; DHA, docosahexaenoic acid; HODE, hydroxyoctadecadienoic acid; HETE, hydroxyeicosatetraenoic acid; LTB-4, leukotriene-4; PUFAs, polyunsaturated fatty acids; TZDs, thiazolidinediones; BMDM, bone marrow-derived macrophages; PM, peritoneal macrophages.

[a]A. Valledor, M. Ricote, G. Pascual, Unpublished results.

Transrepression is thought to be the primary mechanism by which nuclear receptors inhibit pro-inflammatory genes in macrophages [17–20].

2. Roles of nuclear receptors in macrophage differentiation

The expression of a number of NRs has been documented in macrophages (Table 1). While GRα, VDR, RARs, and LXRs are constitutively expressed in macrophages, ERα and PPARγ expression increases during macrophage differentiation [19,21,22]. In addition, PPARγ expression is upregulated during the inflammatory response, and can be induced *in vitro* by interleukin (IL)-4 and other immunoregulatory molecules [21,23]. In contrast, interferon (IFN)-γ and lipopolysaccharide (LPS) repress the expression of PPARγ [24].

In macrophages, NRs have three general physiologic roles. First, they negatively regulate inflammatory responses mediated by AP-1 and NF-κB transcription factors. Emerging evidence suggests that these actions represent important functions of GRα, ERα, PPARs and LXRs in the macrophage. NRs namely PPARs and LXRs also regulate lipid homeostasis. These two roles will be extensively discussed later in this review. The third role, mediated by a smaller subset of nuclear receptors, influences specialized programs of macrophage differentiation.

The macrophage lineage has the capability to give rise to a family of related cells that execute specialized roles, such as microglia, osteoclasts, Kupffer and dendritic cells [25]. Ligands for a number of NRs have been shown to affect the differentiation of these specialized macrophages. For example, precursors of the monocyte hematopoietic lineage stimulated with macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL) can differentiate into mature bone-resorbing osteoclasts [26]. Interestingly, this differentiation program can be inhibited by the addition of either estrogenic [27] or PPARγ ligands [28]. In contrast, glucocorticoids also decrease bone resorption, but appear to do so by increasing osteoclast apoptosis [29].

In the presence of granulocyte-colony macrophage stimulating factor (GM-CSF) and IL-4, dendritic cells can be generated by *in vitro* differentiation of macrophage precursors. Corticosteroids, anti-estrogens or vitamin D analogs

inhibit this differentiation program [30–33]. VDR ligands can also affect the tolerogenic properties of mature dendritic cells, favoring the induction of regulatory rather than effector T cell responses [34]. In addition, vitamin D analogs enhance the differentiation of monocytes into macrophages, suggesting that VDR plays a role balancing monocytic lineage developmental choices [35]. However the *in vivo* significance of these findings remains to be established. In a similar manner the thyroid hormone promotes the growth and morphologic differentiation of microglia [36].

3. Endogenous ligands (systemic vs. local)

Ligand availability represents one of the most important determinants of nuclear receptor activity. Classical steroid hormone receptors such as GR regulate macrophage gene expression in response to circulating hormones that are produced under the control of the hypothalamic–pituitary–adrenal axis. In contrast, PPARs and LXRs regulate gene expression by responding to locally produced metabolites of fatty acid and cholesterol (Fig. 1).

Estrogen is an endocrine hormone regulated by the hypothalamic–gonadal axis. In addition differentiated macrophages express and regulate the enzyme aromatase, which converts serum dehydroepiandrosterone (DHEA) into the immunomodulatory estrogens 3β,17β-androstenediol and androstenedione [37]. Also, macrophages serve as an extra-renal source of 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). 25-Hydroxyvitamin D3-1α-hydroxylase ($25(OH)D_3$-1α-hydroxylase), the key enzyme in $1,25-(OH)_2D_3$ production, is expressed in monocyte-derived macrophages. In addition, following LPS stimulation microglia and dendritic cells are able to produce $1,25(OH)_2D_3$ [32,38]. These studies suggest that the high localized production of $1,25(OH)_2D_3$ may serve as a paracrine signal during bacterial infection, favoring macrophage differentiation [32].

During inflammatory responses, PPARs can be activated by eicosanoids, which are produced by metabolism of

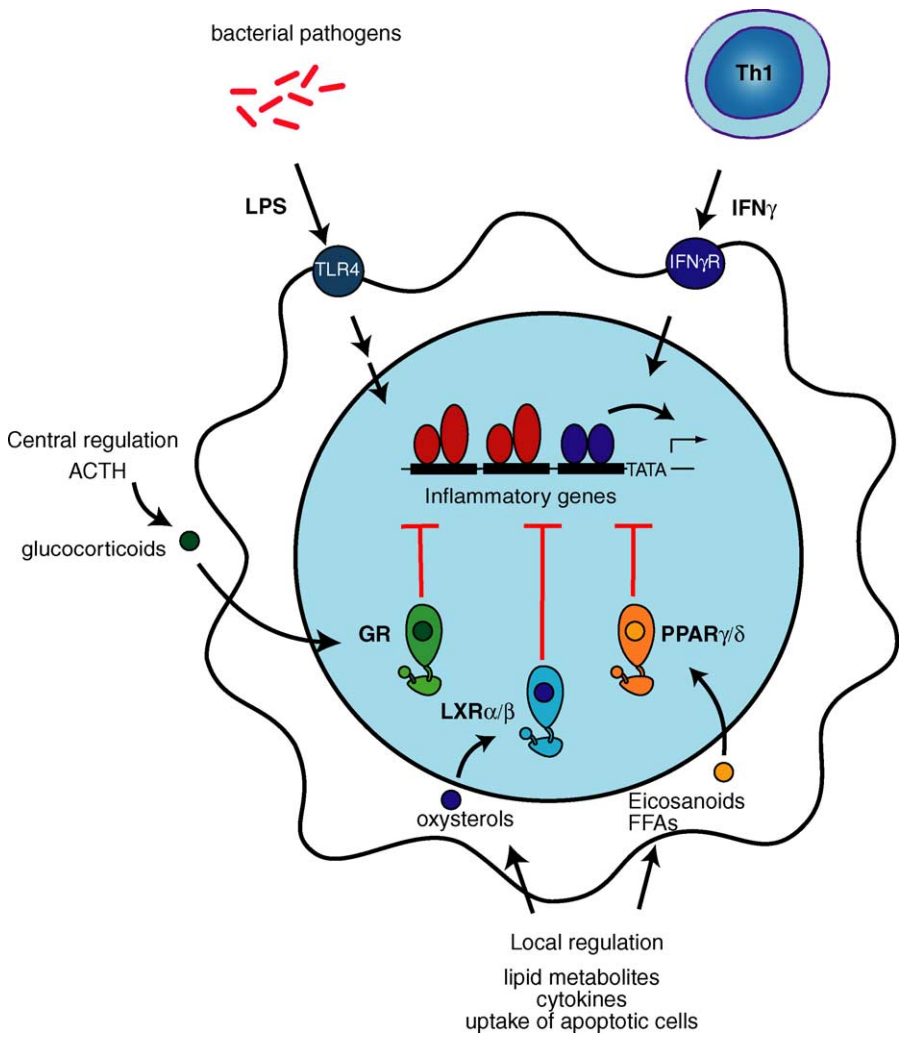

Fig. 1. PPARs, LXRs and GR inhibit inflammatory response genes in macrophages. GR regulates macrophage gene expression in response to circulating hormones that are produced under the control of the hypothalamic–pituitary–adrenal axis. PPARs and LXRs regulate gene expression by responding to locally produced ligands. ACTH, adrenocorticotrope hormone; FFAs, free-fatty acids; IFN-γ, interferon-γ; LPS, lipopolysaccharide; Th1, T helper cells.

arachidonic acid and other long chain polyunsaturated fatty acids (PUFAs) [39]. For example, ligands for PPARα are leukotriene (LT)B4 and 8(*S*)-hydroxyecosatetraenoic acid (HETE), whereas 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ2), 15-HETE and 13-hydroxyoctadecadienoic acid (HODE) act as ligands for PPARγ. 13-HODE and 15-HETE can be enzymatically generated by the IL-4 inducible 12/15-lipoxygenase, suggesting that IL-4 can coordinately regulate the expression and activity of PPARγ [23,40]. PPARγ is also activated by the thiazolidinedione class of drugs (TZDs) that act as insulin sensitizers and are used in the treatment of type 2 diabetes mellitus [41].

