

PPAR Alpha

Subjects: Biochemistry & Molecular Biology | Cell Biology | Immunology

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Definition

Peroxisome proliferator-activated receptor α is a potent regulator of systemic and cellular metabolism and energy homeostasis, but it also suppresses various inflammatory reactions.

1. Introduction

Innate immunity comprises a sophisticated set of defensive processes, which are evolutionarily very old and originated concomitantly with the development of multicellular organisms. The defense against invading pathogens is a crucial physiological mechanism that guarantees survival. The development of these mechanisms is a manifestation of a constant race between pathogens (including unicellular pro- and eukaryotic invaders) and host. The biological processes involved in the innate immune response are very complex and tightly regulated on multiple levels, because they may be very harmful when left unsupervised. Recent advances in the elucidation of such a regulation revealed a dense network of connections among immune cell functions, signaling pathways, and cellular metabolism.

2. Peroxisome Proliferator-Activated Receptor alpha (PPAR α) and Its Role in Inflammation

Tissue injury and the onset of infection immediately evoke an innate immune response and trigger inflammation. As pointed out by Roman scholar Aulus Cornelius Celsus in the first century, local acute inflammation is manifested by calor, rubor, dolor, and tumor, i.e., increased temperature, redness, pain, and edema [1]. These symptoms reflect the action of proinflammatory lipid mediators, histamine, and cytokines released by tissue-infiltrating leukocytes that induce vasodilation and increase endothelial permeability and expression of adhesion molecules on the endothelial surface and in the extracellular matrix underneath. These events lead to extravasation of circulation leukocytes, chemotaxis, and accumulation of interstitial fluid, causing edema (tumor). The increased interstitial flow and metabolic activity of proliferating cells generate local heat and flushing (calor and rubor). Inflammatory pain (dolor) is evoked by activation of transient receptor potential cation channel vanilloid subfamily member 1 (TRPV1), which is present on sensory neurons of the peripheral nervous system [2]. The TRPV1 activation leads to an influx of Ca^{2+} and membrane depolarization, followed by the opening of voltage-gated sodium channels and creation of an action potential [2]. TRPV1 receptors are present not only on neurons, but also on immunocompetent cells (T lymphocytes, mast cells), epithelia, keratinocytes, and vascular endothelial cells [3]. TRPV1 channels are activated by various lipid inflammatory mediators, such as COX-2 products (prostaglandins), lipoxygenase 15-LOX products (e.g., 15-hydroperoxyeicosatetraenoic acid, 15-HPETE), and polyamines of molecules released after cell injury, e.g., ATP and adenosine [2]. The links between PPAR α and molecular events that spark inflammation and underlie its main symptoms are outlined below (Figure 1).

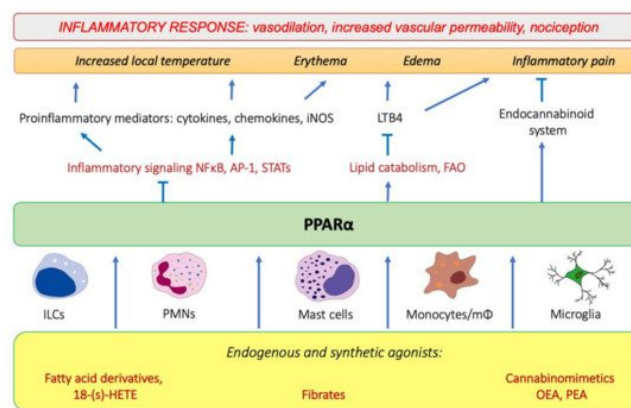


Figure 1. The involvement of PPAR α in the modulation of inflammation through interfering with the main inflammatory transcription factors (NF- κ B, nuclear factor κ B; AP-1, activation protein 1; STATs, signal transducers and activators of transcription) through activating lipid catabolic pathways and participating in the endocannabinoid system (see Section 7). iNOS, inducible nitric oxide synthase; FAO, fatty-acid oxidation; LTB $_4$, leukotriene B $_4$; OEA, oleylethanolamide; PEA, palmitoylethanolamide.

