Biochimica et Biophysica Acta 1812 (2011) 982–994

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Liver X receptors as regulators of macrophage inflammatory and metabolic pathways☆,☆☆

Noelia A-González [b,1], Antonio Castrillo [a,b,*]

[a] Instituto de Investigaciones Biomédicas 'Alberto Sols,' Consejo Superior de Investigaciones Científicas-Universidad Autónoma de Madrid, Spain
[b] Department of Biochemistry and Molecular Biology, Universidad de Las Palmas de Gran Canaria, ULPGC, Las Palmas, Spain

ARTICLE INFO

Article history:
Received 3 November 2010
Received in revised form 14 December 2010
Accepted 17 December 2010
Available online 28 December 2010

Keywords:
Liver X receptors
Macrophage
Cholesterol, Inflammation
Innate immunity
Phagocytosis
Autoimmunity

ABSTRACT

The liver X receptors (LXRα and LXRβ) are members of the nuclear receptor family of transcription factors that play essential roles in the transcriptional control of lipid metabolism. LXRs are endogenously activated by modified forms of cholesterol known as oxysterols and control the expression of genes important for cholesterol uptake, efflux, transport, and excretion in multiple tissues. In addition to their role as cholesterol sensors, a number of studies have implicated LXRs in the modulation of innate and adaptive immune responses. Both through activation and repression mechanisms, LXRs regulate diverse aspects of inflammatory gene expression in macrophages. The ability of LXRs to coordinate metabolic and immune responses constitutes an attractive therapeutic target for the treatment of chronic inflammatory disorders. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

1. Introduction

Nuclear receptors (NRs) are a large family ligand-activated transcription factors that regulate several important processes, including development, reproduction and metabolism [1–3]. NRs respond to lipophilic hormones, vitamins, dietary lipids, or other intracellular signals [4]. By virtue of this ligand-dependent activity, NRs serve as a molecular bridge between the whole body environment and the genome [5,6]. Genetic studies in humans and mice demonstrated that NRs control a wide variety of metabolic processes by regulating the expression of genes encoding enzymes, transporters and other proteins involved in metabolic homeostasis [7,8]. Indeed, an important role of this family of proteins in metabolic disease is exemplified by NR ligands used in the clinic or under exploratory development for the treatment of diabetes mellitus, dyslipidemia or hypercholesterolemia [9]. In addition to their roles in metabolic processes, some NRs also regulate several innate and adaptive immune responses [10]. Thus, there is increasing interest in defining the specific transcriptional programs controlled by NRs in immune cells.

Nearly all members of the NR family present a conserved architecture divided in functional domains: an N-terminal region that frequently contains a ligand-independent activation function (AF-1), a DNA binding domain (DBD), a C-terminal ligand binding domain (LBD) that accommodates small lipophilic molecules and a ligand-dependent transcriptional activation function, AF-2 (1). NR members can be divided in three main subfamilies: The broadly characterized subfamily of steroid hormone receptors that mediate most of the biological actions of steroid hormones, shuttle between the cytoplasm and nucleus and bind DNA as homodimers, such as the first identified member the glucocorticoid receptor (GR)[11,12]. A second subfamily of structurally related receptors whose endogenous ligands are still not identified (or may not be even required for their activity) and are considered "orphan" receptors. A third set of NRs considered as "adopted" orphan receptors, that were identified prior to the discovery of their regulatory ligands and now have been deorphanized with the aid of chemical, structural and genomic technologies [13,14]. In many cases, the ligands have turned out to be intermediates or end products of metabolic pathways [15]. This subset of adopted NRs is constitutively nuclear and binds to DNA as obligate heterodimers with the retinoid X receptor (RXR). RXR heterodimers

☆ We thank A. Corbí, L. Boscá, J.L. Rodriguez-Fernandez and P. Tontonoz for fruitful discussions. We apologize that owing to space limitations many primary references could not be cited. Work in AC laboratory is supported by grants from the Spanish CSIC 200820I078, Ministry of I+D MICINN grants SAF2005-03270 and 2008-00057, Ramon y Cajal Program, BM05-228 from "La Caixa," 67/05 form FUNCIS and Ramon Areces Foundations.

☆☆ This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

* Corresponding author. Instituto de Investigaciones Biomédicas 'Alberto Sols,' Consejo Superior de Investigaciones Científicas-Universidad Autónoma de Madrid, Arturo Duperier 4, 28029 Madrid, Spain.
E-mail address: acastrillo@iib.uam.es (A. Castrillo).
[1] Present Address: Yale University School of Medicine, New Haven, CT 06520, USA.

0925-4439/$ – see front matter
doi:10.1016/j.bbadis.2010.12.015

typically bind to repeats of the hormone response element (HRE) AGGTCA in the regulatory regions of their target genes [14]. The spacing and orientation of the response elements dictates which heterodimer will bind to the site [14]. In the absence of ligand, they are believed to be bound to DNA and complexed with corepressor proteins, such as silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) and nuclear receptor corepressor (NCoR) [16,17]. Under these conditions, transcription of target genes is actively repressed. Ligand binding induces a structural change that displaces the corepressor, facilitates interaction with coactivators including the steroid receptor co-activator (SRC) family of proteins and promotes the transcription of target genes [18]. Among this set of receptors, the Peroxisome Proliferators Activated Receptors (PPARs) and liver X receptors (LXRs) have been extensively studied during the last decade [19–22]. Here we review the general features of LXR biology (along with parallel or prior work mainly from PPARs and GR), and also the work that has enhanced our understanding of LXR functions in macrophages with special attention to the crosstalk between inflammatory and metabolic pathways and recent developments that point to LXRs as important regulators of innate and adaptive immune responses.

2. General aspects of LXRs as transcription factors

The LXR nuclear receptors, LXRα (*NR1H3*) and LXRβ (*NR1H2*), are encoded in separate chromosomes and were both identified around 15 years ago. The LXRα isoform was discovered by two independent groups and named it RLD-1[23] and LXR [24] whereas other groups identified the LXRβ isoform and called it UR [25], NER [26], OR-1 [27], and RIP-15 [28]. LXRs bind to DNA as obligate heterodimers with RXRs and the LXR/RXR heterodimer activity can be regulated by ligands for either receptor [29]. In nearly all LXR target genes identified until now LXRα/RXR and LXRβ/RXR can interact with similar affinities to the response elements (LXRE) in their promoter regions containing the HRE motif AGGTCA separated by four nucleotides (DR-4) [24]. Various modified forms of cholesterol, including 22-(R), 24-(S) and 27-hydroxycholesterol and 24-(S), 25-epoxycholesterol can induce LXR transcriptional activity endogenously at physiological concentrations [30–32]. Recently, elevated concentrations of D-glucose and β-sitosterol were also reported to be activators of LXRs [33,34]. In addition, potent synthetic LXR ligands have been developed, including T0901317 and GW3965 [35,36]. These ligands that do not present LXR isoform selectivity have been widely used over the last decade to clarify the biological actions of LXRs.

LXRα and LXRβ share more than 75% sequence similarities in their DBD and LBD both in humans and rodents [37]. Despite these similarities, LXR tissue distribution differs significantly. While LXRβ is more ubiquitously expressed, LXRα expression predominates in metabolic tissues such as the liver, adipose tissue, intestine, kidney, and tissue macrophages [7]. However, the mechanisms that control the expression of both LXR isoforms are not completely understood. Whereas LXRβ seems to be constitutive in many cell types, expression of LXRα in macrophages is induced by synthetic PPARγ ligands [38] and also during some inflammatory situations, such as bacterial infections [39]. In human, but not in mouse cells, the expression of LXRα gene is auto regulated, suggesting that the biological actions of LXR activators may have more implications in these cells [40,41]. In addition, studies have shown that LXRα is phosphorylated on serine 198 in the hinge region [42,43], although the in vivo relevance of LXR phosphorylation is still unclear. Also, a recent study has demonstrated that LXRs are targets for O-linked beta-*N*-acetylglucosamine modification, a process that can have further implications in glucose-sensing mechanisms [44]. Together, these studies show that the expression of LXRα is not only species and tissue specific, but it is also likely to be regulated at several levels in response to certain metabolic and inflammatory signaling pathways.

3. LXRs as transcriptional regulators of cholesterol homeostasis

Over the past 10 years, considerable evidence indicates that LXRα and LXRβ are crucial regulators of cholesterol metabolism in mammals. The identification of the CYP7A1 gene (a member of the cytochrome P450 family that is crucial for bile acid synthesis) as a direct target for LXR in mice provided the first insight into the role of LXRs in cholesterol metabolism [45]. However, direct regulation of CYP7A1 expression by LXRs is not conserved in human cells. Subsequent studies in LXR-deficient mice and in cells treated with synthetic LXR ligands have revealed that LXRs play an important role in the pathway of reverse cholesterol transport, in which excess cholesterol is transported in high-density lipoprotein (HDL) particles from peripheral cells to the liver for excretion in bile [37,46]. The LXR effects on reverse cholesterol transport are likely dependent on the ability of LXRs to control the expression of various enzymes in different tissues. For example LXRs control the expression of ABCG5 and ABCG8 membrane transporters, which, in addition to the above mentioned CYP7A1, promote cholesterol elimination through the bile [47]. In the intestine, LXR-dependent induction of ABCG5 and ABCG8 results in decreased absorption of cholesterol by intestinal cells. Importantly, LXRs also regulate the expression of several genes involved in reverse cholesterol transport in peripheral cells such as macrophages [48]. In response to an elevation in intracellular cholesterol content, LXRs induce expression of the cholesterol efflux transporters ABCA1 [49–52] and ABCG1 [53], the apolipoproteins apoE and apoCs [54,55], and the lipoprotein remodeling enzyme PLTP [32,35].

Although the above mentioned studies focused on cholesterol metabolism, LXRs have also a significant role in the control of fatty acid metabolism. Mice carrying a targeted disruption in the LXRα gene are deficient in expression of SREBP-1c (sterol regulatory element binding protein) [56], FAS (fatty acid synthase) [57], SCD-1 (stearoyl CoA desaturase-1) [7], and ACC (acetyl CoA carboxylase) [45]. Administration of the synthetic LXR ligands to mice elevates plasma triglyceride levels in part through the induction of the hepatic lipogenic pathway. The master regulator of this lipogenic pathway SREBP-1c, as well as FAS and PLTP have been shown to be direct targets of LXR [35,56–58]. The LXR-dependent increase in hepatic triglycerides constitutes an obstacle for the development of LXR ligands as therapeutic agents. However, since LXRα is the dominant isoform expressed in the liver, where LXRβ is expressed poorly [7], it is thought that an LXRβ-selective agonist may retain efficacy without increasing hepatic lipogenesis [59]. Therefore, it is possible that the identification of LXRβ-selective agonists can have significant therapeutic value.

4. LXRs and macrophage gene expression

Macrophages are professional phagocytic cells that are present in virtually all tissues and that play crucial roles host defense [60]. They differentiate from circulating peripheral blood mononuclear cells, which migrate into tissues in the steady state or in response to inflammation [61,62]. In addition to their role as effector immune cells, macrophages also play important metabolic roles due to their exceptional phagocytic capacity and dynamic lipid metabolism [63,64]. Thus, it is important to highlight that macrophages, not only orchestrate inflammatory responses and host defense against pathogens but are also critical for the clearance of apoptotic cells and oxidized lipoproteins. These characteristics make the macrophage a prototypic effector cell that link innate immune responses with metabolism and tissue homeostasis. In this regard, the role of LXR in macrophage biology has special relevance in the context of atherosclerosis, now recognized to be a chronic inflammatory disease as well as a disorder of lipid metabolism [65]. The accumulation of large amounts of cholesterol under hypercholesterolemic conditions is a

critical step in the conversion of macrophages into foam cells during the early stages of atherogenesis [66]. To deal with this cumulative progression, LXRs reduce the cellular cholesterol levels by promoting cholesterol efflux via the upregulation of the ABC family transporters, resulting in increased reverse cholesterol transport. Ten years ago, independent studies demonstrated that ABCA1 is a direct target for regulation by LXRα and LXRβ [49–52]. ABCA1 expression and cholesterol efflux are induced in macrophages in response to oxLDL, oxysterols and synthetic LXR ligands and this regulation is lost in LXR-deficient macrophages. Importantly, the ability of LXRs to promote cholesterol efflux is not observed in cells obtained from Tangier disease patients (that lack functional ABCA1), demonstrating that ABCA1 is essential for LXR-mediated efflux [49]. The relevance of ABCA1 in atherosclerosis is highlighted by several studies in murine models, including a myeloid-specific ABCA1 deficiency that results in increased atherogenesis, while transgenic expression of the ABCA1 gene reduced lesion formation [67–69].

Lipid loading and LXR ligands also induced the expression of ABCG1 transporter in macrophages [53]. Regulation of ABCG1 expression could result in additional pathway for cholesterol efflux from macrophages or may act in concert with ABCA1. Characterization of ABCG1−/− mice revealed massive lipid accumulation in their lungs without affecting plasma lipid/lipoprotein levels [70]. Three independent studies revealed discordant results regarding the role of ABCG1 in murine models of atherosclerosis [71–73]. However, work with double mutant Abcg1−/−Abca1−/− mice demonstrated that loss of both sterol transporters resulted in increased lipid accumulation in macrophages than in ABCA1 and ABCG1 single knockout cells [74,75], demonstrating that both transporters are important for sterol homeostasis.

Additionally, macrophage LXRs contribute to the reverse cholesterol transport pathway by a mechanism that involves the induction of a subset of apolipoproteins capable of serving as acceptors for cholesterol and lipoprotein remodeling enzymes. LXR agonists induce the expression of ApoE in macrophages and adipose tissue but not in liver [54] and several studies have demonstrated the important role of apoE in macrophage cholesterol efflux. For example, mice over-expressing apoE specifically in macrophages show significantly reduced lesion formation, while deletion of apoE in the macrophage resulted in increased susceptibility to the disease [76]. Other studies have demonstrated that LXRs regulate the expression of ApoC cluster (ApocI, ApocII, and ApocIV) in macrophages [55] and it is likely that they participate to some extent in LXR-dependent reverse cholesterol transport. Other targets for LXR regulation in the macrophage are the lipoprotein lipase (LPL) and phospholipid transfer protein (PLTP) [58,77]. It is possible that expression of these enzymes in macrophages within the artery wall help to clear serum cholesterol-rich lipoproteins by facilitating the reverse cholesterol pathway [78,79]. Together, these studies suggest that LXRs regulate macrophage cholesterol efflux not only by inducing cholesterol transporter proteins (ABCA1 and ABCG1) but also through increased production of cholesterol acceptors (apoE and apoCs) and lipoprotein remodeling proteins (PLTP and LPL) [19].