LXRs are activated by specific oxidized forms of cholesterol (oxysterols) [42–44], such as 24(*S*)-hydroxycholesterol and 22(*R*)-hydroxycholesterol, or by certain intermediates of the cholesterol biosynthetic pathway such as 24(*S*),25-epoxycholesterol [44,45]. In macrophages, sterol 27-hydrolase (CYP27) is able to modify cholesterol into a naturally occurring ligand for LXRs [46,47]. NRs can regulate macrophage gene expression in response to changes in cellular lipids and arachidonic acid metabolites that occur during inflammatory responses.

4. Nuclear receptors in macrophage-mediated inflammation

Glucocorticoids are widely used to control a variety of inflammatory diseases including asthma, inflammatory bowel disease, systemic lupus erythematosus, dermatitis and arthritis [48–50]. Endogenous glucocorticoids are released in response to a variety of stressors (starvation, pain, trauma, infection, etc.) and are essential for maintenance of homeostatic functions (Fig. 1; [51]). The mechanistic basis of the anti-inflammatory actions of glucocorticoids remains poorly understood [48,49]. Accumulating evidence suggests that these effects largely result from inhibition of signal-dependent transcription factors that mediate inflammatory programs of gene activation such as NF-κB, AP-1 and STATs [49,52]. Genes that are strongly repressed by GR agonists include GM-CSF [53], cytokines (tumor necrosis factor (TNF)-α, IL-4, IL-5, IL-1, IL-6, IL-8, IL-12) [54,55], and inflammatory mediators (inducible nitric oxide synthase (iNOS) [56,57] and cyclooxygenase (COX)-2) [58]. Despite the requirement for the GR LBD and DBD for transrepression activity, the majority of the promoters and enhancers for these genes do not contain functional glucocorticoid response elements (GREs) [49,59,60]. These observations suggest that GR-mediated transrepression involves mechanisms distinct from classical GR transactivation of target genes [61]. One established mechanism involves direct interaction between GR and negatively regulated transcription factors such as AP-1 and NF-κB [59,60]. Glucocorticoids also inhibit signaling of mitogen-activated protein kinase pathways that mediate the expression of inflammatory genes [62,63]. A third proposed mechanism for transrepression involves competition for coactivator complexes [64,65]. Modification of the degree of phosphorylation of the C-terminal repeat of RNA polymerase at NF-κB target genes has also been suggested as the basis for the GR-mediated transrepression [66]. Recent work has shown that GR directly inhibits NF-κB-induced histone acetyltransferase (HAT) activity and recruits histone deacetylases [67]. These observations demonstrate that GR has multiple modes of action and shows the complexity of the crosstalk between signaling pathways.

Similar to GR, other NRs including ER, VDR, PPARs and LXRs antagonize the expression of an overlapping set of NF-κB and AP-1 regulated genes in macrophages (Fig. 1 and [18–20,68–73]). This transrepression function requires both the LBD and DBD, but there is no direct binding to HREs in the enhancer or promoter regions of these genes [20,70,73–75]. Mechanisms similar to GR-mediated transrepression have been suggested for other nuclear receptors. However to date, the mechanism of transrepression is not yet clear. VDR also inhibits inflammatory gene expression by downregulating NF-κB activation or by inducing the expression of both transforming growth factor (TGF)-β and IL-4 [76]. Likewise 1,25-$(OH)_2D_3$ has been shown to ameliorate experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease [76].

In the last few years, PPARs and LXRs have emerged as key regulators of inflammatory and immune responses in macrophages [77–91]. Natural and synthetic PPARγ ligands have been shown to exert anti-inflammatory effects in murine models of atherosclerosis, inflammatory bowel disease, allergic encephalomyelitis and psoriasis [77–81,86–91]. In those studies, PPARγ agonists were shown to inhibit the induction of inflammatory genes by LPS, IL-1β and IFN-γ. However, the mechanism and the validity of the anti-inflammatory role for PPARs is very controversial. 15d-PGJ2 was found to inhibit NF-κB-dependent transcription through a PPARγ-independent mechanism [92,93] and the doses of TZDs that exert maximal inhibitory effects on LPS-inducible genes are significantly higher than the concentration at which these compounds bind efficiently to PPARγ [19,94]. Furthermore, two reports have shown that deletion of the PPARγ gene in stem cell-derived macrophages does not alter basal or stimulated cytokine production [94,95]. In addition, these studies showed that high concentrations of PPARγ ligands still inhibit cytokine responses to LPS stimulation in PPARγ-null cells. These findings suggest that PPARγ ligands exert some of their anti-inflammatory effects independently of the expression of PPARγ.

More recent studies using mRNA expression profiling and PPARγ knockout macrophages demonstrated that the inhibitory effects of rosiglitazone on LPS and IFN-γ responses are PPARγ-dependent when the drug is used at concentrations close to their binding affinity. However,

at higher concentrations the inhibitory effects are PPARγ-independent [24]. Several lines of evidence suggest that PPARγ-independent effects of rosiglitazone are due to activation of PPARδ [24]. These studies establish overlapping transrepression functions of PPARγ and PPARδ in macrophages. A recent manuscript has suggested that PPARδ represses inflammatory genes including the chemokine monocyte-chemoattractant protein-1 (MCP-1), IL-1β and the metalloproteinase MMP-9 by an unconventional ligand-dependent transcriptional mechanism involving the binding of PPARδ to transcriptional repressors [96].

Interestingly, rosiglitazone has recently been shown to reduce circulating concentrations of inflammatory markers of cardiovascular disease in type 2 diabetic patients such as C-reactive protein, MMP-9 and TNF-α [97]. These findings suggest that negative regulation of gene expression may also be the basis for some of the insulin-sensitizing effects of rosiglitazone observed in diabetic patients.

Recently, 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 IL-1β, IL-6, MMP-9, iNOS, COX-2, MCP-1 and MCP-3, macrophage inflammatory protein (MIP)-1β and IP-10 [20,73]. LXR-deficient mice exhibited enhanced responses to inflammatory stimuli and LXR ligands reduced inflammation in murine models of contact dermatitis [20] and atherosclerosis [84,85]. These observations suggest that LXR and PPAR agonists may exert their anti-atherogenic effect at least in part by limiting the production of inflammatory mediators in the arterial wall [98].

5. Nuclear receptors in macrophage-mediated lipid homeostasis

Tight regulation of cellular lipid levels is necessary for the maintenance of normal cellular functions. LXRs and PPARs are critical orchestrators of macrophage lipid homeostasis (Fig. 2). Like most cells, macrophages take up circulating lipoproteins via the low-density lipoprotein (LDL) receptor [99]. Excess cholesterol inhibits proteolytic activation of sterol regulatory element binding proteins (SREBPs), which are transcription factors that promote cholesterol and triglyceride biosynthesis and LDL receptor expression [100]. Resident macrophages also secrete molecules that modify extracellular LDL, e.g. by oxidation (oxLDL), converting it into a form that is efficiently recognized by macrophage scavenger receptors, such as

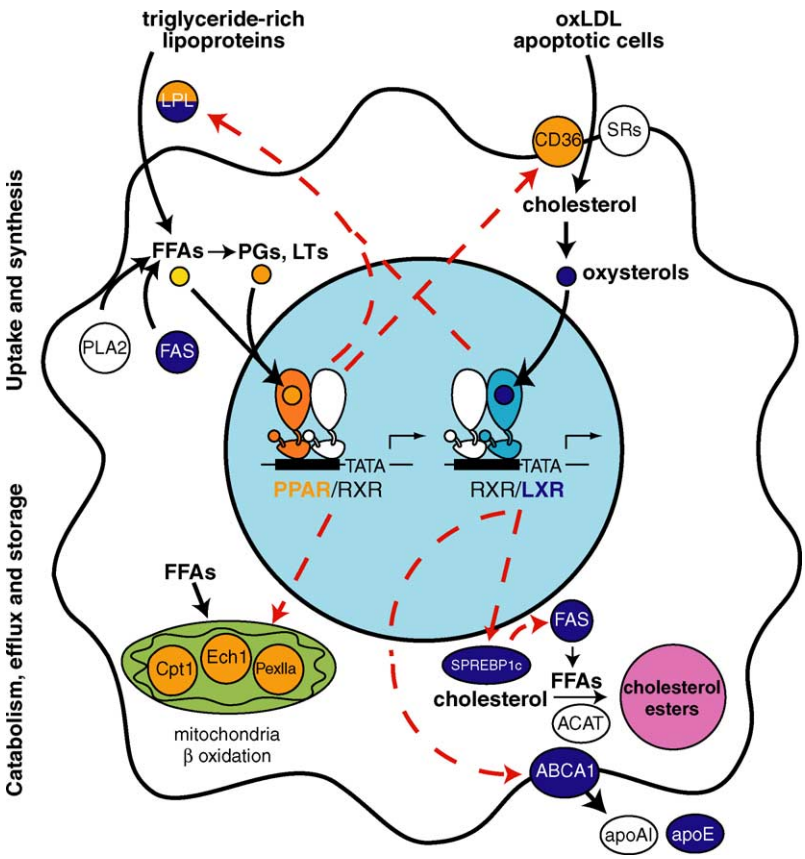

Fig. 2. LXRs and PPARs regulate the expression of genes involved in macrophage lipid homeostasis. LXR target genes are indicated in blue, while PPAR target genes are shown in orange. ACAT, acetyl-coenzyme A acyltransferase; FFAs, free fatty acids; LTs, leukotriens; PGs, prostaglandins; PLA2, phospholipase A2; SRs, scavenger receptors.