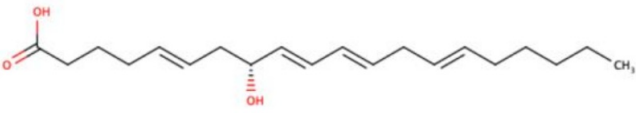
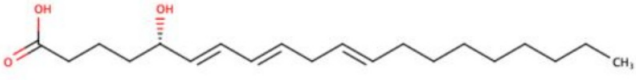
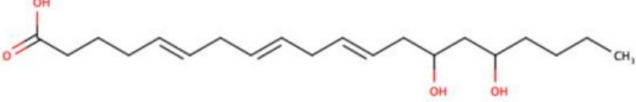
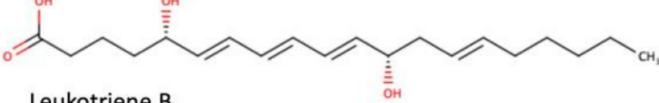
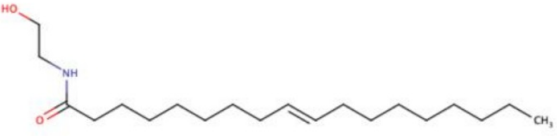
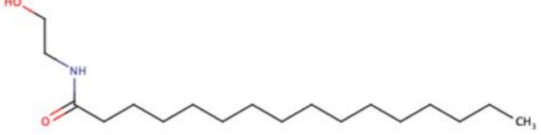
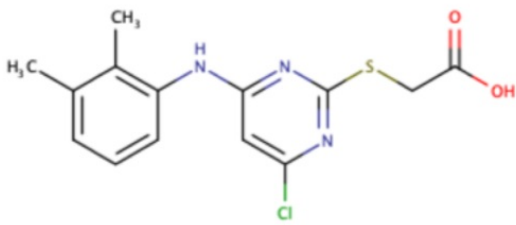
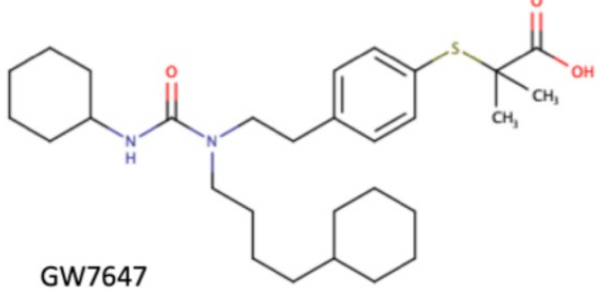
2.1. PPAR α as a Nuclear Receptor Present in Peripheral Tissues and Immunocompetent Cells

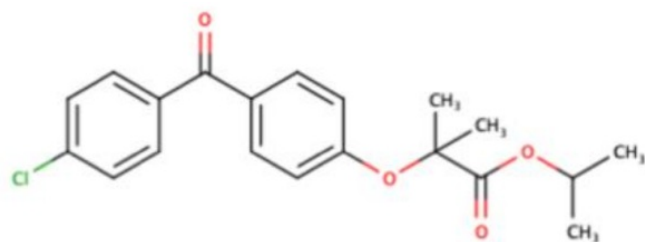
Peroxisome proliferator-activated receptors (PPARs) belong to a family of nuclear receptors that act as transcription factors activated by lipid-soluble ligands. Such ligands are able to cross the plasma membrane directly and bind the intracellular target proteins. PPARs are represented by three isotypes, PPAR α , PPAR β/δ , and PPAR γ , encoded by separate genes. They show tissue-specific expression patterns and mainly govern lipid, carbohydrate, and amino-acid metabolism, as well as exert other pleiotropic functions, including immunomodulatory activities. All three PPAR isotypes exhibit potent anti-inflammatory properties and have a strong impact on various aspects of the physiology of the immune system. In this review, we focus on peroxisome proliferator-activated receptor alpha (PPAR α), which is particularly responsible for the regulation of fatty-acid catabolism and ketogenesis [4][5], also in addition to being deeply involved in the modulation of innate immunity responses. Below, we outline the active participation of PPAR α in physiological processes that operate behind all four cardinal symptoms of inflammation, i.e., alleviating edema and pain and contributing to resolution of acute phase.