In addition to the relevance of LXR function in cellular cholesterol efflux and ABC transporter expression, recent work has uncovered a novel mechanism by which LXR also modulates cellular cholesterol uptake in several cell types. In a series of elegant studies, Zelcer et al. demonstrated that LXR decreases cholesterol uptake by inducing the expression of a novel E3 ubiquitin ligase that they designated as "Idol" (inducible degrader of the LDL receptor). Expression of Idol in several cell types, including macrophages, induces the ubiquitination of the LDLR, resulting in its degradation by the proteosome pathway and subsequent reduction in LDL cholesterol binding and uptake [80]. Overexpression of Idol in vivo in mice decreases LDLR protein levels and significantly increases plasma cholesterol. Subsequent studies by the same authors demonstrated that Idol also targets two other members of the LDLR family, very low density lipoprotein receptor VLDL and apoER2, for degradation in a similar manner to that of LDLR [81]. This new mechanism that can control cholesterol levels through the LXR–Idol pathway may represent a novel therapeutic drug target in cardiovascular disease.

5. LXRs and atherosclerosis

The studies outlined above showed that LXR activity regulates the expression of genes involved in reverse cholesterol transport, bile acid metabolism, and intestinal cholesterol absorption. All these processes are considered anti-atherogenic. However, LXRs also promote fatty acid and triglyceride synthesis, which are considered independent risk factors for cardiovascular disease. During the last decade, these two apparent contrasting effects have stimulated independent efforts to elucidate the role of LXR activity in the context of hypercholesterolemia. However, the observation that LXRαβ−/− mice, even fed a regular diet, accumulate lipid loaded macrophages in several tissues over time [82,83] indicates that LXR-dependent pathways are crucial for normal cholesterol homeostasis. It is now clear from more than a dozen studies that the expression and activation of LXR is crucial to prevent atherogenesis (see a specific review by Calkin and Tontonoz) [84]. The initial demonstration that LXR activity inhibited the development of atherosclerosis in mice came from work by Joseph et al. [85] who showed that LXR agonist GW3965 was able to decrease lesion formation in both apoE−/− and LDLR−/− mice. Furthermore, GW3965 treatment increased expression of ABCA1 and ABCG1 in the aortas of these atherosclerotic mice, suggesting that direct actions of LXR ligands on vascular gene expression are likely to contribute to their anti-atherogenic effects. Subsequent studies also observed a reduction in lesion formation in murine models of atherosclerosis using other synthetic ligands, such as T0901317, DMHCA, WAY-252623 or ATI-829 ([86] and reviewed in ref. [84]). Interestingly, some of these studies demonstrated that LXR agonist treatment is able to modulate preexisting atherosclerotic lesions, resulting in remodeling and regression of these plaques. Other studies have investigated the influence of gain or loss of LXR function on atherosclerosis models by using transgenic/adenoviral or knockout strategies [82,83,87–89]. Two different studies demonstrated that global LXRα deficiency on either apoE−/− and LDLR−/− was associated with accelerated atherosclerosis, suggesting that LXRβ is not sufficient to compensate for the loss of LXRα under those hypercholesterolemic settings [89,90]. In one of them, Bradley et al. [90] also showed in the ApoE−/− model that LXRα deficiency was associated with massive cholesterol accumulation in peripheral tissues. Both studies showed decreased lesion formation without triglyceride accumulation by stimulating LXRβ activity with synthetic agonists in an LXRα-deficient background.

The physiological relevance of endogenous hematopoietic LXRs during atherogenesis was shown by Tangirala et al. [82]. Transplantation of bone marrow from LXRα,β−/− mice into apoE−/− and LDLR−/− mice resulted in a significant increase in lesion development [82]. Interestingly, the same authors found that isolation of LXR-deficient macrophages under those hypercholesterolemic conditions presented increased cholesterol accumulation. Another study by Teupser et al. [88] investigated the contribution of macrophage LXRα on the development of atherosclerosis. In this report, the authors found that overexpression of LXRα gene under the control of a macrophage-specific promoter in LDLR−/− mice resulted in a striking reduction in atherosclerosis lesion formation [88]. Another recent study by Moschetta and colleagues demonstrated that intestinal-specific LXR activation alleviates atherosclerosis by inducing the reverse cholesterol transport pathway without inducing hepatic steatosis [91]. These observations, together, indicate that the LXR pathway may be a tractable target for intervention in cardiovascular disease.

Work from several groups have demonstrated that macrophage endoplasmic reticulum (ER) stress in response to toxic lipids or inflammatory stimuli constitutes an additional mechanism involved in the atherogenic process (see recent review by Ira Tabas and references therein [92]). Regarding LXR and ER stress, a recent study by Erbay et al. [93] showed that inhibition of the fatty acid binding protein FABP4 (also called aP2) in macrophages decreases the ER stress and reduces atherosclerotic lesion formation in murine models. The authors proposed a mechanism by which FABP4 inhibition alleviates atherosclerosis through the induction of SCD-1 expression by LXRα in macrophages. Upregulation of LXRα/SCD-1 pathway in the context of FABP4 inhibition leads to increased conversion of saturated fats into monounsaturated lipids. Previous studies from the same group reported elevated PPARγ activity, increased expression of LXRα, enhanced cholesterol efflux and reduced inflammation in FABP4−/− macrophages [94,95]. The mechanism by which FABP4 represses LXRα expression and the contribution of other atheroprotective actions of LXR and/or PPAR signaling pathways in the context of FABP4 inhibition, however, is still unclear.

Together, these studies indicate that macrophage LXRs play an important role as anti-atherogenic factors through several mechanisms, including the induction of reverse cholesterol transport and by reducing the inflammatory environment (see below).

6. Macrophage activation pathways "at a glance"

As outlined above, macrophages are professional phagocytic cells that play crucial roles in host defense and also participate in the regulation of the inflammatory response and the maintenance of tissue homeostasis [60]. As sentinels of the immune system in multiple locations, macrophages present striking heterogeneity in their functions. Some of them are considered pro-inflammatory, such as the release of reactive toxic species or cytokine and chemokine production. These functions are crucial for efficient elimination of pathogens and communication with other components of the immune system. In contrast, macrophages also participate in the resolution of inflammation, wound healing and the maintenance of peripheral self tolerance through several different mechanisms. Thus, macrophages can display different specialized forms of activation (so called 'macrophage polarization') and plasticity in response to host homeostatic signals or external environmental challenges [61].

It is now clearly established that chronic inflammatory reactions triggered by tissue resident macrophages constitute a critical step in the development and perpetuation of many diseases. For example, atherosclerosis, type-2 diabetes and autoimmune disorders are chronic inflammatory diseases in which macrophages and other immune cells present aberrant regulation of metabolic and inflammatory pathways [22]. The incidence of these chronic disorders has increased dramatically in industrialized countries and a high percentage of these people present susceptibility to several combined chronic disorders such as metabolic syndrome and cancer. Therefore, there is substantial interest in understanding the molecular mechanisms that link metabolic processes with macrophage inflammatory responses. Indeed, alleviation of inflammation or inhibition of macrophage activation pathways leads to significant beneficial responses in obesity, insulin resistance and atherosclerosis [22,96].

The ability of macrophages to adopt different activation programs requires ways to classify them into distinct subtypes. One of these functional subsets is the classically activated macrophages (M1) that develop in response to interferon gamma (IFNγ) released by Th1 cells or microbial components (such as bacterial lipopolysaccharide, LPS) and produce several inflammatory cytokines, microbicidal species and favor antigen presentation and cellular immunity. M1 responses are therefore essential to combat intracellular infections such as *Mycobacterium tuberculosis* and HIV [61]. M1 macrophage responses, however, can also be injurious to normal cells and tissues if unchecked at the resolution of immune responses and contribute to the pathogenesis of several metabolic diseases, including atherosclerosis and obesity-induced insulin resistance [22].

A second subset of macrophage responses is displayed by the alternatively activated (M2) macrophages, whose maturation is controlled by IL-4 and IL-13 cytokines, and interfere with IFNγ-Th1 mediated responses [61]. In addition, M2 activated macrophages present increased expression of MHC-II, some sugar binding proteins (such as DC-SIGN, Mannose Receptor and Dectin-1), and enzymes and molecules involved in anti-inflammatory and anti-parasitic mechanisms (Arginase-1, Fizz1 and Ym1/2) [97]. Thus, the M2 macrophage phenotype is usually linked to Th-2 responses and is particularly relevant in cellular and humoral responses to parasitic and extracellular infections. Although the M1/M2 macrophage categories can be generally associated to their functional phenotypes observed during intracellular or extracellular microbial infections, there are distinct (or perhaps a mixture of both phenotypes) macrophage responses important in non-infectious pathologies. Some examples of "mixed" macrophage phenotypes are observed in chronic pathologies, such as foam cells in atherosclerosis, tumor-associated macrophages in cancer, adipose tissue macrophages during obesity/T2D or activated microglia in models of Parkinson's/Alzheimer's diseases (readers are referred to recent reports for a more specialized revision [22,98–100]).

Due to their remarkable heterogeneity, it is also evident that different resident tissue macrophages throughout the body should have distinct phenotypes under homeostatic conditions. For example, alveolar macrophages in the lung (the main sentinels in the airways) are continuously exposed to some airborne particles and perhaps present some constitutive activation but also have important lipid functions in collaboration with pneumocytes [101]. In contrast, microglia cells in the CNS are probably exposed to an anti-inflammatory environment as they are the main immune cells in the vulnerable nervous tissue and also due to their special location, as they are separated from the rest of the body through the blood–brain barrier [99]. Therefore, tissue macrophages can present features of M1/M2 polarization, but also some of them may need to adopt an inactivated or "deactivated" state under certain situations to prevent some unwanted actions of the specialized M1/M2 activation [61]. This macrophage deactivated phenotype, characterized by decreased antigen presentation and inhibition of inflammation is induced by immunosuppresive cytokines IL-10 and TGF-β and also by glucocorticoids. In addition, macrophages involved in the clearance of apoptotic cells present an immunosuppressive phenotype due to their active production of IL-10 and TGF-β and other anti-inflammatory mediators [102,103].

7. LXRs and other nuclear receptors in inflammation pathways

Several NRs, in addition to their roles in development and metabolism, can function as modulators of the innate and adaptive immune responses. Due to their clinical implications and their potent anti-inflammatory properties, the steroid glucocorticoid responses mediated by GR have been extensively investigated [10,104]. Numerous studies have also implicated PPARs and more recently LXRs in the modulation of macrophage inflammatory gene expression. Although the GR and PPAR mediated actions in macrophages will not be revised here (readers should visit recent reports by Glass and Saijo [10] and Chawla [105] for more details), some important concepts were identified by studying these receptors and will be briefly mentioned here.

As outlined above, some NRs, in addition to the positive regulation of transcription that is generally achieved by binding to their specific HREs, can also inhibit the transcriptional activity of other transcription factors which usually requires protein–protein interactions without direct DNA binding [10]. Interestingly, several repression mechanisms mediated by NRs can influence the activity of other

transcription factors involved in inflammation, such as NF-κB, AP1 and STAT. Many different mechanisms have been described in order to explain the NR-dependent repression of inflammatory gene expression and are usually referred as "transrepression." Since the early studies by the Evans and Karin laboratories that reported a mutual repression of GR and AP-1 activities [106,107], several different mechanisms of transpression have been described for GR [10,108], PPAR and LXR (see review by Glass and Saijo [10] and others in this series of BBA reviews). A novel transrepression mechanism was reported in 2005 by Pascual et al. [109] who demonstrated how ligand-activated PPARγ inhibits the expression of inducible nitric oxide synthase (iNOS) that was studied as a prototypic inflammatory gene that is sensitive to NR-dependent transrepression. This mechanism includes a ligand-dependent SUMOylation (through the SUMO E2 ligase, Ubc9 and the SUMO E3 ligase protein inhibitor of activated STAT1, PIAS1) of the PPARγ LBD that targets the receptor to correpresor complexes present in inflammatory promoters, thereby preventing the recruitment of the ubiquitin-conjugating enzyme (Ubch5) and the subsequent degradation machinery necessary for correpresor removal in response to pro-inflammatory challenges [109]. Under these circumstances, the NCoR complex remains bound to the promoter region and the expression of inflammatory genes is preserved as a repressed state [109].