CD36 [101]. Unlike native LDL, oxLDL fails to down-regulate scavenger receptors resulting in massive cholesterol accumulation and conversion of macrophages into foam cells, a major hallmark of early atherosclerotic lesions [102–105]. The lipid content in macrophages is also influenced by phagocytosis of apoptotic bodies and necrotic cells, a process mediated by CD36 and other scavenger receptors [106]. Several studies have shown that the CD36 gene is a direct target of PPARγ [94,95,107,108]. The observation that oxidized lipids present in oxLDL, including 9-HODE and 13-HODE, have the capability to activate PPARγ [107,108] suggests that this NR is involved in a positive feedback loop that drives foam cell formation. However, despite enhancing CD36 expression, TZDs do not significantly induce cellular cholesterol accumulation in mouse or human primary macrophages [95,109]. Indeed, an anti-atherogenic role has been recently established for PPARγ based on the use of different murine models of atherosclerosis [77–81].

Lipid efflux is critical for maintaining macrophage lipid homeostasis. Members of the ATP-binding cassette (ABC) family of transporters have been recently implicated in mediating lipid efflux from a variety of cells, including macrophages. In particular, ABCA1 transports intracellular phospholipids and cholesterol to exogenous nascent HDL particles, which contain lipid-poor apolipoprotein (apo) acceptors, such as apoAI [110]. This mechanism plays an important role in reverse cholesterol transport, the process by which cholesterol is mobilized from peripheral cells to the liver for its conversion to bile acids [111]. Mutations in ABCA1 result in Tangier disease, a condition in which patients have extremely low levels of circulating HDL, massive accumulation of cholesterol in tissue macrophages, and an increased risk for developing atherosclerosis [112,113]. Therefore, upregulation of ABCA1 potentially exerts protective effects by clearing excess cholesterol from macrophages in the arterial wall. Studies have established the connection between nuclear receptor action and reverse cholesterol transport by demonstrating that LXRs directly regulate ABCA1 expression and cholesterol efflux in human and murine cells, including macrophages [114–117]. In line with these observations LXR ligands have been recently shown to inhibit the development of atherosclerosis in mice [82,84,85].

Crosstalk between the PPAR and the LXR pathways has been shown to be important in the regulation of lipid efflux. Two independent studies demonstrated that PPARα and PPARγ upregulate the expression of ABCA1 and promote cholesterol efflux in human macrophages through a transcriptional cascade mediated by LXRα [81,109]. The ability of TZDs to stimulate cholesterol efflux was completely abolished in PPARγ-null embryonic stem cells [81,118]. However, discrepancies exist between different macrophage models, as other groups have observed little or no effect of PPARγ agonists on ABCA1 or LXRα expression in murine primary macrophages [24,80].

LXRs and PPARs affect lipid efflux in macrophages by additional mechanisms. First, PPARα agonists reduced cholesterol esterification resulting in increased availability of free cholesterol for efflux via the ABCA1 pathway [119]. Second, PPARα stimulates cholesterol efflux from macrophage-derived foam cells via upregulation of the CLA-1/SR-BI system [120]. However, in conflict with these studies, PPARα and PPARγ have been also shown to down-regulate the expression of macrophage cholesteryl ester hydrolase (CEH) [119,121], an enzyme required for hydrolysis and release of cholesterol from foam cells. Finally, both LXRs and PPARγ are able to directly induce the expression of another member of the ATP binding cassette family, ABCG1 [24,118,122], although the exact relevance of this regulation in lipid homeostasis needs to be determined.

Surprisingly, recent studies using microarray technology revealed that, in contrast to adipose tissue, only a limited subset of genes in macrophages is subject to positive regulation by PPARγ [24]. In addition to CD36 and ABCG1, PPARγ targets in macrophages include adipose differentiation-related protein (ADRP), α-mannosidase II, carnitine palmitoyl transferase (Cpt1) and the peroxisomal enzymes Ech1 and Pex11a. Interestingly, these experiments also revealed the considerable overlap between PPARδ and PPARγ in the positive regulation of macrophage gene expression. However, the net effect of PPARδ activation in macrophage lipid homeostasis is controversial. Hydrolysis and uptake of triglycerides present in very low-density lipoproteins (VLDL) can activate PPARδ in macrophages [123,124]. Treatment of macrophages with VLDL results in triglyceride accumulation and upregulation of ADRP in a PPARδ-dependent manner [123]. Furthermore, by upregulating genes involved in cholesterol uptake, including CD36 and SR-A, and downregulating genes implicated in lipid metabolism and efflux, such as cholesterol 27-hydroxylase (Cyp27) and apoE, PPARδ is thought to play a role in macrophage cholesterol accumulation [125]. This contrasts with the capability of PPARδ to upregulate ABCA1 expression and cholesterol efflux [126]. However, recent studies using PPARδ-deficient mice confirmed a pro-atherogenic role for this nuclear receptor. Lesion reduction in PPARδ−/− mice was not related to changes in lipid uptake or efflux, but to the decreased expression of genes involved in inflammation and macrophage recruitment [96].

Macrophages participate in lipoprotein metabolism by secreting apolipoproteins (apo) and enzymes involved in lipoprotein modification. Treatment of human and murine macrophages with LXR agonists results in the induction of several apolipoproteins, including apoE, apoCI, apoCIV and apoCII [127,128]. PPARγ ligands also induce the expression of apoE [118]. Each of these apolipoproteins plays specific roles in lipid homeostasis. In particular, ApoE, a component of VLDL, intermediate-density lipoproteins (IDL) and chylomicron remnants, plays an

important anti-atherogenic role [129]. In the artery wall, secreted apoE promotes cholesterol efflux thereby reducing macrophage cholesterol ester accumulation [130–133], yet the relative importance of apoE-dependent cholesterol efflux, as compared with the ABCA1/apoAI-dependent system has not been established. LXR, PPARα and γ ligands, have been also shown to positively modulate macrophage expression of lipoprotein modifying enzymes, including phospholipid transfer protein (PLTP) [134–136] and lipoprotein lipase (LPL) [118,137,138]. Intriguingly, despite the positive effect on mRNA expression, PPARα and γ activation was reported to result in a net reduction in LPL secretion and activity [138]. The effect of changes on LPL is not clear since this enzyme has been attributed both pro and anti-atherogenic properties [139–143]. The combined action of PLTP and LPL may result in enhanced generation of pre-β-HDL particles; LPL hydrolyzes VLDL and generates phospholipids and apolipoproteins that are subsequently transferred to pre-β-HDL particles by the action of PLTP [144–147]. The coordinated effects of LXR on LPL synthesis and cholesterol efflux probably enhance the clearance of cholesterol-rich lipoproteins from the arterial wall.

Despite their role in reverse cholesterol transport, LXR agonists promote fatty acid and triglyceride biosynthesis. In many cellular types, including macrophages, the expression of the transcription factor SREBP-1c is induced by LXR activation [148,149]. SREBP1c positively regulates the expression of a number of enzymes involved in fatty acid synthesis and triglyceride formation, including fatty acid synthase and stearoyl coenzyme A desaturase. LXRs can also directly bind and activate fatty acid synthase [150]. The positive regulation of lipogenesis by LXRs may be a mechanism to facilitate cholesterol esterification. In addition, fatty acid synthesis and its subsequent desaturation may provide ligands for other nuclear receptors, including PPARs [151].

The fact that synthetic LXR agonists are potent triggers of lipogenesis limits their potential use in the treatment of atherosclerosis. Recent studies show that unliganded LXR/RXR heterodimers actively repress target genes by recruiting corepressors (NCoR and SMRT) [15]. In LXR-deficient macrophages, corepressors fail to be associated to LXR target genes, which results in increased ABCA1 expression, but not SREBP1c. These findings suggest that the development of selective LXR modulators that disrupt the binding of LXR to corepressors without promoting coactivator recruitment may enhance cholesterol efflux without triggering lipogenesis.