As a transcription factor, PPAR α is involved in the activation of gene transcription, which is carried out by binding the heterodimer of PPAR α and the pan-PPAR obligatory partner, retinoid X receptor (RXR), to consensus motifs in the target promoters. The active heterodimer is formed when both partners have their agonists bound. The most potent endogenous PPAR α agonists include fatty acids and their derivatives: saturated stearic and palmitic acids, fatty acyl amides such as oleylethanolamide (OEA) and palmitoylethanolamide (PEA), LOX products such as 5-(S)-HETE and 8-(S)-HETE, and leukotriene B $_4$ (LTB $_4$) [6][7][8][9]. There is the only one bona fide RXR ligand known so far, which is 9-cis-13,14-dihydroretinoic acid,

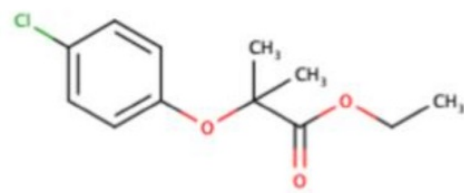
successfully identified after many years of searching, whereas 9-cis-retinoic acid, frequently used experimentally, is one of the most potent pharmacological RXR agonists [10][11]. Pharmacological PPAR α agonists, such as fibrates, are clinically used to normalize blood lipid profile, particularly to lower concentrations of cholesterol and low-density lipoprotein fractions [12]. Fenofibrate and gemfibrozil are the most widely prescribed drugs from a fibrate group, and they are generally very well tolerated [13]. Nevertheless, some adverse effects have been reported in patients chronically taking fibrates, with myopathy and rhabdomyolysis being the most common problems [14]. The structures of endogenous ligands, as well as the most important synthetic agonists and antagonists, are presented in **Table 1**.

Table 1. Chemical structures of PPAR α endogenous agonists, synthetic agonists used in experimental studies, clinically used pharmacological agonists, and synthetic antagonists, including examples of novel N-phenylsulfonylamide compounds (the structures of 3- and 10- series according to [15]).

PPAR α Agonists and Antagonists	
Natural agonists	 <p>8-(S)-HETE</p>
	 <p>5-(S)-HETE</p>
	 <p>14,15-diHETrE</p>
	 <p>Leukotriene B₄</p>
	 <p>OEA</p>
 <p>PEA</p>	
Synthetic agonists	 <p>Wy-14643 (pirinixic acid)</p>
	 <p>GW7647</p>