Prior to these mechanistic studies, work by the Tontonoz laboratory in 2003 described an LXR-dependent repression of inflammatory gene expression in activated macrophages [110]. These studies indicated that, in addition to inducing genes involved in reverse cholesterol transport, LXRs inhibit a set of inflammatory genes after, LPS, TNF-α, or IL-1β stimulation [48,110,111]. Examples of such genes include those involved in generation of bioactive molecules such as iNOS and COX-2, cytokines IL-6 and IL-1β, the chemokines monocyte chemoattractant protein-1 (MCP-1) and MCP-3, and MMP-9. LXR ligands are able to repress the expression of those genes in macrophages derived from WT, LXRα−/−, and LXRβ−/− mice but are unable to do so in macrophages from LXRαβ−/− mice, indicating that both LXR isoforms can mediate the anti-inflammatory activity of the specific agonists [110]. Experiments in vivo confirmed the antiinflammatory effects of LXRs; for example LXRαβ−/− mice exhibit an exacerbated systemic inflammatory response when challenged intraperitoneally with bacterial LPS. Also, structurally unrelated LXR agonists reduce skin inflammation in a model of irritant contact dermatitis [110,112]. Around that time, the Feingold laboratory reported a similar result using the allergic dermatitis model in mice and also found that LXR ligands presented similar anti-inflammatory actions to those observed with a steroid-based drug [112]. More recent studies by Ghisletti et al. [113] described a parallel mechanism comparable to the one described for PPARγ-dependent transrepression by which LXRs inhibit the expression of inflammatory genes. In this case, ligand-activated LXRs preserve the integrity of the corepressor complexes at the inflammatory promoters by interacting with HDAC4 E3 ligase and SUMO2/3 to prevent inflammatory signal-dependent activation [113]. This NCoR-dependent transrepression mechanism has also been shown to be involved in the inhibition of C-reactive protein expression in hepatocytes [114]. Other studies demonstrated that SUMOylation of LXRs is required for the suppression of STAT1-dependent inflammatory responses induced by in IFNγ [115]. Moreover, a recent report demonstrated that the ability of LXRs to prevent NCoR turnover and suppress the acute phase response in the liver requires the G protein pathway suppressor 2 (GPs2) for the docking of SUMOylated LXR within the target promoters [116]. Thus, ligand-dependent SUMOylation of PPARs and LXRs plays a relevant role antagonizing several inflammatory situations. However, an integrative mechanism that explains how the cellular pool of liganded receptor/s can promote transactivation (through NCoR/SMRT clearance) and transrepression (through SUMO-NCoR retention) in the same cell at the same time remains to be elucidated.

Transcriptional profiling studies by Ogawa et al. demonstrated that GR, PPAR and LXR ligands are able to inhibit the expression of a significant proportion of genes induced by LPS/TLR4 signaling in macrophages [117]. Interestingly, some groups of genes were transcriptionally repressed by all three receptors, although the complete list of transrepression signature of each individual receptor is only partially overlapping suggesting that GR, PPAR and LXR are likely using distinct coregulators for their repressive functions. Moreover, detailed analysis of the promoter regions of the repressed genes demonstrated that many of them present regulatory regions containing NFκB, AP-1 and ISRE consensus binding sites but not HREs, indicating that the anti-inflammatory properties of these receptors are, to a large extent, mediated through transrepression mechanisms [117]. However, the potential for these nuclear receptors to directly upregulate the expression of anti-inflammatory molecules through transactivation mechanisms under physiological or pathological circumstances has only been partially explored. For example, studies by the Karin and Baldwin laboratories reported that glucocorticoids induce the expression of IκBα, thereby preventing the binding of NFκB to its target promoters as a plausible mechanism for the anti-inflammatory action of glucocorticoids in certain cells [118,119]. Other studies have proposed a role for PPARγ as a regulator of macrophage M1/M2 transition. First, Glass and colleagues described the induction of PPARγ expression by the Th2 cytokine IL-4, which also stimulates cellular generation of natural PPARγ ligands through the 12/15-lipoxygenase pathway [120]. More recently, contributions from several laboratories showed that PPARγ and PPARδ are important players in the polarization of macrophages with anti-inflammatory properties by inducing alternative M2-dependent genes (such as arginase I and others) and through collaboration with other transcription factors (such as STAT6) important for M2 polarization [121–128].

Despite their important role in the reverse cholesterol pathway and their inhibitory effects on inflammatory gene expression, the contribution of LXRs in macrophage polarization in the context of obesity and insulin resistance appear to be less prevalent [129]. However, LXRs also participate in the regulation of glucose metabolism in the liver and adipose tissue and LXR agonists showed a significant effect as insulin-sensitizing factors in murine models of diet-induced obesity [130,131].

LXRs have also been shown to positively regulate the expression of the anti-inflammatory enzyme arginase II in macrophages [132]. Both arginase I and arginase II enzymes participate in the final steps of the urea cycle and catalyze the conversion of L-arginine to L-ornithine. Arginase activity in macrophages contributes to the metabolization of nitrogen into polyamines, a process that is important for cellular proliferation and wound healing. In addition, arginase expression contributes to substrate competition with other arginine-dependent enzymes, such as iNOS, and has thus the potential to exert anti-inflammatory effects by the inhibition of nitric oxide production. Interestingly, stable expression of arginase II in macrophages leads to decreased nitric oxide (NO) production but not iNOS expression after engagement of TLR signaling [132]. Even though arginase activity may function to prevent excessive NO production and promote wound healing, iNOS activity is a crucial cytotoxic mechanism to control pathogen growth and deficient NO production could in turn compromise anti-microbial responses. Consistent with this idea, inhibition of arginase activity in macrophages (either pharmacologically or genetically) favors host immune responses against infections with *Leishmania major, Mycobacterium tuberculosis or Toxoplasma gondii* [133,134]. Conversely, induction of arginase I expression by PPARγ/δ agonists (as well as other markers of M2 polarization) promotes the growth of *L. major* in macrophages [127], whereas macrophage-specific PPARγ−/− mice are less susceptible to infection by *L. major* in vivo [122].

8. LXRs in innate and adaptive immune responses

As summarized above, LXRs inhibit the LPS or cytokine-induced expression of inflammatory genes in macrophages [110,111,113,117,135], suggesting that pharmacological strategies that promote LXR activity may be useful to reduce the deleterious effects of inflammatory diseases. In the last several years, many research groups have studied the role of LXRs in different mouse models of inflammatory disease. In models of diet-induced atherogenic inflammation, such as ApoE−/− and LDLR−/− mice, administration of LXR ligands reduced the aortic expression of inflammatory genes, such as of MMP-9 and tissue factor while inducing expression of the cholesterol transporters ABCA1 and ABCG1 [110,136].

The biological functions of LXRs are important to maintain homeostasis in the CNS by controlling lipid metabolism and many of these aspects have been extensively investigated by the Gustafsson group [137–139]. Recent studies have also explored a potential impact of LXRs in the brain with special focus on some inflammatory conditions in models of Alzheimer's disease [140,141], experimental autoimmune encephalitis (EAE)[142] or ischemic stroke [141,143–146]. Interestingly, these studies demonstrated, by either synthetic LXR ligand administration or receptor deletion, that LXRs play an important role in controlling inflammatory signaling in vivo in the brain.

LXRs also present some therapeutic value in the context of skin inflammation. As mentioned before, LXR ligands effectively limit the inflammatory response in models of allergic dermatitis [110,112]. In addition, modulation of LXR activity alleviates the damage in the skin caused by photoaging and also modulates inflammatory gene expression in keratinocytes derived from skin biopsies of human psoriatic lesions [147,148]. Other recent reports demonstrated the potential for LXRs to reduce inflammation and tissue damage in the lung [149,150].

The connection between inflammatory pathways and LXR signaling may have an impact in anti-microbial responses in normal physiology, because as mentioned above, profound reduction of inflammatory gene expression in macrophages may compromise host defense against pathogens. Surprisingly, as first reported by Joseph et al. in 2004 [39], loss of LXR function leads to ineffective innate immune responses. Mice lacking LXRs are more susceptible to infection with the Gram-positive intracellular pathogen *Listeria monocytogenes* (LM). Susceptibility to infection was recapitulated by transplantation of bone marrow from LXR-deficient mice into WT mice, suggesting that LXR function in hematopoietic cells is required for a correct immune response against LM [39]. The celerity of the disease observed in LXR-deficient mice is consistent with a defect in innate immunity and correlated with accelerated rates of macrophage apoptosis, indicating that altered macrophage function in response to infection was a major contributor to the observed susceptibility. Interestingly, macrophage survival has been also suggested as an important mechanism that contributes to mount an appropriate response to LM infection [151,152]. Surprisingly, LXRα−/− were found to be particularly sensitive to LM infection and macrophage apoptosis. The survival of macrophages in response to infection is sustained, at least in part, by LXRα-dependent expression of the anti-apoptotic gene AIM/Spα [153]. Moreover, stable expression of either AIM or LXRα in macrophages promotes both macrophage survival and anti-microbial mechanisms during LM infection [39]. At the same time, Valledor et al. [154] independently found that LXR signaling also inhibits macrophage apoptosis in response to cytokine withdrawal, toxic drugs or infection with the bacteria *Bacillus anthracis, Escherichia coli* or *Salmonella typhimurium.* They found that LXR activity was important for the induction of anti-apoptotic genes, including AIM, Bcl-xL and Birc1a and the inhibition of a other pro-apoptotic genes in response to inflammatory stimuli [154]. In addition to being induced in the setting of bacterial infection, AIM expression was also found to be upregulated during macrophage cholesterol loading in an LXR-dependent manner [155]. The ability of the LXR pathway to enhance macrophage survival in the context of infection and lipid overload (in part through the induction of AIM and other anti-apoptotic genes) also highlights that common pathways are utilized for both metabolic and immune control. Recently, Korf et al. demonstrated that mice lacking LXRα were also more susceptible to infection with *Mycobacterium tuberculosis*, likely through dysregulation of Th1/Th17 function in the lungs upon bacterial infection [156].

An additional connection between lipid metabolism and immunity in macrophages via the LXR pathway was demonstrated in other studies by the Tontonoz laboratory [157], where they demonstrated that infections with bacterial pathogens, such as *E. coli* or the RNA virus influenza A inhibit the function of LXRs in cholesterol homeostasis. Expression of ABCA1, ABCG1, apoE and the efflux of cholesterol to extracellular acceptors was significantly inhibited in bacterial or viral infected macrophages. These effects can be mimicked by activation of members of the Toll-like receptor (TLR) family, specifically TLR3, which recognizes double-stranded RNA generated during viral infections or TLR4, the LPS receptor. In addition, the use of macrophages deficient in various components of the TLR signaling pathway demonstrated that TLR3/4-dependent inhibition of cholesterol efflux was mediated by the transcription factor IRF3 and is independent of MyD88 and NFκB [157]. Interference with LXR-dependent cholesterol metabolism by infections might aggravate the process of foam cell accumulation during atherogenesis and exacerbate atherosclerotic lesions formation. This idea has been investigated in recent studies demonstrating that LXRs can also modulate the TLR-dependent foam cell formation in *Chlamydia pneumoniae* infected macrophages [158–160]. Moreover, *Chlamydia pneumoniae*-induced atherosclerosis in the ApoE−/− model was significantly accelerated in the absence of LXRα that presented increased serum inflammation and accumulation of lipids and myeloid cells in the aortas of these animals [159].

In addition to the importance of LXRs in macrophages, recent studies have focused their research in the biology of LXRs in other cells of the immune system, such as dendritic cells and lymphocytes [20,161–165]. One of the key recent findings was reported by Bensinger et al. [164], who demonstrated an unexpected link between sterol metabolism, LXR, and adaptive immune responses. They showed that T cell activation by mitogens correlates with the downregulation of LXR cholesterol efflux target genes and the simultaneous induction of the SREBP-2 pathway for cholesterol synthesis. In addition, signals that promote lymphocyte expansion also induce the expression of oxysterol sulfotransferase (SULT2B1), an enzyme that catalyzes the transfer of sulfate groups to oxysterols, inactivating them as LXR ligands. These important characteristics found in lymphocytes improve the uptake and de novo synthesis of cholesterol for membrane formation and allow lymphocytes to undergo rapid proliferation in response to antigens. Activation of LXRs with synthetic agonists inhibits T cell proliferation by promoting cholesterol efflux and thus limiting cellular sterol content. Conversely, increased proliferation was observed in LXR-deficient lymphocytes, resulting in enhanced homeostatic and antigen-driven responses. Interestingly, LXR agonists did not inhibit lymphocyte expansion in cells obtained from LXRβ-deficient mice (which is the main LXR isoform expressed in lymphocytes). The authors also found that the effects of LXR activation in T cell proliferation were significantly reduced in cells lacking ABCG1 [164]. These results indicate that during the T cell activation process the LXR-dependent cholesterol transport must be downregulated by limiting the cellular content of active oxysterols (through SULT2B1), and through the inhibition of ABCG1 expression. The ability of LXR cholesterol metabolic pathways to modulate lymphocyte expansion reported by Bensinger et al. [164] indicate that cellular sterol metabolism is a novel signaling pathway regulating T cell function and acquired immune responses.

9. LXRs and apoptotic cell clearance

As outlined above, tissue macrophages also play a key role in the clearance of apoptotic cells. In multicellular organisms billions of apoptotic cells are generated every day that culminate in recognition and ingestion by phagocytes [166]. The uptake/engulfment of apoptotic cells (also known as "efferocytosis" taken from the Latin "effero," meaning to take the corpse to the grave [167]) is a complex process that occurs through a series of controlled events. Apoptotic cells generate "find me" signals, such as lipids or recently identified nucleotides ATP/UTP, to recruit macrophages and other phagocytes at sites of cell death [168–170]. When macrophages reach the dying cells, they recognize "eat me" signals exposed on the surface of the apoptotic cells. These elements displayed on the outside of the dying cell are usually lipid or carbohydrate changes, such as phosphatidylserine (PtdSer), a membrane lipid normally restricted to the inner leaflet of the plasma membrane [166]. Recognition of PtdSer is mediated either directly through PtdSer receptors, including Bai1 and Tim-4, or through bridging molecules including MFGE8, GAS6, ProS or C1q that bind PtdSer on the outside of the dying cell and phagocyte receptors such as TAM family (Tyro3, Axl, and Mer) and $\alpha v\beta_3$-integrin (see recent review and references by Ravichandran [171]). Efficient disposal of apoptotic cells prevents the loss of cellular integrity, uncontrolled release of intracellular contents and secondary necrosis. In addition, macrophages ingesting apoptotic cells activate tolerogenic pathways in an effort to prevent immune responses against intracellular antigens. Immunosuppression is mediated through the inhibition of M1 classic activation and the release of anti-inflammatory molecules such as IL-10 and TGFβ [102,103]. If the engulfment process or tolerogenic pathways are impaired, chronic accumulation of immunogenic targets can have pathological consequences, including several autoimmune disorders, such as systemic lupus erythematosus (SLE) (see recent review [172]). Given the important role of several NRs in lipid metabolism and inflammatory pathways and that engulfment of dying cells significantly increases the amount of intracellular lipids, we and others have recently studied the role of LXRs and PPARs during the clearance of apoptotic cells by macrophages.