6. Conclusions and future directions

Macrophages express several members of the NR superfamily and are able to produce endogenous ligands for these receptors. Natural and synthetic ligands for these receptors influence inflammatory responses, specialized macrophage functions and lipid homeostasis. Recent progress in defining the physiological roles of these receptors suggests that they may be important targets for the development of new classes of ligands useful in the prevention and treatment of hyperlipidemia, diabetes and chronic inflammatory diseases, including atherosclerosis. While these findings have important biological and pharmacological implications, regulation of macrophage gene expression by members of the nuclear receptor family remains relatively unexplored. Future studies using engineered mouse models and functional genomic approaches are needed to clearly establish the mechanisms by which nuclear receptors exert their anti-atherogenic and anti-inflammatory actions. These findings should allow the development of nuclear receptor-selective modulators that retain therapeutic actions with reduced side effects. For example, it may be possible to develop ligands for GR that retain the ability to inhibit NF-κB, without inducing gluconeogenesis [152]. Such ligands could exert anti-inflammatory effects without many of the undesirable side effects of currently available steroid hormone analogs.

Acknowledgments

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References

[1] Evans RM. The steroid and thyroid hormone receptor superfamily. Science 1988;240:889–95.
[2] Chambon P. The molecular and genetic dissection of the retinoid signaling pathway. Recent Prog Horm Res 1995;50:317–32.
[3] Kastner P, Mark M, Chambon P. Nonsteroid nuclear receptors: what are genetic studies telling us about their role in real life? Cell 1995;83:859–69.
[4] Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. The nuclear receptor superfamily: the second decade. Cell 1995;83:835–9.
[5] Chawla A, Repa J, Evans R, Mangelsdorf D. Nuclear receptors and lipid physiology: opening the X-files. Science 2001;294:1866–70.
[6] Francis GA, Fayard E, Picard F, Auwerx J. Nuclear receptors and the control of metabolism. Annu Rev Physiol 2003;65:261–311.
[7] Glass CK, Rose DW, Rosenfeld MG. Nuclear receptor coactivators. Curr Opin Cell Biol 1997;9:222–32.
[8] McKenna NJ, Lanz RB, O'Malley BW. Nuclear receptor coregulators: cellular and molecular biology. Endocr Rev 1999;20(3):321–44.
[9] Perissi V, Staszewski LM, Mclnerney EM, Kurokawa R, Krones A, Rose DW, Lambert MH, Milburn MV, Glass CK, Rosenfield MG. Molecular determinants of nuclear receptor-corepressor interaction. Genes Dev 1999;13:3198–3208.
[10] Rosenfeld MG, Glass CK. Coregulator codes of transcriptional regulation by nuclear receptors. J Biol Chem 2001;276(40):36865–8.

[11] McKenna NJ, O'Malley BW. Combinatorial control of gene expression by nuclear receptors and coregulators. Cell 2002;108(4):465–74.
[12] Glass CK, Rosenfeld MG. The coregulator exchange in transcriptional functions of nuclear receptors. Genes Dev 2000;14:121–41.
[13] Chen JD, Evans RM. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature 1995;377:454–7.
[14] Horlein AJ, Naar AM, Heinzel T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Soderstrom M, Glass CK, et al. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature 1995;377(6548):397–404.
[15] Wagner BL, Valledor AF, Shao G, Daige CL, Bischoff ED, Petrowski M, Jepsen K, Baek SH, Heyman RA, Rosenfeld MG, Schulman IG, Glass CK. Promoter-specific roles for liver X receptor/corepressor complexes in the regulation of ABCA1 and SREBP1 gene expression. Mol Cell Biol 2003;23(16):5780–9.
[16] Hu X, Li S, Wu J, Xia C, Lala DS. Liver X receptors interact with corepressors to regulate gene expression. Mol Endocrinol 2003; 17(6):1019–26.
[17] Schule R, Rangarajan P, Yang N, Kliewer S, Ransone LJ, Bolado J, Verma IM, Evans RM. Retinoic acid is a negative regulator of AP-1-responsive genes. Proc Natl Acad Sci USA 1991;88:6092–6.
[18] Ray A, Prefontaine KE. Physical association and function antagonism between the p65 subunit of transcription factor NF-κB and the glucocorticoid receptor. Proc Natl Acad Sci USA 1994;91:752–6.
[19] Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature 1998;391(6662):79–82.
[20] Joseph SB, Castrillo A, Laffitte BA, Mangelsdorf DJ, Tontonoz P. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. Nat Med 2003;9(2):213–9.
[21] Ricote M, Huang J, Fajas L, Li A, Welch J, Najib J, Witztum JL, Auwerx J, Palinski W, Glass CK. Expression of the peroxisome proliferator-activated receptor γ (PPARγ) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. Proc Natl Acad Sci USA 1998; 95:7614–9.
[22] Cutolo M, Carruba G, Villaggio B, Coviello DA, Dayer JM, Campisi I, Miele M, Stefano R, Castagnetta LA. Phorbol diester 12-*O*-tetradecanoylphorbol 13-acetate (TPA) up-regulates the expression of estrogen receptors in human THP-1 leukemia cells. J Cell Biochem 2001;83(3):390–400.
[23] Huang JT, Welch JS, Ricote M, Binder CJ, Willson TM, Kelly C, Witztum JL, Funk CD, Conrad D, Glass CK. Interleukin-4-dependent production of PPAR-γ ligands in macrophages by 12/15-lipoxygenase. Nature 1999;400:378–82.
[24] Welch JS, Ricote M, Akiyama TE, Gonzalez FJ, Glass CK. PPARgamma and PPARdelta negatively regulate specific subsets of lipopolysaccharide and IFN-gamma target genes in macrophages. Proc Natl Acad Sci USA 2003;100(11):6712–7.
[25] Gordon S. The macrophage. Bioessays 1995;17(11):977–86.
[26] Roodman GD. Cell biology of the osteoclast. Exp Hematol 1999; 27(8):1229–41.
[27] Shevde NK, Bendixen AC, Dienger KM, Pike JW. Estrogens suppress RANK ligand-induced osteoclast differentiation via a stromal cell independent mechanism involving c-Jun repression. Proc Natl Acad Sci USA 2000;97(14):7829–34.
[28] Bendixen AC, Shevde NK, Dienger KM, Willson TM, Funk CD, Pike JW. IL-4 inhibits osteoclast formation through a direct action on osteoclast precursors via peroxisome proliferator-activated receptor gamma 1. Proc Natl Acad Sci USA 2001;98(5):2443–8.
[29] Dempster DW, Moonga BS, Stein LS, Horbert WR, Antakly T. Glucocorticoids inhibit bone resorption by isolated rat osteoclasts by enhancing apoptosis. J Endocrinol 1997;154(3):397–406.
[30] Komi J, Lassila O. Nonsteroidal anti-estrogens inhibit the functional differentiation of human monocyte-derived dendritic cells. Blood 2000;95(9):2875–82.
[31] Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, Allavena P, Di Carlo V. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000;164(9):4443–51.
[32] Fritsche J, Mondal K, Ehrnsperger A, Andreesen R, Kreutz M. Regulation of 25-hydroxyvitamin D3-1{alpha}-hydroxylase and production of 1{alpha},25-dihydroxyvitamin D3 by human dendritic cells. Blood 2003.
[33] Griffin MD, Kumar R. Effects of 1alpha, 25(OH)2D3 and its analogs on dendritic cell function. J Cell Biochem 2003;88(2):323–6.
[34] Adorini L. Immunomodulatory effects of vitamin D receptor ligands in autoimmune diseases. Int Immunopharmacol 2002;2(7):1017–28.
[35] Nakajima H, Kizaki M, Ueno H, Muto A, Takayama N, Matsushita H, Sonoda A, Ikeda Y. All-*trans* and 9-*cis* retinoic acid enhance 1,25-dihydroxyvitamin D3-induced monocytic differentiation of U937 cells. Leuk Res 1996;20(8):665–76.
[36] Lima FR, Gervais A, Colin C, Izembart M, Neto VM, Mallat M. Regulation of microglial development: a novel role for thyroid hormone. J Neurosci 2001;21(6):2028–38.
[37] Schmidt M, Kreutz M, Loffler G, Scholmerich J, Straub RH. Conversion of dehydroepiandrosterone to downstream steroid hormones in macrophages. J Endocrinol 2000;164(2):161–9.
[38] Neveu I, Naveilhan P, Menaa C, Wion D, Brachet P, Garabedian M. of 1,25-dihydroxyvitamin D3 by rat brain macrophages *in vitro* synthesis. J Neurosci Res 1994;38(2):214–20.
[39] Soderstrom M, Wigren J, Surapureddi S, Glass CK, Hammarstrom S. Novel prostaglandin D(2)-derived activators of peroxisome proliferator-activated receptor-gamma are formed in macrophage cell cultures. Biochim Biophys Acta 2003;1631(1):35–41.
[40] Yang XY, Wang LH, Mihalic K, Xiao W, Chen T, Li P, Wahl LM, Farrar WL. Interleukin (IL)-4 indirectly suppresses IL-2 production by human T lymphocytes via peroxisome proliferator-activated receptor gamma activated by macrophage-derived 12/15-lipoxygenase ligands. J Biol Chem 2002;277(6):3973–8.
[41] Willson TM, Cobb JE, Cowan DJ, Wiethe RW, Correa ID, Prakash SR, Beck KD, Moore LB, Kliewer SA, Lehmann JM. The structure–activity relationship between peroxisome proliferator-activated receptor gamma agonism and the antihyperglycemic activity of thiazolidinediones. J Med Chem 1996;39(3):665–8.
[42] Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ. An oxysterol signalling pathway mediated by the nuclear receptor LXRα. Nature 1996;383:728–31.
[43] Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, Sundseth SS, Winegar DA, Blanchard DE, Spencer TA, Willson TM. Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. J Biol Chem 1997;272(6): 3137–40.
[44] Janowski BA, Grogan MJ, Jones SA, Wisely GB, Kliewer SA, Corey EJ, Mangelsdorf DJ. Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta. Proc Natl Acad Sci USA 1999;96(1):266–71.
[45] Rowe AH, Argmann CA, Edwards JY, Sawyez CG, Morand OH, Hegele RA, Huff MW. Enhanced synthesis of the oxysterol 24(*S*), 25-epoxycholesterol in macrophages by inhibitors of 2,3-oxydosgualene: lanosterolcyclase: a novel mechanism for the attenuation of foam cell formation. Circ Res 2003;93:717–25.
[46] Babiker A, Andersson O, Lund E, Xiu RJ, Deeb S, Reshef A, Leitersdorf E, Diczfalusy U, Bjorkhem I. Elimination of cholesterol in macrophages and endothelial cells by the sterol 27-hydroxylase mechanism. Comparison with high density lipoprotein-mediated reverse cholesterol transport. J Biol Chem 1997;272(42):26253–561.
[47] Fu X, Menke JG, Chen Y, Zhou G, MacNaul KL, Wright SD, Sparrow CP, Lund EG. 27-Hydroxycholesterol is an endogenous ligand for liver X receptor in cholesterol-loaded cells. J Biol Chem 2001;276(42):38378–87.