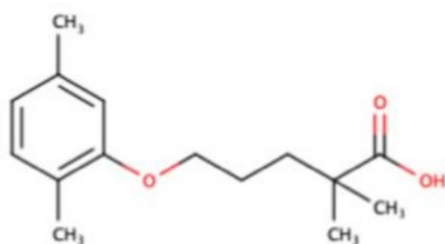


Fenofibrate

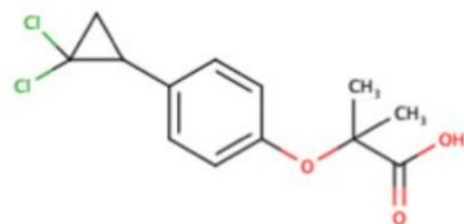


Clofibrate

Agonists
applied in
clinic: fibrate
derivatives



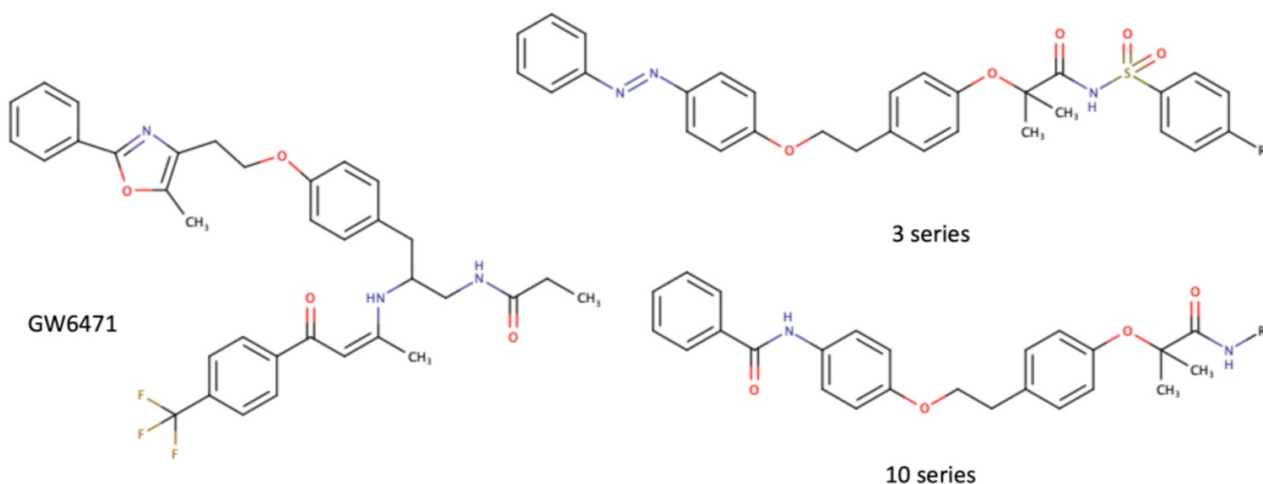
Gemfibrozil



Ciprofibrate

N-(phenylsulfonyl)amide derivatives:

Synthetic
antagonists



Interestingly, in addition to the tissues with a high rate of fatty-acid catabolism, such as the liver, cardiac muscle, and kidneys, PPAR α is generally expressed in CD45⁺ leukocytes [16], including numerous innate immune cell populations: basophils [17], eosinophils [18], monocytes and macrophages [19][20][21][22], Kupffer cells [23], Langerhans cells [24], osteoclasts [25], and microglia [26].

The classical PPAR α targets include the genes encoding enzymes from the fatty-acid mitochondrial and peroxisomal β -oxidation (acyl-CoA dehydrogenases, acyl-CoA oxidases), ω -oxidation and ω -hydroxylation (cytochromes P450), and ketogenesis (3-hydroxy-3-methylglutaryl-CoA synthase) [27][28][29]. Importantly, in addition to this canonical mode of action, PPAR α is able to transrepress certain genes through at least three mechanisms [30]: (i) initiating protein-protein interactions and sequestration of coactivators that are common to PPAR α and other pathways, (ii) cross-coupling of the PPAR α /RXR complex with other transcription factors, which leads to mutual cross-inhibition of both participating proteins, and (iii) interference with signal-transducing proteins, i.e., where the PPAR α /RXR complex inhibits phosphorylation of MAP-kinase cascade members.