Gonzalez et al. [173] demonstrated that engulfment of apoptotic thymocytes (ATs) in vitro, but not bacteria or inert beads, is severely compromised in LXR-deficient macrophages. Phagocytosis of apoptotic cells by macrophages is significantly enhanced by the treatment with an LXR agonist. These LXR-dependent pathways are also active in vivo, as demonstrated by three complementary approaches. First, LXR-null resident macrophages presented less engulfment capacity than WT controls upon an intraperitoneal challenge of ATs. Second, forced apoptosis of cortical thymocytes of mice injected with dexamethasone (WT and LXR-deficient thymocytes present comparable sensitivity to apoptosis) resulted in accumulation of large amounts of unengulfed ATs in LXR-deficient thymi, indicating that loss of LXR function results in defective clearance of an acute burden of apoptotic cells. Third, loss of LXR function for apoptotic cell clearance leads to defective disposal of unwanted cells in vivo and impaired tissue homeostasis as many free apoptotic cells are visualized in LXR-deficient mice, including spleen, thymus, lung and testis [173]. Transcriptional profiling and in vitro expression assays identified the apoptotic cell receptor Mer (that belongs to the Tyro3, Axl, and Mer (TAM) receptor tyrosine kinase family; see recent review by Lemke [174]) as a novel LXR target gene. These TAM receptors and their ligands Gas6 and Protein S are required for the optimal phagocytosis of apoptotic cells in the mature immune, nervous, and reproductive systems [174]. In our studies in mouse macrophages, the expression of Axl, Tyro3, their ligands GAS6/ProS, and other bridging molecules such as MFGE8 was not altered by LXR ligands. In contrast, expression of Mer was induced in macrophages and in vivo in several tissues in response to LXR agonists, and reduction of Mer expression resulted in reduced phagocytosis induced by LXR ligand, indicating that LXR signaling promotes the clearance of apoptotic cells, at least in part, through induction of Mer expression. A recent report has also investigated the role of LXRs in the context of apoptotic cell clearance by human peripheral blood monocyte derived macrophages in vitro. In this study, Rébé et al. [175] found that LXR activation induces the expression of retinoid acid receptor α (RARα) by direct binding and transactivation of the RARα promoter in human macrophages. Combination of specific ligands for LXR and RAR synergistically induces the expression of tissue transglutaminase (TGM2), a known retinoid-regulated gene [176,177] and an important factor involved in phagocytosis [178]. Consistent with these changes in gene expression, human macrophages cultured with LXR ligand, RAR ligand, or combination of both stimulated the ability of these macrophages to engulf apoptotic cells. This study suggests that activation of LXRs in human macrophages can further promote RARα-dependent gene expression (including TGM2) that can additionally contribute to the clearance of apoptotic cells [175].

Ingestion of apoptotic cells is coupled to the suppression of inflammation and leads to increased cholesterol content inside the macrophages. Previous work demonstrated that ABCA1 is important for efficient phagocytosis of apoptotic cells [179]. Also, macrophages engulfing apoptotic cells promote the expression of ABCA1 [180–182], thereby promoting cholesterol efflux and compensating the levels of intracellular lipids. We found that the expression of Mer and many other known LXR targets involved in lipid metabolism were upregulated by apoptotic cells in WT, but not in LXR-deficient macrophages, suggesting that LXR regulates the expression of a specific subset of genes that accelerate corpse removal and maintain lipid metabolism in response to apoptotic cell uptake [173]. We also found that LXR is involved in the macrophage deactivation process induced by apoptotic cells, as inhibition of inflammatory cytokine production by macrophages engulfing apoptotic cells is severely impaired in LXR-null cells. Moreover, we observed that intact LXR function is required for correct transactivation of anti-inflammatory cytokines such as TGF-β and IL-10 in response to apoptotic cells. These clearance and immunosuppressive defects might cause the initiation and maintenance of systemic autoimmune reactions and chronic inflammation in LXR-deficient mice. This idea is also supported by several mouse models in which defective apoptotic cell clearance leads to an autoimmune phenotype, including mice lacking Mer, MFGE8, C1q, Tim-4 or $\alpha_v\beta_{3/5}$ [183–187]. Also, some groups of patients with systemic lupus erythematosus (SLE) present both in vitro and in vivo deficiencies in their ability to clear apoptotic cells [172]. We observed that LXR-null mice show age-dependent splenomegaly, lymphadenopathy and elevated levels of antibodies to nuclear proteins (ANA antinuclear antibodies), double-stranded DNA (dsDNA), and histones were detected in their serum. Moreover, LXRαβ−/− mice presented infiltration of immune cells and deposition of IgG-containing immune complexes in several tissues including skin, lung and kidney that contribute to compromised renal functions [173]. These results are consistent with the development of age-dependent, systemic autoimmune disease due to autoantibody production and chronic inflammation. We have also shown that pharmacological activation of LXR might have therapeutical effects against autoimmunity. Chronic administration of the synthetic LXR agonist GW3965 to $B6^{lpr/lpr}$ (a mild model of lupus-like disease) ameliorated the progression of autoimmune disease in these mice [173]. Together, our contributions demonstrate that LXRs participate in transcriptional responses crucial to maintain tissue homeostasis in response to apoptotic cells. Engulfment of apoptotic cells activates LXRs, likely through the accumulation of sterol-derived ligands for LXRs, and facilitates effective clearance by a feed-forward mechanism through the induction of Mer. Also, LXRs participate in the immunosuppression actions of apoptotic cells by inhibiting the production of pro-inflammatory mediators and are crucial for the maintenance of immune tolerance.

In addition to these investigations with LXRs, recent studies have also implicated other NRs in the phagocytosis of apoptotic cells. An interesting study was recently reported by Chawla and colleagues [188] that found a parallel pathway triggered by apoptotic cells through the activation of PPARδ signaling in macrophages that is important for apoptotic cell clearance and immune tolerance. Remarkably, global or macrophage-specific PPARδ-null mice developed spontaneous autoimmunity. They showed that PPARδ regulates expression of various bridging molecules, such as complement 1qb (C1qb) and MFGE8 [188]. Defective expression of these opsonins in other mouse models contribute to systemic autoimmune disease and some aberrant forms of these proteins in humans are found in patients with SLE [185,189].

Using pharmacological tools and in vitro assays, several reports have previously suggested a possible involvement of PPARγ during the clearance of apoptotic cells in macrophages and dendritic cells [190–193], although the in vivo relevance of these observations remains to be established. Other studies have also demonstrated that glucocorticoid-treated macrophages have increased capacity to engulf apoptotic cells [194,195]. Recent work has additionally demonstrated that these effects are likely due to GR-dependent transactivation of MFGE8, C1qa, ProS and Mer [196,197].

10. Conclusions

Over the past several years, significant progress has been made to increase our understanding of LXR functions in physiology and disease. It is clear that regulation of cellular and systemic cholesterol levels, with special relevance in the reverse cholesterol transport pathway, is the prominent function of LXRs. The recently identified LXR–Idol pathway that can modulate circulating LDL cholesterol levels reinforces the idea of LXRs as whole body cholesterol sensors.

In macrophages, LXRs not only play a crucial role in the modulation of lipid metabolism but also display important functions in inflammation and host defense. A significant portion of the anti-inflammatory effects of LXRs are likely accomplished through transrepression mechanisms and a similar scenario may also be applied for PPARs and GR specific functions during inflammation. Some aspects of this dual role of LXRs and other NRs as regulators of both activation and repression raise new questions and deserve further investigation. Given that correpresor clearance or retention is crucial for ligand-dependent transactivation or transrepression, respectively, what are the specific signals that coexist in the same cell and guide a liganded nuclear receptor to a positively or a negatively regulated gene? Are there other post-translational modifications (in addition to SUMOylation) important to discriminate between transactivation or transrepression? Are there other coregulator partners being recruited to the transrepressive or transactivating promoters in response to specific challenges in vivo? Are these molecular mechanisms fully operative in human monocytes, macrophages or dendritic cells? These and other questions may be relevant to design new ligands that could dissociate between transactivation of lipid metabolic genes and transrepression of inflammatory genes. New developments related to PPARγ changes in specific phosphorylation sites in response to ligand that can dissociate between its adipogenic and antidiabetic capacities [198] indicate that additional

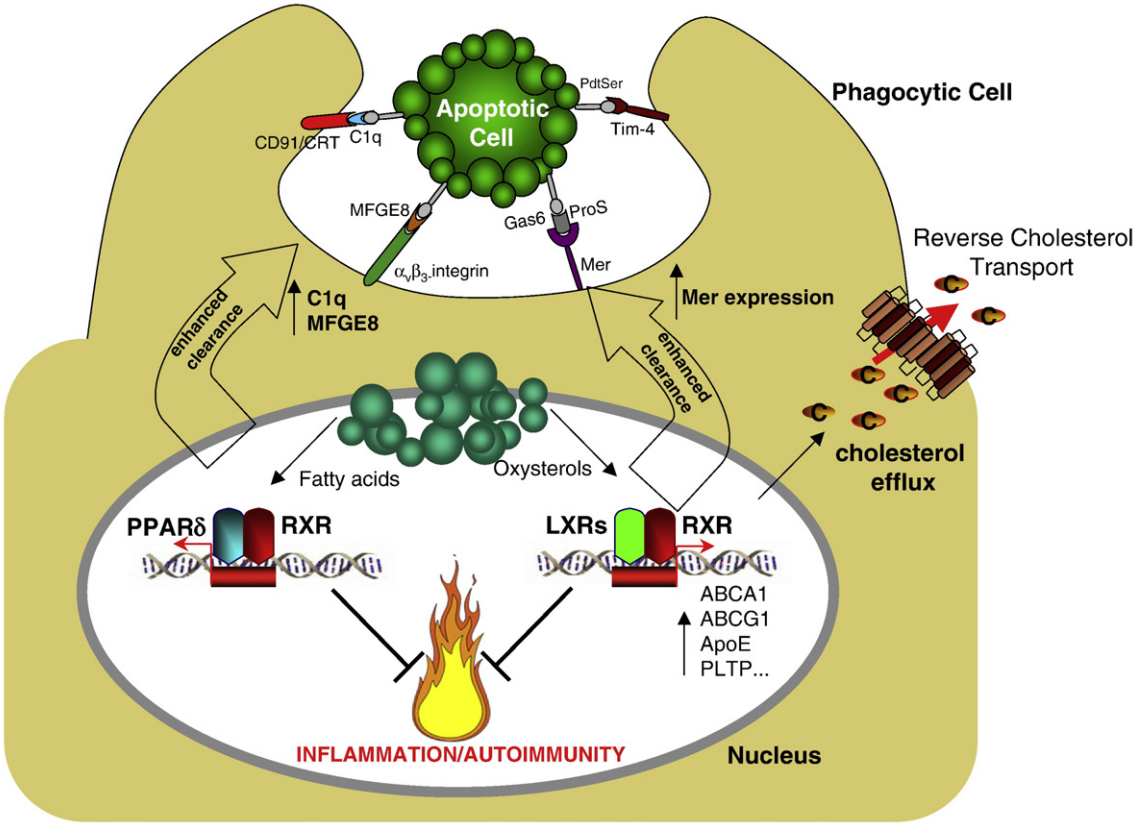

Fig. 1. Nuclear receptors LXRs and PPARδ contribute to efficient engulfment of apoptotic cells by macrophages. Phagocytes express membrane receptors that recognize "eat me" signals displayed on the surface of apoptotic cells. Bridging molecules also contribute to the binding and engulfment of the dying cell. Intracellular processing of apoptotic cells releases native or oxidized sterols and fatty acids derivatives that are capable of transactivating LXRs and PPARδ, respectively. Activation of LXRs promotes the expression of the tyrosine kinase receptor, Mer, thereby promoting further clearance of apoptotic cells. Ingestion of apoptotic cells also enhance the expression of genes involved in cholesterol efflux in an LXR-dependent manner. Activation of PPAR-δ, on the other hand, induces the production of opsonins C1q and MFGE-8 that help the coating of apoptotic cells and their recognition by surface receptors. Both nuclear receptor signaling cascades also lead to a potent immunosuppressive action on the macrophage, contributing to avoid an immune response to self-antigens and inflammation.

molecular explanations for LXRs are also plausible. It has also been shown by Medzhitov and colleagues [199] that GR activation inhibits the expression of many pro-inflammatory genes in recurrent LPS challenges (a model of endotoxin tolerance) in macrophages, whereas numerous anti-microbial genes important to clear infections remain unchanged or even exhibit upregulated expression in dexamethasone treated macrophages. Since many anti-microbial and anti-inflammatory genes are regulated by common transcription factors, their results suggest that additional co-factors/modifications are responsible for this selective repression [199].

We propose an additional point of view to integrate some of our recent advances. As outlined above, both LXRs and PPARs induce the expression of specific targets in macrophages that may predispose these cells to exhibit a more anti-inflammatory, tissue repair phenotype. For example, regulation of the arginase family of enzymes by PPARγ/δ and LXRs may have implications in macrophage transcriptional programs by reducing their inflammatory status. In addition, efficient disposal of dying cells triggers potent immunosuppressive signals such as IL-10 and TGF-β cytokines, and both LXRs and PPARδ regulate this apoptotic clearance process in vivo by inducing the expression of phagocytic receptor Mer and bridging molecules C1qb and MFGE8 (see Fig. 1). It is likely that GR (through the induction of ProS) and perhaps other NRs such as RARα or PPARγ may also be involved in these responses in vivo as well. Defects in apoptotic cell clearance observed in LXR and PPARδ null mice lead to age-dependent systemic autoimmune disease, a phenotype also observed in Mer, MFGE8 and C1q-deficient mice. In addition, Mer signaling is directly linked to pleiotropic anti-inflammatory properties by antagonizing TLR signaling in macrophages and dendritic cells [174]. Therefore, activation of LXRs during the normal disposal of apoptotic cells in vivo by tissue resident macrophages promotes further clearance and anti-inflammatory gene expression. Together, some of our recent results indicate that LXR signaling couples the engulfment of apoptotic cells to the suppression of inflammatory pathways and further illustrate that the activation and transrepression functions of LXRs are both important for normal immune homeostasis. Future work along these lines will continue to define the roles of LXRs in immunity and metabolism.