[48] Barnes PJ. Inhaled glucocorticoids for asthma. N Engl J Med 1995;332(13):868–75.
[49] McKay LI, Cidlowski JA. Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. Endocr Rev 1999;20:435–59.
[50] Morand EF, Leech M. Glucocorticoid regulation of inflammation: the plot thickens. Inflamm Res 1999;48(11):557–60.
[51] Schimmer B, Parker K. ACTH, adrenocortical steroids and their synthetic analogs. In: Hardman JG, Limbird LE, Goodman Gilman A, editors. Goodman and Gilman's pharmacological basis of therapeutics. New York: McGraw Hill; 1996.
[52] Herrlich P, Ponta H. Mutual cross-modulation of steroid-retinoic acid receptor and AP-1 transcription factor activities: a novel property with practical implications. Trends Endocrinol Metab 1994;5: 341–56.
[53] Adcock IM, Barnes PJ. Ligand-induced differentiation of glucocorticoid receptor (GR) trans-repression and transactivation. Biochem Soc Trans 1996;24(2):267S.
[54] Almawi WY, Beyhum HN, Rahme AA, Rieder MJ. Regulation of cytokine and cytokine receptor expression by glucocorticoids. J Leukoc Biol 1996;60(5):563–72.
[55] Joyce DA, Steer JH, Abraham LJ. Glucocorticoid modulation of human monocyte/macrophage function: control of TNF-alpha secretion. Inflamm Res 1997;46(11):447–51.
[56] Kleinert H, Euchenhofer C, Ihrig-Biedert I, Forstermann U. Glucocorticoids inhibit the induction of nitric oxide synthase II by down-regulating cytokine-induced activity of transcription factor nuclear factor-kappa B. Mol Pharmacol 1996;49(1):15–21.
[57] Tanaka J, Fujita H. Glucocorticoid and mineralocorticoid receptors in microgial cells: the two receptors mediate differential effects of corticosteroids. Glia 1997;20(1):23–7.
[58] Koehler L, Hass R, DeWitt DL, Resch K, Goppelt-Struebe M. Glucocorticoid-induced reduction of prostanoid synthesis in TPA-differentiated U937 cells is mainly due to a reduced cyclooxygenase activity. Biochem Pharmacol 1990;40(6):1307–16.
[59] Caldenhoven E, Liden J, Wissnik S, Van de Stoipe A, Raaijmakers J, Koenderman L, Okret S, Gustafsson J-A, Van der Sagg PT. Negative cross-talk between RelA and the glucocorticoid receptor: a possible mechanism for the antiinflammatory action of glucocorticoids. Mol Endocrinol 1995;9:401–12.
[60] Scheinman RI, Gualberto A, Jewell CM, Cidlowski JA, Baldwin Jr AS. Characterization of mechanisms involved in transrepression of NF-κB activated glucocorticoid receptors. Mol Cell Biol 1995;15: 242–4.
[61] Heck S, Bender K, Kullmann M, Gottlicher M, Herrlich P, Cato AC. I kappaB alpha-independent downregulation of NF-kappaB activity by glucocorticoid receptor. EMBO J 1997;16(15):4698–707.
[62] Caelles C, Gonzales-Sancho JM, Munoz A. Nuclear hormone receptor antagonism with AP-1 by inhibition of the JNK pathway. Genes Dev 1997;11:3351–64.
[63] Rogatsky I, Logan SK, Garabedian MJ. Antagonism of glucocorticoid receptor transcriptional activation by the c-Jun N-terminal kinase. Proc Natl Acad Sci USA 1998;95(5):2050–5.
[64] Kamei Y, Xu L, Heinzel T, Torchia J, Kurokawa R, Gloss B, Lin S-C, Heyman R, Rose D, Glass C, Rosenfeld M. A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. Cell 1996;85:403–14.
[65] McKay L, Cidlowski J. CBP (CREB binding protein) integrates NF-kB (nuclear factor-κB) and glucocorticoid receptor physical interactions and antagonism. Mol Endocrinol 2000;14:1222–34.
[66] Nissen RM, Yamamoto KR. The glucocorticoid receptor inhibits NFkappaB by interfering with serine-2 phosphorylation of the RNA polymerase II carboxy-terminal domain. Genes Dev 2000; 14(18):2314–29.
[67] Ito K, Barnes PJ, Adcock IM. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits interleukin-1beta-induced histone H4 acetylation on lysines 8 and 12. Mol Cell Biol 2000;20(18): 6891–903.
[68] Frazier-Jessen MR, Kovacs EJ. Estrogen modulation of JE/monocyte chemoattractant protein-1 mRNA expression in murine macrophages. J Immunol 1995;154(4):1838–45.
[69] Stein B, Yang MX. Repression of the interleukin-6 promoter by estrogen receptor is mediated by NF-κB and C/EBPβ. Mol Cell Biol 1995;15:4971–9.
[70] D'Ambrosio D, Cippitelli M, Cocciolo MG, Mazzeo D, Di Lucia P, Lang R, Sinigaglia F, Panina-Bordignon P. Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. J Clin Invest 1998;101(1):252–62.
[71] Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 1998;391(6662):82–6.
[72] Chinetti G, Griglio S, Antonucci M, Torra IP, Delerive P, Majd Z, Fruchart J-C, Chapman J, Najib J, Staels B. Activation of proliferator-activated receptors α and γ induces apoptosis of human monocyte-derived macrophages. J Biol Chem 1998;273(40): 25573–80.
[73] Castrillo A, Joseph SB, Marathe C, Mangelsdorf DJ, TontonozP. Liver X receptor-dependent repression of matrix metalloproteinase-9 expression in macrophages. J Biol Chem 2003;278(12):10443–9.
[74] Li M, Pascual G, Glass C. Peroxisome proliferator-activated receptor γ-dependent repression of the inducible nitric oxide synthase gene. Mol Cell Biol 2000;20(13):4699–707.
[75] Valentine JE, Kalkhoven E, White R, Hoare S, Parker MG. Mutations in the estrogen receptor ligand binding domain discriminate between hormone-dependent transactivation and transrepression. J Biol Chem 2000;275(33):25322–9.
[76] Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J 2001;15(14):2579–85.
[77] Li A, Brown K, Silvestre M, Willson T, Palinski W, Glass C. Peroxisome proliferator-activated receptor γ ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. J Clin Invest 2000;106(4):523–31.
[78] Collins AR, Meehan WP, Kintscher U, Jackson S, Wakino S, Noh G, Palinski W, Hsueh WA, Law RE. Troglitazone inhibits formation of early atherosclerotic lesions in diabetic and nondiabetic low density lipoprotein receptor-deficient mice. Arterioscler Thromb Vasc Biol 2001;21(3):365–71.
[79] Chen Z, Ishibashi S, Perrey S, Osuga J, Gotoda T, Kitamine T, Tamura Y, Okazaki H, Yahagi N, Iizuka Y, Shionoiri F, Ohashi K, Harada K, Shimano H, Nagai R, Yamada N. Troglitazone inhibits atherosclerosis in apolipoprotein E-knockout mice: pleiotropic effects on CD36 expression and HDL. Arterioscler Thromb Vasc Biol 2001;21(3):372–7.
[80] Claudel T, Leibowitz MD, Fievet C, Tailleux A, Wagner B, Repa JJ, Torpier G, Lobaccaro JM, Paterniti JR, Mangelsdorf DJ, Heyman RA, Auwerx J. Reduction of atherosclerosis in apolipoprotein E knockout mice by activation of the retinoid X receptor. Proc Natl Acad Sci USA 2001;98(5):2610–5.
[81] Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, Joseph SB, Liao D, Nagy L, Edwards PA, Curtiss LK, Evans RM, Tontonoz P. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Mol Cell 2001;7(1):161–71.
[82] Tangirala RK, Bischoff ED, Joseph SB, Wagner BL, Walczak R, Laffitte BA, Daige CL, Thomas D, Heyman RA, Mangelsdorf DJ, Wang X, Lusis AJ, Tontonoz P, Schulman IG. Identification of macrophage liver X receptors as inhibitors of atherosclerosis. Proc Natl Acad Sci USA 2002;99(18):11896–901.
[83] Duez H, Chao YS, Hernandez M, Torpier G, Poulain P, Mundt S, Mallat Z, Teissier E, Burton CA, Tedgui A, Fruchart JC, Fievet C, Wright SD, Staels B. Reduction of atherosclerosis by the peroxisome proliferator-activated receptor alpha agonist fenofibrate in mice. J Biol Chem 2002;277(50):48051–7.