References

[1] P. Chambon, How I became one of the fathers of a superfamily, Nat. Med. 10 (2004) 1027–1031.
[2] R. Evans, A transcriptional basis for physiology, Nat. Med. 10 (2004) 1022–1026.
[3] E.V. Jensen, From chemical warfare to breast cancer management, Nat. Med. 10 (2004) 1018–1021.
[4] A. Chawla, J.J. Repa, R.M. Evans, D.J. Mangelsdorf, Nuclear receptors and lipid physiology: opening the X-files, Science 294 (2001) 1866–1870.
[5] S.A. Kliewer, J.M. Lehmann, T.M. Willson, Orphan nuclear receptors: shifting endocrinology into reverse, Science 284 (1999) 757–760.
[6] T.M. Willson, J.T. Moore, Genomics versus orphan nuclear receptors–a half-time report, Mol. Endocrinol. 16 (2002) 1135–1144.
[7] J.J. Repa, D.J. Mangelsdorf, The role of orphan nuclear receptors in the regulation of cholesterol homeostasis, Annu. Rev. Cell Dev. Biol. 16 (2000) 459–481.
[8] D.J. Mangelsdorf, C. Thummel, M. Beato, P. Herrlich, G. Schutz, K. Umesono, B. Blumberg, P. Kastner, M. Mark, P. Chambon, et al., The nuclear receptor superfamily: the second decade, Cell 83 (1995) 835–839.
[9] R.M. Evans, G.D. Barish, Y.X. Wang, PPARs and the complex journey to obesity, Nat. Med. 10 (2004) 355–361.
[10] C.K. Glass, K. Saijo, Nuclear receptor transrepression pathways that regulate inflammation in macrophages and T cells, Nat. Rev. Immunol. 10 (2010) 365–376.
[11] C. Weinberger, S.M. Hollenberg, E.S. Ong, J.M. Harmon, S.T. Brower, J. Cidlowski, E.B. Thompson, M.G. Rosenfeld, R.M. Evans, Identification of human glucocorticoid receptor complementary DNA clones by epitope selection, Science 228 (1985) 740–742.
[12] M.V. Govindan, M. Devic, S. Green, H. Gronemeyer, P. Chambon, Cloning of the human glucocorticoid receptor cDNA, Nucleic Acids Res. 13 (1985) 8293–8304.
[13] T.M. Willson, S.A. Jones, J.T. Moore, S.A. Kliewer, Chemical genomics: functional analysis of orphan nuclear receptors in the regulation of bile acid metabolism, Med. Res. Rev. 21 (2001) 513–522.
[14] D.J. Mangelsdorf, R.M. Evans, The RXR heterodimers and orphan receptors, Cell 83 (1995) 841–850.
[15] B. Blumberg, R.M. Evans, Orphan nuclear receptors—new ligands and new possibilities, Genes Dev. 12 (1998) 3149–3155.
[16] M.G. Rosenfeld, V.V. Lunyak, C.K. Glass, Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response, Genes Dev. 20 (2006) 1405–1428.
[17] V. Perissi, K. Jepsen, C.K. Glass, M.G. Rosenfeld, Deconstructing repression: evolving models of co-repressor action, Nat. Rev. Genet. 11 (2010) 109–123.
[18] B.W. O'Malley, J. Qin, R.B. Lanz, Cracking the coregulator codes, Curr. Opin. Cell Biol. 20 (2008) 310–315.
[19] S.W. Beaven, P. Tontonoz, Nuclear receptors in lipid metabolism: targeting the heart of dyslipidemia, Annu. Rev. Med. 57 (2006) 313–329.
[20] S.J. Bensinger, P. Tontonoz, Integration of metabolism and inflammation by lipid-activated nuclear receptors, Nature 454 (2008) 470–477.
[21] W. Huang, C.K. Glass, Nuclear receptors and inflammation control: molecular mechanisms and pathophysiological relevance, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 1542–1549.
[22] J.M. Olefsky, C.K. Glass, Macrophages, inflammation, and insulin resistance, Annu. Rev. Physiol. 72 (2010) 219–246.
[23] R. Apfel, D. Benbrook, E. Lernhardt, M.A. Ortiz, G. Salbert, M. Pfahl, A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily, Mol. Cell. Biol. 14 (1994) 7025–7035.
[24] P.J. Willy, K. Umesono, E.S. Ong, R.M. Evans, R.A. Heyman, D.J. Mangelsdorf, LXR, a nuclear receptor that defines a distinct retinoid response pathway, Genes Dev. 9 (1995) 1033–1045.
[25] C. Song, J.M. Kokontis, R.A. Hiipakka, S. Liao, Ubiquitous receptor: a receptor that modulates gene activation by retinoic acid and thyroid hormone receptors, Proc. Natl Acad. Sci. USA 91 (1994) 10809–10813.
[26] D.M. Shinar, N. Endo, S.J. Rutledge, R. Vogel, G.A. Rodan, A. Schmidt, NER, a new member of the gene family encoding the human steroid hormone nuclear receptor, Gene 147 (1994) 273–276.
[27] M. Teboul, E. Enmark, Q. Li, A.C. Wikstrom, M. Pelto-Huikko, J.A. Gustafsson, OR-1, a member of the nuclear receptor superfamily that interacts with the 9-cis-retinoic acid receptor, Proc. Natl Acad. Sci. USA 92 (1995) 2096–2100.
[28] W. Seol, H.S. Choi, D.D. Moore, Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors, Mol. Endocrinol. 9 (1995) 72–85.
[29] P.J. Willy, D.J. Mangelsdorf, Unique requirements for retinoid-dependent transcriptional activation by the orphan receptor LXR, Genes Dev. 11 (1997) 289–298.
[30] B.A. Janowski, P.J. Willy, T.R. Devi, J.R. Falck, D.J. Mangelsdorf, An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha, Nature 383 (1996) 728–731.
[31] B.M. Forman, B. Ruan, J. Chen, G.J. Schroepfer Jr., R.M. Evans, The orphan nuclear receptor LXRalpha is positively and negatively regulated by distinct products of mevalonate metabolism, Proc. Natl Acad. Sci. USA 94 (1997) 10588–10593.
[32] J.M. Lehmann, S.A. Kliewer, L.B. Moore, T.A. Smith-Oliver, B.B. Oliver, J.L. Su, S.S. Sundseth, D.A. Winegar, D.E. Blanchard, T.A. Spencer, T.M. Willson, Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway, J. Biol. Chem. 272 (1997) 3137–3140.
[33] N. Mitro, P.A. Mak, L. Vargas, C. Godio, E. Hampton, V. Molteni, A. Kreusch, E. Saez, The nuclear receptor LXR is a glucose sensor, Nature 445 (2007) 219–223.
[34] J. Plat, J.A. Nichols, R.P. Mensink, Plant sterols and stanols: effects on mixed micellar composition and LXR (target gene) activation, J. Lipid Res. 46 (2005) 2468–2476.
[35] J.R. Schultz, H. Tu, A. Luk, J.J. Repa, J.C. Medina, L. Li, S. Schwendner, S. Wang, M. Thoolen, D.J. Mangelsdorf, K.D. Lustig, B. Shan, Role of LXRs in control of lipogenesis, Genes Dev. 14 (2000) 2831–2838.
[36] J.L. Collins, A.M. Fivush, M.A. Watson, C.M. Galardi, M. Lewis, L. Moore, D. Parks, J. Wilson, T.K. Tippin, J.G. Binz, K.D. Plunket, D.G. Morgan, E.J. Beaudet, K.D. Whitney, S.A. Kliewer, T.M. Willson, Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines, J. Med. Chem. 45 (2002) 1963–1966.
[37] P. Tontonoz, D.J. Mangelsdorf, Liver x receptor signaling pathways in cardiovascular disease, Mol. Endocrinol. 17 (2003) 985–993.
[38] A. Chawla, W.A. Boisvert, C.H. Lee, B.A. Laffitte, Y. Barak, S.B. Joseph, D. Liao, L. Nagy, P.A. Edwards, L.K. Curtiss, R.M. Evans, P. Tontonoz, A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis, Mol. Cell 7 (2001) 161–171.
[39] S.B. Joseph, M.N. Bradley, A. Castrillo, K.W. Bruhn, P.A. Mak, L. Pei, J. Hogenesch, M. O'Connell Test, article sample title placed here, Cell 119 (2004) 299–309.
[40] K.D. Whitney, M.A. Watson, B. Goodwin, C.M. Galardi, J.M. Maglich, J.G. Wilson, T.M. Willson, J.L. Collins, S.A. Kliewer, Liver X receptor (LXR) regulation of the LXRalpha gene in human macrophages, J. Biol. Chem. 276 (2001) 43509–43515.
[41] B.A. Laffitte, S.B. Joseph, R. Walczak, L. Pei, D.C. Wilpitz, J.L. Collins, P. Tontonoz, Autoregulation of the human liver X receptor alpha promoter, Mol. Cell. Biol. 21 (2001) 7558–7568.
[42] M. Chen, M.N. Bradley, S.W. Beaven, P. Tontonoz, Phosphorylation of the liver X receptors, FEBS Lett. 580 (2006) 4835–4841.
[43] I.P. Torra, N. Ismaili, J.E. Feig, C.F. Xu, C. Cavasotto, R. Pancratov, I. Rogatsky, T.A. Neubert, E.A. Fisher, M.J. Garabedian, Phosphorylation of liver X receptor alpha selectively regulates target gene expression in macrophages, Mol. Cell. Biol. 28 (2008) 2626–2636.
[44] E.H. Anthonisen, L. Berven, S. Holm, M. Nygard, H.I. Nebb, L.M. Gronning-Wang, Nuclear receptor liver X receptor is O-GlcNAc-modified in response to glucose, J. Biol. Chem. 285 (2010) 1607–1615.

[45] D.J. Peet, S.D. Turley, W. Ma, B.A. Janowski, J.M. Lobaccaro, R.E. Hammer, D.J. Mangelsdorf, Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha, Cell 93 (1998) 693–704.
[46] J.J. Repa, D.J. Mangelsdorf, The liver X receptor gene team: potential new players in atherosclerosis, Nat. Med. 8 (2002) 1243–1248.
[47] J.J. Repa, K.E. Berge, C. Pomajzl, J.A. Richardson, H. Hobbs, D.J. Mangelsdorf, Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta, J. Biol. Chem. 277 (2002) 18793–18800.
[48] A. Castrillo, P. Tontonoz, Nuclear receptors in macrophage biology: at the crossroads of lipid metabolism and inflammation, Annu. Rev. Cell Dev. Biol. 20 (2004) 455–480.
[49] A. Venkateswaran, B.A. Laffitte, S.B. Joseph, P.A. Mak, D.C. Wilpitz, P.A. Edwards, P. Tontonoz, Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha, Proc. Natl Acad. Sci. USA 97 (2000) 12097–12102.
[50] P. Costet, Y. Luo, N. Wang, A.R. Tall, Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor, J. Biol. Chem. 275 (2000) 28240–28245.
[51] K. Schwartz, R.M. Lawn, D.P. Wade, ABC1 gene expression and ApoA-I-mediated cholesterol efflux are regulated by LXR, Biochem. Biophys. Res. Commun. 274 (2000) 794–802.
[52] J.J. Repa, S.D. Turley, J.A. Lobaccaro, J. Medina, L. Li, K. Lustig, B. Shan, R.A. Heyman, J.M. Dietschy, D.J. Mangelsdorf, Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers, Science 289 (2000) 1524–1529.
[53] A. Venkateswaran, J.J. Repa, J.M. Lobaccaro, A. Bronson, D.J. Mangelsdorf, P.A. Edwards, Human white/murine ABC8 mRNA levels are highly induced in lipid-loaded macrophages, A transcriptional role for specific oxysterols, J. Biol. Chem. 275 (2000) 14700–14707.
[54] B.A. Laffitte, J.J. Repa, S.B. Joseph, D.C. Wilpitz, H.R. Kast, D.J. Mangelsdorf, P. Tontonoz, LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes, Proc. Natl Acad. Sci. USA 98 (2001) 507–512.
[55] P.A. Mak, B.A. Laffitte, C. Desrumaux, S.B. Joseph, L.K. Curtiss, D.J. Mangelsdorf, P. Tontonoz, P.A. Edwards, 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. 277 (2002) 31900–31908.
[56] J.J. Repa, G. Liang, J. Ou, Y. Bashmakov, J.M. Lobaccaro, I. Shimomura, B. Shan, M.S. Brown, J.L. Goldstein, D.J. Mangelsdorf, Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta, Genes Dev. 14 (2000) 2819–2830.
[57] S.B. Joseph, B.A. Laffitte, P.H. Patel, M.A. Watson, K.E. Matsukuma, R. Walczak, J.L. Collins, T.F. Osborne, P. Tontonoz, Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors, J. Biol. Chem. 277 (2002) 11019–11025.
[58] B.A. Laffitte, S.B. Joseph, M. Chen, A. Castrillo, J. Repa, D. Wilpitz, D. Mangelsdorf, P. Tontonoz, The phospholipid transfer protein gene is a liver X receptor target expressed by macrophages in atherosclerotic lesions, Mol. Cell. Biol. 23 (2003) 2182–2191.
[59] V. Molteni, X. Li, J. Nabakka, F. Liang, J. Wityak, A. Koder, L. Vargas, R. Romeo, N. Mitro, P.A. Mak, H.M. Seidel, J.A. Haslam, D. Chow, T. Tuntland, T.A. Spalding, A. Brock, M. Bradley, A. Castrillo, P. Tontonoz, E. Saez, N-Acylthiadiazolines, a new class of liver X receptor agonists with selectivity for LXRbeta, J. Med. Chem. 50 (2007) 4255–4259.
[60] S. Gordon, The macrophage: past, present and future, Eur. J. Immunol. 37 (Suppl 1) (2007) S9–S17.
[61] S. Gordon, P.R. Taylor, Monocyte and macrophage heterogeneity, Nat. Rev. Immunol. 5 (2005) 953–964.
[62] F. Geissmann, M.G. Manz, S. Jung, M.H. Sieweke, M. Merad, K. Ley, Development of monocytes, macrophages, and dendritic cells, Science 327 (2010) 656–661.
[63] N. Shibata, C.K. Glass, Regulation of macrophage function in inflammation and atherosclerosis, J. Lipid Res. 50 (Suppl) (2009) S277–S281.
[64] P. Libby, P.M. Ridker, G.K. Hansson, Inflammation in atherosclerosis: from pathophysiology to practice, J. Am. Coll. Cardiol. 54 (2009) 2129–2138.
[65] R. Ross, Atherosclerosis–an inflammatory disease, N. Engl. J. Med. 340 (1999) 115–126.
[66] C.K. Glass, J.L. Witztum, Atherosclerosis. the road ahead, Cell 104 (2001) 503–516.
[67] R.J. Aiello, D. Brees, P.A. Bourassa, L. Royer, S. Lindsey, T. Coskran, M. Haghpassand, O.L. Francone, Increased atherosclerosis in hyperlipidemic mice with inactivation of ABCA1 in macrophages, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 630–637.
[68] M. van Eck, I.S. Bos, W.E. Kaminski, E. Orso, G. Rothe, J. Twisk, A. Bottcher, E.S. Van Amersfoort, T.A. Christiansen-Weber, W.P. Fung-Leung, T.J. Van Berkel, G. Schmitz, Leukocyte ABCA1 controls susceptibility to atherosclerosis and macrophage recruitment into tissues, Proc. Natl Acad. Sci. USA 99 (2002) 6298–6303.
[69] M. Haghpassand, P.A. Bourassa, O.L. Francone, R.J. Aiello, Monocyte/macrophage expression of ABCA1 has minimal contribution to plasma HDL levels, J. Clin. Invest. 108 (2001) 1315–1320.
[70] M.A. Kennedy, G.C. Barrera, K. Nakamura, A. Baldan, P. Tarr, M.C. Fishbein, J. Frank, O.L. Francone, P.A. Edwards, ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation, Cell Metab. 1 (2005) 121–131.
[71] A. Baldan, L. Pei, R. Lee, P. Tarr, R.K. Tangirala, M.M. Weinstein, J. Frank, A.C. Li, P. Tontonoz, P.A. Edwards, Impaired development of atherosclerosis in hyperlipidemic Ldlr−/− and ApoE−/− mice transplanted with Abcg1−/− bone marrow, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2301–2307.
[72] R. Out, M. Hoekstra, R.B. Hildebrand, J.K. Kruit, I. Meurs, Z. Li, F. Kuipers, T.J. Van Berkel, M. Van Eck, Macrophage ABCG1 deletion disrupts lipid homeostasis in alveolar macrophages and moderately influences atherosclerotic lesion development in LDL receptor-deficient mice, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2295–2300.
[73] M. Ranalletta, N. Wang, S. Han, L. Yvan-Charvet, C. Welch, A.R. Tall, Decreased atherosclerosis in low-density lipoprotein receptor knockout mice transplanted with Abcg1−/− bone marrow, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2308–2315.
[74] L. Yvan-Charvet, M. Ranalletta, N. Wang, S. Han, N. Terasaka, R. Li, C. Welch, A.R. Tall, Combined deficiency of ABCA1 and ABCG1 promotes foam cell accumulation and accelerates atherosclerosis in mice, J. Clin. Invest. 117 (2007) 3900–3908.
[75] R. Out, M. Hoekstra, K. Habets, I. Meurs, V. de Waard, R.B. Hildebrand, Y. Wang, G. Chimini, J. Kuiper, T.J. Van Berkel, M. Van Eck, Combined deletion of macrophage ABCA1 and ABCG1 leads to massive lipid accumulation in tissue macrophages and distinct atherosclerosis at relatively low plasma cholesterol levels, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 258–264.
[76] L.K. Curtiss, ApoE in atherosclerosis : a protein with multiple hats, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 1852–1853.
[77] Y. Zhang, J.J. Repa, K. Gauthier, D.J. Mangelsdorf, Regulation of lipoprotein lipase by the oxysterol receptors, LXRalpha and LXRbeta, J. Biol. Chem. 276 (2001) 43018–43024.
[78] C.M. Desrumaux, P.A. Mak, W.A. Boisvert, D. Masson, D. Stupack, M. Jauhiainen, C. Ehnholm, L.K. Curtiss, Phospholipid transfer protein is present in human atherosclerotic lesions and is expressed by macrophages and foam cells, J. Lipid Res. 44 (2003) 1453–1461.
[79] J.G. Strauss, S. Frank, D. Kratky, G. Hammerle, A. Hrzenjak, G. Knipping, A. von Eckardstein, G.M. Kostner, R. Zechner, 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. 276 (2001) 36083–36090.
[80] N. Zelcer, C. Hong, R. Boyadjian, P. Tontonoz, LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor, Science 325 (2009) 100–104.
[81] C. Hong, S. Duit, P. Jalonen, R. Out, L. Scheer, V. Sorrentino, R. Boyadjian, K.W. Rodenburg, E. Foley, L. Korhonen, D. Lindholm, J. Nimpf, T.J. van Berkel, P. Tontonoz, N. Zelcer, The E3 ubiquitin ligase IDOL induces the degradation of the low density lipoprotein receptor family members VLDLR and ApoER2, J. Biol. Chem. 285 (2010) 19720–19726.
[82] R.K. Tangirala, E.D. Bischoff, S.B. Joseph, B.L. Wagner, R. Walczak, B.A. Laffitte, C.L. Daige, D. Thomas, R.A. Heyman, D.J. Mangelsdorf, X. Wang, A.J. Lusis, P. Tontonoz, I.G. Schulman, Identification of macrophage liver X receptors as inhibitors of atherosclerosis, Proc. Natl Acad. Sci. USA 99 (2002) 11896–11901.
[83] G.U. Schuster, P. Parini, L. Wang, S. Alberti, K.R. Steffensen, G.K. Hansson, B. Angelin, J.A. Gustafsson, Accumulation of foam cells in liver X receptor-deficient mice, Circulation 106 (2002) 1147–1153.
[84] A.C. Calkin, P. Tontonoz, Liver x receptor signaling pathways and atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 1513–1518.
[85] S.B. Joseph, E. McKilligin, L. Pei, M.A. Watson, A.R. Collins, B.A. Laffitte, M. Chen, G. Noh, J. Goodman, G.N. Hagger, J. Tran, T.K. Tippin, X. Wang, A.J. Lusis, W.A. Hsueh, R.E. Law, J.L. Collins, T.M. Willson, P. Tontonoz, Synthetic LXR ligand inhibits the development of atherosclerosis in mice, Proc. Natl Acad. Sci. USA 99 (2002) 7604–7609.
[86] N. Terasaka, A. Hiroshima, T. Koieyama, N. Ubukata, Y. Morikawa, D. Nakai, T. Inaba, T-0901317, a synthetic liver X receptor ligand, inhibits development of atherosclerosis in LDL receptor-deficient mice, FEBS Lett. 536 (2003) 6–11.
[87] M. Lehrke, C. Lebherz, S.C. Millington, H.P. Guan, J. Millar, D.J. Rader, J.M. Wilson, M.A. Lazar, Diet-dependent cardiovascular lipid metabolism controlled by hepatic LXRalpha, Cell Metab. 1 (2005) 297–308.
[88] D. Teupser, D. Kretzschmar, C. Tennert, R. Burkhardt, W. Wilfert, D. Fengler, R. Naumann, A.E. Sippel, J. Thiery, Effect of macrophage overexpression of murine liver X receptor-alpha (LXR-alpha) on atherosclerosis in LDL-receptor deficient mice, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 2009–2015.
[89] E.D. Bischoff, C.L. Daige, M. Petrowski, H. Dedman, J. Pattison, J. Juliano, A.C. Li, I.G. Schulman, Non-redundant roles for LXRalpha and LXRbeta in atherosclerosis susceptibility in low density lipoprotein receptor knockout mice, J. Lipid Res. 51 (2010) 900–906.
[90] M.N. Bradley, C. Hong, M. Chen, S.B. Joseph, D.C. Wilpitz, X. Wang, A.J. Lusis, A. Collins, W.A. Hseuh, J.L. Collins, R.K. Tangirala, P. Tontonoz, Ligand activation of LXR beta reverses atherosclerosis and cellular cholesterol overload in mice lacking LXR alpha and apoE, J. Clin. Invest. 117 (2007) 2337–2346.
[91] G. Lo Sasso, S. Murzilli, L. Salvatore, I. D'Errico, M. Petruzzelli, P. Conca, Z.Y. Jiang, L. Calabresi, P. Parini, A. Moschetta, Intestinal specific LXR activation stimulates reverse cholesterol transport and protects from atherosclerosis, Cell Metab. 12 (2010) 187–193.
[92] I. Tabas, The role of endoplasmic reticulum stress in the progression of atherosclerosis, Circ. Res. 107 (2010) 839–850.
[93] E. Erbay, V.R. Babaev, J.R. Mayers, L. Makowski, K.N. Charles, M.E. Snitow, S. Fazio, M.M. Wiest, S.M. Watkins, M.F. Linton, G.S. Hotamisligil, Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis, Nat. Med. 15 (2009) 1383–1391.
[94] L. Makowski, K.C. Brittingham, J.M. Reynolds, J. Suttles, G.S. Hotamisligil, The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome

proliferator-activated receptor gamma and IkappaB kinase activities, J. Biol. Chem. 280 (2005) 12888–12895.
[95] M. Furuhashi, G. Tuncman, C.Z. Gorgun, L. Makowski, G. Atsumi, E. Vaillancourt, K. Kono, V.R. Babaev, S. Fazio, M.F. Linton, R. Sulsky, J.A. Robl, R.A. Parker, G.S. Hotamisligil, Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2, Nature 447 (2007) 959–965.
[96] G.S. Hotamisligil, E. Erbay, Nutrient sensing and inflammation in metabolic diseases, Nat. Rev. Immunol. 8 (2008) 923–934.
[97] S. Gordon, F.O. Martinez, Alternative activation of macrophages: mechanism and functions, Immunity 32, 593–604.
[98] R. Medzhitov, T. Horng, Transcriptional control of the inflammatory response, Nat. Rev. Immunol. 9 (2009) 692–703.
[99] C.K. Glass, K. Saijo, B. Winner, M.C. Marchetto, F.H. Gage, Mechanisms underlying inflammation in neurodegeneration, Cell 140 (2010) 918–934.
[100] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (2010) 883–899.
[101] J.A. Whitsett, S.E. Wert, T.E. Weaver, Alveolar surfactant homeostasis and the pathogenesis of pulmonary disease, Annu. Rev. Med. 61 (2010) 105–119.
[102] V. Fadok, D. Bratton, A. Konowal, P. Freed, J. Westcott, P. Henson, Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF, J. Clin. Invest. 101 (1998) 890–898.
[103] R.E. Voll, M. Herrmann, E.A. Roth, C. Stach, J.R. Kalden, I. Girkontaite, Immunosuppressive effects apoptotic cells, Nature 390 (1997) 350–351.
[104] D.D. Sakai, S. Helms, J. Carlstedt-Duke, J.A. Gustafsson, F.M. Rottman, K.R. Yamamoto, Hormone-mediated repression: a negative glucocorticoid response element from the bovine prolactin gene, Genes Dev. 2 (1988) 1144–1154.
[105] A. Chawla, Control of macrophage activation and function by PPARs, Circ. Res. 106 (2010) 1559–1569.
[106] H.F. Yang-Yen, J.C. Chambard, Y.L. Sun, T. Smeal, T.J. Schmidt, J. Drouin, M. Karin, Transcriptional interference between c-Jun and the glucocorticoid receptor: mutual inhibition of DNA binding due to direct protein–protein interaction, Cell 62 (1990) 1205–1215.
[107] R. Schule, P. Rangarajan, S. Kliewer, L.J. Ransone, J. Bolado, N. Yang, I.M. Verma, R.M. Evans, Functional antagonism between oncoprotein c-Jun and the glucocorticoid receptor, Cell 62 (1990) 1217–1226.
[108] R. Newton, N.S. Holden, Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? Mol. Pharmacol. 72 (2007) 799–809.
[109] G. Pascual, A.L. Fong, S. Ogawa, A. Gamliel, A.C. Li, V. Perissi, D.W. Rose, T.M. Willson, M.G. Rosenfeld, C.K. Glass, A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma, Nature 437 (2005) 759–763.
[110] S.B. Joseph, A. Castrillo, B.A. Laffitte, D.J. Mangelsdorf, P. Tontonoz, Reciprocal regulation of inflammation and lipid metabolism by liver X receptors, Nat. Med. 9 (2003) 213–219.
[111] A. Castrillo, S.B. Joseph, C. Marathe, D.J. Mangelsdorf, P. Tontonoz, Liver X receptor-dependent repression of matrix metalloproteinase-9 expression in macrophages, J. Biol. Chem. 278 (2003) 10443–10449.
[112] A.J. Fowler, M.Y. Sheu, M. Schmuth, J. Kao, J.W. Fluhr, L. Rhein, J.L. Collins, T.M. Willson, D.J. Mangelsdorf, P.M. Elias, K.R. Feingold, Liver X receptor activators display anti-inflammatory activity in irritant and allergic contact dermatitis models: liver-X-receptor-specific inhibition of inflammation and primary cytokine production, J. Invest. Dermatol. 120 (2003) 246–255.
[113] S. Ghisletti, W. Huang, S. Ogawa, G. Pascual, L. M., T.M. Willson, M.G. Rosenfeld, C.K. Glass, Parallel SUMOylation-dependent pathways mediate gene- and signal-specific transrepression by LXRs and PPARgamma. Mol. Cell 25 (2007) 57–70.
[114] F. Blaschke, Y. Takata, E. Caglayan, A. Collins, P. Tontonoz, W.A. Hsueh, R.K. Tangirala, A nuclear receptor corepressor-dependent pathway mediates suppression of cytokine-induced C-reactive protein gene expression by liver X receptor, Circ. Res. 99 (2006) e88–e99.
[115] J.H. Lee, S.M. Park, O.S. Kim, C.S. Lee, J.H. Woo, S.J. Park, E.H. Joe, I. Jou, Differential SUMOylation of LXRalpha and LXRbeta mediates transrepression of STAT1 inflammatory signaling in IFN-gamma-stimulated brain astrocytes, Mol. Cell 35 (2009) 806–817.
[116] N. Venteclef, T. Jakobsson, A. Ehrlund, A. Damdimopoulos, L. Mikkonen, E. Ellis, L.M. Nilsson, P. Parini, O.A. Janne, J.A. Gustafsson, K.R. Steffensen, E. Treuter, GPS2-dependent corepressor/SUMO pathways govern anti-inflammatory actions of LRH-1 and LXRbeta in the hepatic acute phase response, Genes Dev. 24 (2010) 381–395.
[117] S. Ogawa, J. Lozach, C. Benner, G. Pascual, R.K. Tangirala, S. Westin, A. Hoffmann, S. Subramaniam, M. David, M.G. Rosenfeld, C.K. Glass, Molecular determinants of crosstalk between nuclear receptors and toll-like receptors, Cell 122 (2005) 707–721.
[118] R.I. Scheinman, P.C. Cogswell, A.K. Lofquist, A.S. Baldwin Jr., Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids, Science 270 (1995) 283–286.
[119] N. Auphan, J.A. DiDonato, C. Rosette, A. Helmberg, M. Karin, Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis, Science 270 (1995) 286–290.
[120] J.T. Huang, J.S. Welch, M. Ricote, C.J. Binder, T.M. Willson, C. Kelly, J.L. Witztum, C.D. Funk, D. Conrad, C.K. Glass, Interleukin-4-dependent production of PPAR-gamma ligands in macrophages by 12/15-lipoxygenase, Nature 400 (1999) 378–382.
[121] M.A. Bouhlel, B. Derudas, E. Rigamonti, R. Dievart, J. Brozek, S. Haulon, C. Zawadzki, B. Jude, G. Torpier, N. Marx, B. Staels, G. Chinetti-Gbaguidi, PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties, Cell Metab. 6 (2007) 137–143.
[122] J.I. Odegaard, R.R. Ricardo-Gonzalez, M.H. Goforth, C.R. Morel, V. Subramanian, L. Mukundan, A. Red Eagle, D. Vats, F. Brombacher, A.W. Ferrante, A. Chawla, Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance, Nature 447 (2007) 1116–1120.
[123] J.I. Odegaard, R.R. Ricardo-Gonzalez, A. Red Eagle, D. Vats, C.R. Morel, M.H. Goforth, V. Subramanian, L. Mukundan, A.W. Ferrante, A. Chawla, Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance, Cell Metab. 7 (2008) 496–507.
[124] A.L. Hevener, J.M. Olefsky, D. Reichart, M.T. Nguyen, G. Bandyopadyhay, H.Y. Leung, M.J. Watt, C. Benner, M.A. Febbraio, A.K. Nguyen, B. Folian, S. Subramaniam, F.J. Gonzalez, C.K. Glass, M. Ricote, Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones, J. Clin. Invest. 117 (2007) 1658–1669.
[125] A.J. Guri, R. Hontecillas, G. Ferrer, O. Casagran, U. Wankhade, A.M. Noble, D.L. Eizirik, F. Ortis, M. Cnop, D. Liu, H. Si, J. Bassaganya-Riera, Loss of PPAR gamma in immune cells impairs the ability of abscisic acid to improve insulin sensitivity by suppressing monocyte chemoattractant protein-1 expression and macrophage infiltration into white adipose tissue, J. Nutr. Biochem. 19 (2008) 216–228.
[126] K. Kang, S.M. Reilly, V. Karabacak, M.R. Gangl, K. Fitzgerald, B. Hatano, C.H. Lee, Adipocyte-derived Th2 cytokines and myeloid PPARdelta regulate macrophage polarization and insulin sensitivity, Cell Metab. 7 (2008) 485–495.
[127] A. Gallardo-Soler, C. Gomez-Nieto, M.L. Campo, C. Marathe, P. Tontonoz, A. Castrillo, I. Corraliza, Arginase I induction by modified lipoproteins in macrophages: a peroxisome proliferator-activated receptor-gamma/delta-mediated effect that links lipid metabolism and immunity, Mol. Endocrinol. 22 (2008) 1394–1402.
[128] A. Szanto, B.L. Balint, Z.S. Nagy, E. Barta, B. Dezso, A. Pap, L. Szeles, S. Poliska, M. Oros, R.M. Evans, Y. Barak, J. Schwabe, L. Nagy, STAT6 transcription factor is a facilitator of the nuclear receptor PPARgamma-regulated gene expression in macrophages and dendritic cells, Immunity 33 (2010) 699–712.
[129] C. Marathe, M.N. Bradley, C. Hong, L. Chao, D. Wilpitz, J. Salazar, P. Tontonoz, Preserved glucose tolerance in high-fat-fed C57BL/6 mice transplanted with PPARgamma−/−, PPARdelta−/−, PPARgammadelta−/−, or LXRalphabeta−/− bone marrow, J. Lipid. Res. 50 (2009) 214–224.
[130] B.A. Laffitte, L.C. Chao, J. Li, R. Walczak, S. Hummasti, S.B. Joseph, A. Castrillo, D.C. Wilpitz, D.J. Mangelsdorf, J.L. Collins, E. Saez, P. Tontonoz, Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue, Proc. Natl Acad. Sci. USA 100 (2003) 5419–5424.
[131] S.R. Commerford, L. Vargas, S.E. Dorfman, N. Mitro, E.C. Rocheford, P.A. Mak, X. Li, P. Kennedy, T.L. Mullarkey, E. Saez, Dissection of the insulin-sensitizing effect of liver X receptor ligands, Mol. Endocrinol. 21 (2007) 3002–3012.
[132] C. Marathe, M.N. Bradley, C. Hong, F. Lopez, C.M. Ruiz de Galarreta, P. Tontonoz, A. Castrillo, The arginase II gene is an anti-inflammatory target of liver X receptor in macrophages, J. Biol. Chem. 281 (2006) 32197–32206.
[133] V. Iniesta, L.C. Gomez-Nieto, I. Corraliza, The inhibition of arginase by N(omega)-hydroxy-L-arginine controls the growth of Leishmania inside macrophages, J. Exp. Med. 193 (2001) 777–784.
[134] K.C. El Kasmi, J.E. Qualls, J.T. Pesce, A.M. Smith, R.W. Thompson, M. Henao-Tamayo, R.J. Basaraba, T. Konig, U. Schleicher, M.S. Koo, G. Kaplan, K.A. Fitzgerald, E.I. Tuomanen, I.M. Orme, T.D. Kanneganti, C. Bogdan, T.A. Wynn, P.J. Murray, Toll-like receptor-induced arginase 1 in macrophages thwarts effective immunity against intracellular pathogens, Nat. Immunol. 9 (2008) 1399–1406.
[135] S. Ghisletti, W. Huang, K. Jepsen, C. Benner, G. Hardiman, M.G. Rosenfeld, C.K. Glass, Cooperative NCoR/SMRT interactions establish a corepressor-based strategy for integration of inflammatory and anti-inflammatory signaling pathways, Genes Dev. 23 (2009) 681–693.
[136] N. Terasaka, A. Hiroshima, A. Ariga, S. Honzumi, T. Koieyama, T. Inaba, T. Fujiwara, Liver X receptor agonists inhibit tissue factor expression in macrophages, FEBS J. 272 (2005) 1546–1556.
[137] S. Andersson, N. Gustafsson, M. Warner, J.A. Gustafsson, Inactivation of liver X receptor beta leads to adult-onset motor neuron degeneration in male mice, Proc. Natl Acad. Sci. USA 102 (2005) 3857–3862.
[138] X. Fan, H.J. Kim, D. Bouton, M. Warner, J.A. Gustafsson, Expression of liver X receptor beta is essential for formation of superficial cortical layers and migration of later-born neurons, Proc. Natl Acad. Sci. USA 105 (2008) 13445–13450.
[139] H.J. Kim, X. Fan, C. Gabbi, K. Yakimchuk, P. Parini, M. Warner, J.A. Gustafsson, Liver X receptor beta (LXRbeta): a link between beta-sitosterol and amyotrophic lateral sclerosis-Parkinson's dementia, Proc. Natl Acad. Sci. USA 105 (2008) 2094–2099.
[140] Q. Jiang, C.Y. Lee, S. Mandrekar, B. Wilkinson, P. Cramer, N. Zelcer, K. Mann, B. Lamb, T.M. Willson, J.L. Collins, J.C. Richardson, J.D. Smith, T.A. Comery, D. Riddell, D.M. Holtzman, P. Tontonoz, G.E. Landreth, ApoE promotes the proteolytic degradation of Abeta, Neuron 58 (2008) 681–693.
[141] N. Zelcer, N. Khanlou, R. Clare, Q. Jiang, E.G. Reed-Geaghan, G.E. Landreth, H.V. Vinters, P. Tontonoz, Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors, Proc. Natl Acad. Sci. USA 104 (2007) 10601–10606.
[142] C. Hindinger, D.R. Hinton, S.J. Kirwin, R.D. Atkinson, M.E. Burnett, C.C. Bergmann, S.A. Stohlman, Liver X receptor activation decreases the severity of experimental autoimmune encephalomyelitis, J. Neurosci. Res. 84 (2006) 1225–1234.
[143] N.F. Fitz, A. Cronican, T. Pham, A. Fogg, A.H. Fauq, R. Chapman, I. Lefterov, R. Koldamova, Liver X receptor agonist treatment ameliorates amyloid pathology