[84] Joseph SB, McKilligin E, Pei L, Watson MA, Collins AR, Laffitte BA, Chen M, Noh G, Goodman J, Hagger GN, Tran J, Tippin TK, Wang X, Lusis AJ, Hsueh WA, Law RE, Collins JL, Willson TM, Tontonoz P. Synthetic LXR ligand inhibits the development of atherosclerosis in mice. Proc Natl Acad Sci USA 2002;99(11):7604–9.

[85] Terasaka N, Hiroshima A, Koieyama T, Ubukata N, Morikawa Y, Nakai D, Inaba T. T-0901317, a synthetic liver X receptor ligand, inhibits development of atherosclerosis in LDL receptor-deficient mice. FEBS Lett 2003;536(1-3):6–11.

[86] Su CG, Wen X, Bailey ST, Jiang W, Rangwala SM, Keilbaugh SA, Flanigan A, Murthy S, Lazar MA, Wu GD. A novel therapy for colitis utilizing PPAR-γ ligands to inhibit the epithelial inflammatory response. J Clin Invest 1999;104(4):383–9.

[87] Desreumaux P, Dubuquoy L, Nutten S, Peuchmaur M, Englaro W, Schoonjans K, Derijard B, Desvergne B, Wahli W, Chambon P, Leibowitz MD, Colombel JF, Auwerx J. Attenuation of colon inflammation through activators of the retinoid X receptor (RXR)/peroxisome proliferator-activated receptor gamma (PPARgamma) heterodimer. A basis for new therapeutic strategies. J Exp Med 2001;193(7):827–38.

[88] Niino M, Iwabuchi K, Kikuchi S, Ato M, Morohashi T, Ogata A, Tashiro K, Onoe K. Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by an agonist of peroxisome proliferator-activated receptor-gamma. J Neuroimmunol 2001;116(1):40–8.

[89] Diab A, Deng C, Smith JD, Hussain RZ, Phanavanh B, Lovett-Racke AE, Drew PD, Racke MK. Peroxisome proliferator-activated receptor-gamma agonist 15-deoxy-Delta(12,14)-prostaglandin J(2) ameliorates experimental autoimmune encephalomyelitis. J Immunol 2002;168(5):2508–15.

[90] Feinstein DL, Galea E, Gavrilyuk V, Brosnan CF, Whitacre CC, Dumitrescu-Ozimek L, Landreth GE, Pershadsingh HA, Weinberg G, Heneka MT. Peroxisome proliferator-activated receptor-gamma agonists prevent experimental autoimmune encephalomyelitis. Ann Neurol 2002;51(6):694–702.

[91] Natarajan C, Bright JJ. Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production. Genes Immun 2002;3(2):59–70.

[92] Rossi A, Kapahi P, Natoli G, Takahashi T, Chen Y, Karin M, Santoro MG. Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IkappaB kinase. Nature 2000;403(6756):103–8.

[93] Straus DS, Pascual G, Li M, Welch J, Ricote M, Hsiang CH, Sengchanthalansgsy LL, Ghosh G, Glass CK. 15-Deoxy-delta^{12,14}-prostaglandin J_2 inhibits multiple steps in the NF-κB signaling pathway. PNAS 2000;97(9):4844–9.

[94] Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM. PPAR-gamma dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. Nat Med 2001;7(1):48–52.

[95] Moore KJ, Rosen ED, Fitzgerald ML, Randow F, Andersson LP, Altshuler D, Milstone DS, Mortensen RM, Spiegelman BM, Freeman MW. The role of PPAR-gamma in macrophage differentiation and cholesterol uptake. Nat Med 2001;7(1):41–7.

[96] Lee CH, Chawla A, Urbiztondo N, Liao D, Boisvert WA, Evans RM. Transcriptional repression of atherogenic inflammation: modulation by PPAR{delta}. Science 2003;302:453–7.

[97] Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002;106(6):679–84.

[98] Tontonoz P, Mangelsdorf DJ. Liver X receptor signaling pathways in cardiovascular disease. Mol Endocrinol 2003;17(6):985–93.

[99] Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986;232:34–47.

[100] Brown MS, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell 1997;89(3):331–40.

[101] Aviram M, Fuhrman B. LDL oxidation by arterial wall macrophages depends on the oxidative status in the lipoprotein and in the cells: role of prooxidants vs. antioxidants. Mol Cell Biochem 1998;188(1-2):149–59.

[102] Navab M, Berliner JA, Watson AD, Hama SY, Territo MC, Lusis AJ, Shih DM, Van Lenten BJ, Frank JS, Demer LL, Edwards PA, Fogelman AM. The yin and yang of oxidation in the development of the fatty streak. Arterioscler Thromb Vasc Biol 1996;16(7):831–42.

[103] Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. N Engl J Med 1989;320:915–24.

[104] Glass C, Witztum J. Atherosclerosis; the road ahead. Cell 2001;104:503–16.

[105] Li AC, Glass CK. The macrophage foam cell as a target for therapeutic intervention. Nat Med 2002;8(11):1235–42.

[106] Gordon S. Pattern recognition receptors: doubling up for the innate immune response. Cell 2002;111(7):927–30.

[107] Tontonoz P, Nagy L, Alvarez JGA, Thomazy VA, Evans RM. PPARγ promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell 1998;93:241–52.

[108] Nagy L, Tontonoz P, Alvarez JGA, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPAR-gamma. Cell 1998;93:229–40.

[109] Chinetti G, Lestavel S, Bocher V, Remaley AT, Neve B, Torra IP, Teissier E, Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V, Staels B. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med 2001;7(1):53–8.

[110] Oram JF, Vaughan AM. ABCA1-mediated transport of cellular cholesterol and phospholipids to HDL apolipoproteins. Curr Opin Lipidol 2000;11(3):253–60.

[111] Tall AR. An overview of reverse cholesterol transport. Eur Heart J 1998;19(Suppl A):A31–5.

[112] Lawn RM, Wade DP, Garvin MR, Wang X, Schwartz K, Porter JG, Seilhamer JJ, Vaughan AM, Oram JF. The Tangier disease gene product ABC1 controls the cellular apolipoprotein-mediated lipid removal pathway. J Clin Invest 1999;104(8):R25–31.

[113] Hobbs HH, Rader DJ. ABC1: connecting yellow tonsils, neuropathy, and very low HDL. J Clin Invest 1999;104(8):1015–7.

[114] Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, Mangelsdorf DJ. Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. Science 2000;289(5484):1524–9.

[115] Costet P, Luo Y, Wang N, Tall AR. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. J Biol Chem 2000;275(36):28240–5.

[116] Schwartz K, Lawn RM, Wade DP. ABC1 gene expression and ApoA-I-mediated cholesterol efflux are regulated by LXR. Biochem Biophys Res Commun 2000;274(3):794–802.

[117] Venkateswaran A, Laffitte BA, Joseph SB, Mak PA, Wilpitz DC, Edwards PA, Tontonoz P. Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. Proc Natl Acad Sci USA 2000;97(22):12097–102.

[118] Akiyama TE, Sakai S, Lambert G, Nicol CJ, Matsusue K, Pimprale S, Lee YH, Ricote M, Glass CK, Brewer Jr HB, Gonzalez FJ. Conditional disruption of the peroxisome proliferator-activated receptor gamma gene in mice results in lowered expression of ABCA1, ABCG1, and apoE in macrophages and reduced cholesterol efflux. Mol Cell Biol 2002;22(8):2607–19.

[119] Chinetti G, Lestavel S, Fruchart JC, Clavey V, Staels B. Peroxisome proliferator-activated receptor alpha reduces cholesterol esterification in macrophages. Circ Res 2003;92(2):212–7.

[120] Chinetti G, Gbaguidi FG, Griglio S, Mallat Z, Antonucci M, Poulain P, Chapman J, Fruchart JC, Tedgui A, Najib-Fruchart J, Staels B. CLA-1/SR-BI is expressed in atherosclerotic lesion macrophages

and regulated by activators of peroxisome proliferator-activated receptors. Circulation 2000;101(20):2411–7.

[121] Ghosh S, Natarajan R. Cloning of the human cholesteryl ester hydrolase promoter: identification of functional peroxisomal proliferator-activated receptor responsive elements. Biochem Biophys Res Commun 2001;284(4):1065–70.

[122] Venkateswaran A, Repa JJ, Lobaccaro JM, Bronson A, Mangelsdorf DJ, Edwards PA. Human white/murine ABC8 mRNA levels are highly induced in lipid-loaded macrophages. A transcriptional role for specific oxysterols. J Biol Chem 2000;275(19):14700–7.

[123] Chawla A, Lee CH, Barak Y, He W, Rosenfeld J, Liao D, Han J, Kang H, Evans RM. PPARdelta is a very low-density lipoprotein sensor in macrophages. Proc Natl Acad Sci USA 2003;100(3):1268–73.

[124] Ziouzenkova O, Perrey S, Asatryan L, Hwang J, MacNaul KL, Moller DE, Rader DJ, Sevanian A, Zechner R, Hoefler G, Plutzky J. Lipolysis of triglyceride-rich lipoproteins generates PPAR ligands: evidence for an antiinflammatory role for lipoprotein lipase. Proc Natl Acad Sci USA 2003;100(5):2730–5.

[125] Vosper H, Patel L, Graham TL, Khoudoli GA, Hill A, Macphee CH, Pinto I, Smith SA, Suckling KE, Wolf CR, Palmer CN. The peroxisome proliferator-activated receptor delta promotes lipid accumulation in human macrophages. J Biol Chem 2001;276(47):44258–65.

[126] Oliver Jr WR, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznaidman ML, Lambert MH, Xu HE, Sternbach DD, Kliewer SA, Hansen BC, Willson TM. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. Proc Natl Acad Sci USA 2001;98(9):5306–11.

[127] Mak PA, Laffitte BA, Desrumaux C, Joseph SB, Curtiss LK, Mangelsdorf DJ, Tontonoz P, Edwards PA. Regulated expression of the apolipoprotein E/C-I/C-IV/C-II gene cluster in murine and human macrophages. A critical role for nuclear liver X receptors alpha and beta. J Biol Chem 2002;277(35):31900–8.

[128] Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, Tontonoz P. LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. Proc Natl Acad Sci USA 2001;98(2):507–12.

[129] Curtiss LK, Boisvert WA. Apolipoprotein E and atherosclerosis. Curr Opin Lipidol 2000;11(3):243–51.

[130] Plump AS, Smith JD, Hayek T, Breslow J. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell 1992;71: 343–53.

[131] Zhang SH, Reddick RL, Piedrahita JA, Meada N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science 1992;258:468–71.

[132] Fazio S, Babaev VR, Murray AB, Hasty AH, Carter KJ, Gleaves LA, Atkinson JB, Linton MF. Increased atherosclerosis in mice reconstituted with apolipoprotein E null macrophages. Proc Natl Acad Sci USA 1997;94(9):4647–52.

[133] Lin CY, Duan H, Mazzone T. Apolipoprotein E-dependent cholesterol efflux from macrophages: kinetic study and divergent mechanisms for endogenous versus exogenous apolipoprotein E. J Lipid Res 1999;40(9):1618–27.

[134] Laffitte BA, Joseph SB, Chen M, Castrillo A, Repa J, Wilpitz D, Mangelsdorf D, Tontonoz P. The phospholipid transfer protein gene is a liver X receptor target expressed by macrophages in atherosclerotic lesions. Mol Cell Biol 2003;23(6):2182–91.

[135] Cao G, Beyer TP, Yang XP, Schmidt RJ, Zhang Y, Bensch WR, Kauffman RF, Gao H, Ryan TP, Liang Y, Eacho PI, Jiang XC. Phospholipid transfer protein is regulated by liver X receptors *in vivo*. J Biol Chem 2002;277(42):39561–5.

[136] Mak PA, Kast-Woelbern HR, Anisfeld AM, Edwards PA. Identification of PLTP as an LXR target gene and apoE as an FXR target gene reveals overlapping targets for the two nuclear receptors. J Lipid Res 2002;43(12):2037–41.

[137] Zhang Y, Repa JJ, Gauthier K, Mangelsdorf DJ. Regulation of lipoprotein lipase by the oxysterol receptors, LXRalpha and LXRbeta. J Biol Chem 2001;276(46):43018–24.

[138] Gbaguidi FG, Chinetti G, Milosavljevic D, Teissier E, Chapman J, Olivecrona G, Fruchart JC, Griglio S, Fruchart-Najib J, Staels B. Peroxisome proliferator-activated receptor (PPAR) agonists decrease lipoprotein lipase secretion and glycated LDL uptake by human macrophages. FEBS Lett 2002;512(1–3):85–90.

[139] Goldberg IJ. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J Lipid Res 1996;37(4): 693–707.

[140] Babaev VR, Patel MB, Semenkovich CF, Fazio S, Linton MF. Macrophage lipoprotein lipase promotes foam cell formation and atherosclerosis in low density lipoprotein receptor-deficient mice. J Biol Chem 2000;275(34):26293–9.

[141] Wilson K, Fry GL, Chappell DA, Sigmund CD, Medh JD. Macrophage-specific expression of human lipoprotein lipase accelerates atherosclerosis in transgenic apolipoprotein ε knockout mice but not in C57BL/6 mice. Arterioscler Thromb Vasc Biol 2001;21(11): 1809–15.

[142] Shimada M, Ishibashi S, Inaba T, Yagyu H, Harada K, Osuga JI, Ohashi K, Yazaki Y, Yamada N. Suppression of diet-induced atherosclerosis in low density lipoprotein receptor knockout mice overexpressing lipoprotein lipase. Proc Natl Acad Sci USA 1996; 93(14):7242–6.

[143] Yagyu H, Ishibashi S, Chen Z, Osunga J, Okazaki K, Perrey S, Kitamine T, Shimada M, Ohashi K, Harada K, Shionoiri F, Yahagi N, Gotoda T, Yazaki Y, Yamada N. Overexpressed lipoprotein lipase protects against atherosclerosis in apolipoprotein E knockout mice. J Lipid Res 1999;40:1677–85.

[144] Strauss JG, Frank S, Kratky D, Hammerle G, Hrzenjak A, Knipping G, von Eckardstein A, Kostner GM, Zechner R. Adenovirus-mediated rescue of lipoprotein lipase-deficient mice. Lipolysis of triglyceride-rich lipoproteins is essential for high density lipoprotein maturation in mice. J Biol Chem 2001;276(39):36083–90.

[145] van Tol A. Phospholipid transfer protein. Curr Opin Lipidol 2002; 13(2):135–9.

[146] Foger B, Santamarina-Fojo S, Shamburek RD, Parrot CL, Talley GD, Brewer Jr HB. Plasma phospholipid transfer protein. Adenovirus-mediated overexpression in mice leads to decreased plasma high density lipoprotein (HDL) and enhanced hepatic uptake of phospholipids and cholesteryl esters from HDL. J Biol Chem 1997;272(43):27393–400.

[147] Jaari S, van Dijk KW, Olkkonen VM, van der Zee A, Metso J, Havekes L, Jauhiainen M, Ehnholm C. Dynamic changes in mouse lipoproteins induced by transiently expressed human phospholipid transfer protein (PLTP): importance of PLTP in prebeta-HDL generation. Comp Biochem Physiol B: Biochem Mol Biol 2001; 128(4):781–92.