and memory deficits caused by high-fat diet in APP23 mice, J. Neurosci. 30 (2010) 6862–6872.
[144] J.R. Morales, I. Ballesteros, J.M. Deniz, O. Hurtado, J. Vivancos, F. Nombela, I. Lizasoain, A. Castrillo, M.A. Moro, Activation of liver X receptors promotes neuroprotection and reduces brain inflammation in experimental stroke, Circulation 118 (2008) 1450–1459.
[145] L. Sironi, N. Mitro, M. Cimino, P. Gelosa, U. Guerrini, E. Tremoli, E. Saez, Treatment with LXR agonists after focal cerebral ischemia prevents brain damage, FEBS Lett. 582 (2008) 3396–3400.
[146] O. Cheng, R.P. Ostrowski, W. Liu, J.H. Zhang, Activation of liver X receptor reduces global ischemic brain injury by reduction of nuclear factor-kappaB, Neuroscience 166 (2010) 1101–1109.
[147] D.S. Gupta, D. Kaul, A.J. Kanwar, D. Parsad, Psoriasis: crucial role of LXR-alpha RNomics, Genes Immun. 11 (2010) 37–44.
[148] K.C. Chang, Q. Shen, I.G. Oh, S.A. Jelinsky, S.F. Jenkins, W. Wang, Y. Wang, M. LaCava, M.R. Yudt, C.C. Thompson, L.P. Freedman, J.H. Chung, S. Nagpal, Liver X receptor is a therapeutic target for photoaging and chronological skin aging, Mol. Endocrinol. 22 (2008) 2407–2419.
[149] H. Gong, J. He, J.H. Lee, E. Mallick, X. Gao, S. Li, G.E. Homanics, W. Xie, Activation of the liver X receptor prevents lipopolysaccharide-induced lung injury, J. Biol. Chem. 284 (2009) 30113–30121.
[150] K. Smoak, J. Madenspacher, S. Jeyaseelan, B. Williams, D. Dixon, K.R. Poch, J.A. Nick, G.S. Worthen, M.B. Fessler, Effects of liver X receptor agonist treatment on pulmonary inflammation and host defense, J. Immunol. 180 (2008) 3305–3312.
[151] L.D. Bauler, C.S. Duckett, M.X. O'Riordan, XIAP regulates cytosol-specific innate immunity to Listeria infection, PLoS Pathog. 4 (2008) e1000142.
[152] R.M. O'Connell, S.K. Saha, S.A. Vaidya, K.W. Bruhn, G.A. Miranda, B. Zarnegar, A.K. Perry, B.O. Nguyen, T.F. Lane, T. Taniguchi, J.F. Miller, G. Cheng, Type I interferon production enhances susceptibility to Listeria monocytogenes infection, J. Exp. Med. 200 (2004) 437–445.
[153] T. Miyazaki, Y. Hirokami, N. Matsuhashi, H. Takatsuka, M. Naito, Increased susceptibility of thymocytes to apoptosis in mice lacking AIM, a novel murine macrophage-derived soluble factor belonging to the scavenger receptor cysteine-rich domain superfamily, J. Exp. Med. 189 (1999) 413–422.
[154] A.F. Valledor, L.C. Hsu, S. Ogawa, D. Sawka-Verhelle, M. Karin, C.K. Glass, Activation of liver X receptors and retinoid X receptors prevents bacterial-induced macrophage apoptosis, Proc. Natl Acad. Sci. USA 101 (2004) 17813–17818.
[155] S. Arai, J.M. Shelton, M. Chen, M.N. Bradley, A. Castrillo, A.L. Bookout, P.A. Mak, P.A. Edwards, D.J. Mangelsdorf, P. Tontonoz, T. Miyazaki, A role for the apoptosis inhibitory factor AIM/Spalpha/Api6 in atherosclerosis development, Cell Metab. 1 (2005) 201–213.
[156] H. Korf, S. Vander Beken, M. Romano, K.R. Steffensen, B. Stijlemans, J.A. Gustafsson, J. Grooten, K. Huygen, Liver X receptors contribute to the protective immune response against Mycobacterium tuberculosis in mice, J. Clin. Invest. 119 (2009) 1626–1637.
[157] A. Castrillo, S.B. Joseph, S.A. Vaidya, M. Haberland, A.M. Fogelman, G. Cheng, P. Tontonoz, Crosstalk between LXR and toll-like receptor signaling mediates bacterial and viral antagonism of cholesterol metabolism, Mol. Cell 12 (2003) 805–816.
[158] F. Cao, A. Castrillo, P. Tontonoz, F. Re, G.I. Byrne, Chlamydia pneumoniae–induced macrophage foam cell formation is mediated by Toll-like receptor 2, Infect. Immun. 75 (2007) 753–759.
[159] Y. Naiki, R. Sorrentino, M.H. Wong, K.S. Michelsen, K. Shimada, S. Chen, A. Yilmaz, A. Slepenkin, N.W. Schroder, T.R. Crother, Y. Bulut, T.M. Doherty, M. Bradley, Z. Shaposhnik, E.M. Peterson, P. Tontonoz, P.K. Shah, M. Arditi, TLR/MyD88 and liver X receptor alpha signaling pathways reciprocally control Chlamydia pneumoniae-induced acceleration of atherosclerosis, J. Immunol. 181 (2008) 7176–7185.
[160] S. Chen, R. Sorrentino, K. Shimada, Y. Bulut, T.M. Doherty, T.R. Crother, M. Arditi, Chlamydia pneumoniae-induced foam cell formation requires MyD88-dependent and -independent signaling and is reciprocally modulated by liver X receptor activation, J. Immunol. 181 (2008) 7186–7193.
[161] R. Geyeregger, M. Zeyda, W. Bauer, E. Kriehuber, M.D. Saemann, G.J. Zlabinger, D. Maurer, T.M. Stulnig, Liver X receptors regulate dendritic cell phenotype and function through blocked induction of the actin-bundling protein fascin, Blood 109 (2007) 4288–4295.
[162] E.J. Villablanca, L. Raccosta, D. Zhou, R. Fontana, D. Maggioni, A. Negro, F. Sanvito, M. Ponzoni, B. Valentinis, M. Bregni, A. Prinetti, K.R. Steffensen, S. Sonnino, J.A. Gustafsson, C. Doglioni, C. Bordignon, C. Traversari, V. Russo, Tumor-mediated liver X receptor-alpha activation inhibits CC chemokine receptor-7 expression on dendritic cells and dampens antitumor responses, Nat. Med. 16 (2010) 98–105.
[163] D. Torocsik, M. Barath, S. Benko, L. Szeles, B. Dezso, S. Poliska, Z. Hegyi, L. Homolya, I. Szatmari, A. Lanyi, L. Nagy, Activation of liver X receptor sensitizes human dendritic cells to inflammatory stimuli, J. Immunol. 184 (2010) 5456–5465.
[164] S.J. Bensinger, M.N. Bradley, S.B. Joseph, N. Zelcer, E.M. Janssen, M.A. Hausner, R. Shih, J.S. Parks, P.A. Edwards, B.D. Jamieson, P. Tontonoz, LXR signaling couples sterol metabolism to proliferation in the acquired immune response, Cell 134 (2008) 97–111.
[165] J.E. Feig, I. Pineda-Torra, M. Sanson, M.N. Bradley, Y. Vengrenyuk, D. Bogunovic, E.L. Gautier, D. Rubinstein, C. Hong, J. Liu, C. Wu, N. van Rooijen, N. Bhardwaj, M.J. Garabedian, P. Tontonoz, E.A. Fisher, LXR promotes the maximal egress of monocyte-derived cells from mouse aortic plaques during atherosclerosis regression, J. Clin. Invest. (2010).
[166] K.S. Ravichandran, U. Lorenz, Engulfment of apoptotic cells: signals for a good meal, Nat. Rev. Immunol. 7 (2007) 964–974.
[167] R.W. Vandivier, P.M. Henson, I.S. Douglas, Burying the dead: the impact of failed apoptotic cell removal (efferocytosis) on chronic inflammatory lung disease, Chest 129 (2006) 1673–1682.
[168] K. Lauber, S. Blumenthal, M. Waibel, S. Wesselborg, Clearance of apoptotic cells: getting rid of the corpses, Mol. Cell 14 (2004) 277–287.
[169] M.R. Elliott, F.B. Chekeni, P.C. Trampont, E.R. Lazarowski, A. Kadl, S.F. Walk, D. Park, R.I. Woodson, M. Ostankovich, P. Sharma, J.J. Lysiak, T.K. Harden, N. Leitinger, K.S. Ravichandran, Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance, Nature 461 (2009) 282–286.
[170] K. Lauber, E. Bohn, S.M. Krober, Y.J. Xiao, S.G. Blumenthal, R.K. Lindemann, P. Marini, C. Wiedig, A. Zobywalski, S. Baksh, Y. Xu, I.B. Autenrieth, K. Schulze-Osthoff, C. Belka, G. Stuhler, S. Wesselborg, Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal, Cell 113 (2003) 717–730.
[171] K.S. Ravichandran, Find-me and eat-me signals in apoptotic cell clearance: progress and conundrums, J. Exp. Med. 207 (2010) 1807–1817.
[172] L.E. Munoz, K. Lauber, M. Schiller, A.A. Manfredi, M. Herrmann, The role of defective clearance of apoptotic cells in systemic autoimmunity, Nat. Rev. Rheumatol. 6 (2010) 280–289.
[173] A.G. N, S.J. Bensinger, C. Hong, S. Beceiro, M.N. Bradley, N. Zelcer, J. Deniz, C. Ramirez, M. Diaz, G. Gallardo, C.R. de Galarreta, J. Salazar, F. Lopez, P. Edwards, J. Parks, M. Andujar, P. Tontonoz, A. Castrillo, Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR, Immunity 31 (2009) 245–258.
[174] G. Lemke, T. Burstyn-Cohen, TAM receptors and the clearance of apoptotic cells, Ann. N. Y. Acad. Sci. 1209 (2010) 23–29.
[175] C. Rebe, M. Raveneau, A. Chevriaux, D. Lakomy, A.L. Sberna, A. Costa, G. Bessede, A. Athias, E. Steinmetz, J.M. Lobaccaro, G. Alves, A. Menicacci, S. Vachenc, E. Solary, P. Gambert, D. Masson, Induction of transglutaminase 2 by a liver X receptor/retinoic acid receptor alpha pathway increases the clearance of apoptotic cells by human macrophages, Circ. Res. 105 (2009) 393–401.
[176] L. Nagy, M. Saydak, N. Shipley, S. Lu, J.P. Basilion, Z.H. Yan, P. Syka, R.A. Chandraratna, J.P. Stein, R.A. Heyman, P.J. Davies, Identification and characterization of a versatile retinoid response element (retinoic acid receptor response element-retinoid X receptor response element) in the mouse tissue transglutaminase gene promoter, J. Biol. Chem. 271 (1996) 4355–4365.
[177] G. Melino, M. Draoui, L. Bellincampi, F. Bernassola, S. Bernardini, M. Piacentini, U. Reichert, P. Cohen, Retinoic acid receptors alpha and gamma mediate the induction of "tissue" transglutaminase activity and apoptosis in human neuroblastoma cells, Exp. Cell Res. 235 (1997) 55–61.
[178] Z. Szondy, Z. Sarang, P. Molnar, T. Nemeth, M. Piacentini, P.G. Mastroberardino, L. Falasca, D. Aeschlimann, J. Kovacs, I. Kiss, E. Szegezdi, G. Lakos, E. Rajnavolgyi, P.J. Birckbichler, G. Melino, L. Fesus, Transglutaminase 2−/− mice reveal a phagocytosis-associated crosstalk between macrophages and apoptotic cells, Proc. Natl Acad. Sci. USA 100 (2003) 7812–7817.
[179] Y. Hamon, C. Broccardo, O. Chambenoit, M. Luciani, F. Toti, S. Chaslin, J. Freyssinet, P. Devaux, J. McNeish, D. Marguet, G. Chimini, ABC1 promotes engulfment of apoptotic cells and transbilayer redistribution of phosphatidylserine, Nat. Cell Biol. 2 (2000) 399–406.
[180] Y. Li, M.C. Gerbod-Giannone, H. Seitz, D. Cui, E. Thorp, A.R. Tall, G.K. Matsushima, I. Tabas, Cholesterol-induced apoptotic macrophages elicit an inflammatory response in phagocytes, which is partially attenuated by the Mer receptor, J. Biol. Chem. 281 (2006) 6707–6717.
[181] R. Kiss, M. Elliott, Z. Ma, Y. Marcel, K. Ravichandran, Apoptotic cells induce a phosphatidylserine-dependent homeostatic response from phagocytes, Curr. Biol. 16 (2006) 2252–2258.
[182] M.C. Gerbod-Giannone, Y. Li, A. Holleboom, S. Han, L.C. Hsu, I. Tabas, A.R. Tall, TNFalpha induces ABCA1 through NF-kappaB in macrophages and in phagocytes ingesting apoptotic cells, Proc. Natl Acad. Sci. USA 103 (2006) 3112–3117.
[183] R. Rodriguez-Manzanet, M.A. Sanjuan, H.Y. Wu, F.J. Quintana, S. Xiao, A.C. Anderson, H.L. Weiner, D.R. Green, V.K. Kuchroo, T and B cell hyperactivity and autoimmunity associatedwith niche-specific defects in apoptotic body clearance in TIM-4-deficient mice, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 8706–8711.
[184] A. Lacy-Hulbert, A.M. Smith, H. Tissire, M. Barry, D. Crowley, R.T. Bronson, J.T. Roes, J.S. Savill, R.O. Hynes, Ulcerative colitis and autoimmunity induced by loss of myeloid alphav integrins, Proc. Natl Acad. Sci. USA 104 (2007) 15823–15828.
[185] M. Botto, C. Dell'Agnola, A. Bygrave, E. Thompson, H.T. Cook, F. Petry, M. Loos, P.P. Pandolfi, M.J. Walport, Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies, Nat. Genet. 19 (1998) 56–59.
[186] R. Hanayama, M. Tanaka, K. Miyasaka, K. Aozasa, M. Koike, Y. Uchiyama, S. Nagata, Autoimmune disease and impaired uptake of apoptotic cells in MFG-E8-deficient mice, Science 304 (2004) 1147–1150.
[187] P.L. Cohen, R. Caricchio, V. Abraham, T. Camenisch, J.C. Jennette, R.A. Roubey, H.S. Earp, G. Matsushima, E. Reap, Delayed apoptotic cell clearance and lupus-like autoimmunity in mice lacking the c-mer membrane tyrosine kinase, J. Exp. Med. 196 (2002) 135–140.
[188] L. Mukundan, J.I. Odegaard, C.R. Morel, J.E. Heredia, J.W. Mwangi, R.R. Ricardo-Gonzalez, Y.P. Goh, A.R. Eagle, S.E. Dunn, J.U. Awakuni, K.D. Nguyen, L. Steinman, S.A. Michie, A. Chawla, PPAR-delta senses and orchestrates clearance of apoptotic cells to promote tolerance, Nat. Med. 15 (2009) 1266–1272.
[189] H. Yamaguchi, T. Fujimoto, S. Nakamura, K. Ohmura, T. Mimori, F. Matsuda, S. Nagata, Aberrant splicing of the milk fat globule-EGF factor 8 (MFG-E8) gene in human systemic lupus erythematosus, Eur. J. Immunol. 40 (2010) 1778–1785.

[190] R. Fernandez-Boyanapalli, S.C. Frasch, D.W. Riches, R.W. Vandivier, P.M. Henson, D.L. Bratton, PPAR{gamma} activation normalizes resolution of acute sterile inflammation in murine chronic granulomatous disease, Blood (2010).
[191] G. Majai, P. Gogolak, C. Ambrus, G. Vereb, J. Hodrea, L. Fesus, E. Rajnavolgyi, PPAR {gamma} modulated inflammatory response of human dendritic cell subsets to engulfed apoptotic neutrophils, J. Leukoc. Biol. (2010).
[192] G. Majai, Z. Sarang, K. Csomos, G. Zahuczky, L. Fesus, PPARgamma-dependent regulation of human macrophages in phagocytosis of apoptotic cells, Eur. J. Immunol. 37 (2007) 1343–1354.
[193] A.M. Johann, A. von Knethen, D. Lindemann, B. Brune, Recognition of apoptotic cells by macrophages activates the peroxisome proliferator-activated receptor-gamma and attenuates the oxidative burst, Cell Death Differ. 13 (2006) 1533–1540.
[194] K.M. Giles, K. Ross, A.G. Rossi, N.A. Hotchin, C. Haslett, I. Dransfield, Glucocorticoid augmentation of macrophage capacity for phagocytosis of apoptotic cells is associated with reduced p130Cas expression, loss of paxillin/pyk2 phosphorylation, and high levels of active Rac, J. Immunol. 167 (2001) 976–986.
[195] Y. Liu, J.M. Cousin, J. Hughes, J. Van Damme, J.R. Seckl, C. Haslett, I. Dransfield, J. Savill, A.G. Rossi, Glucocorticoids promote nonphlogistic phagocytosis of apoptotic leukocytes, J. Immunol. 162 (1999) 3639–3646.
[196] A. McColl, S. Bournazos, S. Franz, M. Perretti, B.P. Morgan, C. Haslett, I. Dransfield, Glucocorticoids induce protein S-dependent phagocytosis of apoptotic neutrophils by human macrophages, J. Immunol. 183 (2009) 2167–2175.
[197] J. Ehrchen, L. Steinmuller, K. Barczyk, K. Tenbrock, W. Nacken, M. Eisenacher, U. Nordhues, C. Sorg, C. Sunderkotter, J. Roth, Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes, Blood 109 (2007) 1265–1274.
[198] J.H. Choi, A.S. Banks, J.L. Estall, S. Kajimura, P. Bostrom, D. Laznik, J.L. Ruas, M.J. Chalmers, T.M. Kamenecka, M. Bluher, P.R. Griffin, B.M. Spiegelman, Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5, Nature 466 (2010) 451–456.
[199] S.L. Foster, D.C. Hargreaves, R. Medzhitov, Gene-specific control of inflammation by TLR-induced chromatin modifications, Nature 447 (2007) 972–978.