[148] Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro J-MA, Shimomura I, Shan B, Brown MS, Goldstein JL, Mangelsdorf DJ. Regulation of mouse sterol regulatory element-binding protein-1c (SREBP-1c) by oxysterol receptors LXRα and LXRβ. Genes Dev 2000;14:2819–30.

[149] Yoshikawa T, Shimano H, Amemiya-Kudo M, Yahagi N, Hasty AH, Matsuzaka T, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Osuga J, Harada K, Gotoda T, Kimura S, Ishibashi S, Yamada N. Identification of liver X receptor-retinoid X receptor as an activator of the sterol regulatory element-binding protein 1c gene promoter. Mol Cell Biol 2001;21(9):2991–3000.

[150] Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF, Tontonoz P. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. J Biol Chem 2002;277(13):11019–25.

[151] Kim JB, Wright HM, Wright M, Spiegelman BM. ADD1/SREBP1 activates PPARgamma through the production of endogenous ligand. Proc Natl Acad Sci USA 1998;95(8):4333–7.

[152] Vayssière BM, Dupont S, Choquart A, Petit F, Garcia T, Marchandeau C, Gronemeyer H, Resche-Rigon M. Synthetic glucocorticoids that dissociate transactivation and AP-1 transrepression exhibit antiinflammatory activity *in vivo*. Mol Endocrinol 1997;11(9): 1245–55.

[153] McLaren J, Prentice A, Charnock-Jones DS, Millican SA, Muller KH, Sharkey AM, Smith SK. Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. J Clin Invest 1996;98(2):482–9.

[154] Mor G, Sapi E, Abrahams VM, Rutherford T, Song J, Hao XY, Muzaffar S, Kohen F. Interaction of the estrogen receptors with the Fas ligand promoter in human monocytes. J Immunol 2003; 170(1):114–22.

[155] Bord S, Horner A, Beavan S, Compston J. Estrogen receptors alpha and beta are differentially expressed in developing human bone. J Clin Endocrinol Metab 2001;86(5):2309–14.

[156] Vegeto E, Belcredito S, Etteri S, Ghisletti S, Brusadelli A, Meda C, Krust A, Dupont S, Ciana P, Chambon P, Maggi A. Estrogen receptor-alpha mediates the brain antiinflammatory activity of estradiol. Proc Natl Acad Sci USA 2003;100(16):9614–9.

[157] Vickers AE, Lucier GW. Estrogen receptor levels and occupancy in hepatic sinusoidal endothelial and Kupffer cells are enhanced by initiation with diethylnitrosamine and promotion with 17alpha-ethinylestradiol in rats. Carcinogenesis 1996;17(6):1235–42.

[158] Yang NN, Venugopalan M, Hardikar S, Glasebrook A. Identification of an estrogen response element activated by metabolites of 17β-estradiol and raloxifene. Science 1996;273:1222–5.

[159] Sacedon R, Vicente A, Varas A, Jimenez E, Munoz JJ, Zapata AG. Glucocorticoid-mediated regulation of thymic dendritic cell function. Int Immunol 1999;11(8):1217–24.

[160] Huang L, Xu J, Kumta SM, Zheng MH. Gene expression of glucocorticoid receptor alpha and beta in giant cell tumour of bone: evidence of glucocorticoid-stimulated osteoclastogenesis by stromal-like tumour cells. Mol Cell Endocrinol 2001;181(1-2): 199–206.

[161] Sartori ML, Masera RG, Staurenghi A, Racca S, Angeli A. Interleukin 2 up-regulates glucocorticoid receptor number in human peripheral blood mononuclear cells and the osteosarcoma cell line Saos-2 *in vitro*. Steroids 1998;63(5-6):349–51.

[162] Pujols L, Mullol J, Roca-Ferrer J, Torrego A, Xaubet A, Cidlowski JA, Picado C. Expression of glucocorticoid receptor alpha- and beta-isoforms in human cells and tissues. Am J Physiol Cell Physiol 2002;283(4):C1324–31.

[163] Hollenberg SM, Weinberger C, Ong ES, Cerelli G, Oro A, Lebo R, Thompson EB, Rosenfeld MG, Evans RM. Primary structure and expression of a functional human glucocorticoid receptor cDNA. Nature 1985;318(6047):635–41.

[164] Hoekstra M, Kruijt JK, Van Eck M, Van Berkel TJ. Specific gene expression of ATP-binding cassette transporters and nuclear hormone receptors in rat liver parenchymal, endothelial, and Kupffer cells. J Biol Chem 2003;278(28):25448–53.

[165] Lu TT, Repa JJ, Mangelsdorf DJ. Orphan nuclear receptors as eLiXiRs and FiXeRs of sterol metabolism. J Biol Chem 2001; 276(41):37735–8.

[166] Willson T, Brown P, Sternbach D, Henke B. The PPARs: from orphan receptors to drug discovery. J Med Chem 2000;43(4):527–50.

[167] Nencioni A, Grunebach F, Zobywlaski A, Denzlinger C, Brugger W, Brossart P. Dendritic cell immunogenicity is regulated by peroxisome proliferator-activated receptor gamma. J Immunol 2002; 169(3):1228–35.

[168] Gosset P, Charbonnier AS, Delerive P, Fontaine J, Staels B, Pestel J, Tonnel AB, Trottein F. Peroxisome proliferator-activated receptor gamma activators affect the maturation of human monocyte-derived dendritic cells. Eur J Immunol 2001;31(10):2857–65.

[169] Bernardo A, Levi G, Minghetti L. Role of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) and its natural ligand 15-deoxy-Delta12,14-prostaglandin J2 in the regulation of microglial functions. Eur J Neurosci 2000;12(7):2215–23.

[170] Mano H, Kimura C, Fujisawa Y, Kameda T, Watanabe-Mano M, Kaneko H, Kaneda T, Hakeda Y, Kumegawa M. Cloning and function of rabbit peroxisome proliferator-activated receptor delta/beta in mature osteoclasts. J Biol Chem 2000;275(11):8126–32.

[171] Ohata M, Yamauchi M, Takeda K, Toda G, Kamimura S, Motomura K, Xiong S, Tsukamoto H. RAR and RXR expression by Kupffer cells. Exp Mol Pathol 2000;68(1):13–20.

[172] Fritsche J, Stonehouse TJ, Katz DR, Andreesen R, Kreutz M. Expression of retinoid receptors during human monocyte differentiation *in vitro*. Biochem Biophys Res Commun 2000;270(1):17–22.

[173] Saneshige S, Mano H, Tezuka K, Kakudo S, Mori Y, Honda Y, Itabashi A, Yamada T, Miyata K, Hakeda Y, et al. Retinoic acid directly stimulates osteoclastic bone resorption and gene expression of cathepsin K/OC-2. Biochem J 1995;309(Pt 3):721–4.

[174] Giguere V, Ong ES, Segui P, Evans RM. Identification of a receptor for the morphogen retinoic acid. Nature 1987;330:624–9.

[175] Petkovich M, Brand NJ, Krust A, Chambon P. A human retinoic acid receptor which belongs to the family of nuclear receptors. Nature 1987;330:444–50.

[176] Kitamura Y, Spleiss O, Li H, Taniguchi T, Kimura H, Nomura Y, Gebicke-Haerter PJ. Lipopolysaccharide-induced switch between retinoid receptor (RXR) alpha and glucocorticoid attenuated response gene (GARG)-16 messenger RNAs in cultured rat microglia. J Neurosci Res 2001;64(6):553–63.

[177] Giguere V. Orphan nuclear receptors: from gene to function. Endocr Rev 1999;20(5):689–725.

[178] Mata de Urquiza AM, Liu S, Sjoberg M, Zetterstrom RH, Griffiths W, Sjovall J, Perlmann T. Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. Science 2000;290(5499):2140–4.

[179] Abu EO, Horner A, Teti A, Chatterjee VK, Compston JE. The localization of thyroid hormone receptor mRNAs in human bone. Thyroid 2000;10(4):287–93.

[180] Lazar MA, Chin WW. Nuclear thyroid hormone receptors. J Clin Invest 1990;86(6):1777–82.

[181] Gascon-Barre M, Demers C, Mirshahi A, Neron S, Zalzal S, Nanci A. The normal liver harbors the vitamin D nuclear receptor in nonparenchymal and biliary epithelial cells. Hepatology 2003;37(5): 1034–42.

[182] Nagpal S, Lu J, Boehm MF. Vitamin D analogs: mechanism of action and therapeutic applications. Curr Med Chem 2001;8(13):1661–79.