2.2. PPAR α -Mediated Transrepression of Main Inflammatory Transcription Factors

Transrepressive activity toward nuclear factor κ B (NF- κ B), activation protein (AP-1), and signal transducers and activators of transcription (STATs) is responsible for PPAR α 's profound anti-inflammatory action. PPAR α physically interacts with the p65 Rel homology domain through its C-terminal fragment and simultaneously binds the JNK-responsive part of c-Jun with its N-terminal fragment (**Figure 2a**) [31]. Formation of this complex sequesters p65 and c-Jun from binding to the IL-6 promoter and blocks IL-1-induced IL-6 production. The direct inhibitory interaction between PPAR α and NF- κ B p65 subunit was also reported in cardiomyocytes [32]. In this case, sirtuin 1 (Sirt1) initiated formation of the Sirt1-PPAR α -p65 complex, which led to PPAR α -dependent p65 inactivation and transrepression of proinflammatory NF- κ B-regulated genes, such as monocyte chemoattractant protein 1 (MCP1, **Figure 2b**) [32]. Sirt1 induced p65 deacetylation, which also had a negative impact on NF- κ B activity because acetylation is required for its activity [33]. The deacetylation effect was absent after treatment with PPAR α antagonist GW6471 or in PPAR α ^{-/-} cells, which indicates PPAR α involvement [32].

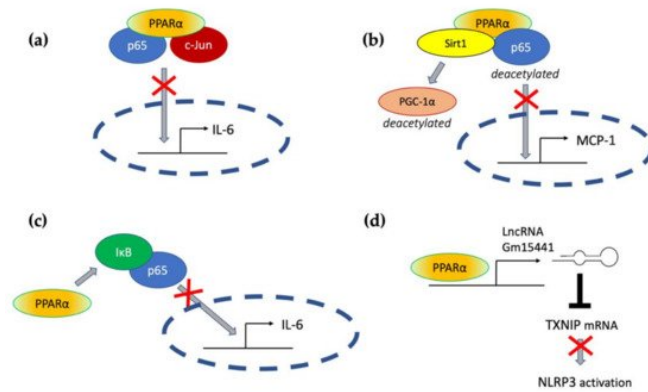


Figure 2. The molecular mechanisms responsible for PPAR α -mediated suppression of proinflammatory signaling pathways (see the main text for explanation) (a) through a direct interaction with p65 and c-Jun, (b) through interaction with Sirt1 and subsequent deacetylation of p65, (c) through activation of I κ B, and (d) through transactivation of long noncoding RNA Gm15441, which interferes with the stability of thioredoxin-interacting protein (TXNIP) mRNA and blocks NLRP3 inflammasome activation.

An additional mechanism responsible for PPAR α interference with the NF- κ B pathway was also identified in hepatocytes, where PPAR α bound and transactivated NF- κ B inhibitor alpha (I κ B α), which increased the amount of this protein [34]. Accumulated I κ B α binds NF- κ B, thereby masking its nuclear localization signal, which arrests it in the cytoplasm and blocks its activity as a transcription factor [35]. PPAR α was also responsible for the decreased phosphorylation of NF- κ B subunits p65 and p50 [34], which was another event with a negative impact on NF- κ B activity, because phosphorylation of its subunits is necessary for their optimal function [36]. The interference of PPAR α with NF- κ B action prevented IL-1 induced IL-6 expression in liver tissues (**Figure 2c**) [34].

The antagonism between PPAR α and NF- κ B and AP-1 underlies blocking of the expression of proinflammatory cytokines and effector proteins in various cell and animal models. PPAR α ligand K-111 (2,2-dichloro-12-(4-chlorophenyl)-dodecanoic acid) inhibited LPS-induced IL-6 production in Raw 264.7 macrophages on the mRNA and protein level [37]. This effect was exerted through the inhibition of stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), NF- κ B p65 phosphorylation, and induction of I κ B α protein level [37]. PPAR α activation in monocytes was shown to inhibit LPS- or IL-1 β -induced expression of tissue factor (TF), a membrane glycoprotein responsible for initiation of coagulation cascade [38][39]. The mechanism involved a previously mentioned blockade of the target gene promoter activity through the antagonism between PPAR α and NF κ B and AP-1 [38].

Interleukins released by immune cells exert their biological functions through specific cell surface receptors, which transduce signals through the Janus family of kinases (JAK) and phosphorylation STAT transcription factors [40]. Various STAT proteins are negatively regulated by PPAR α . For example, a bidirectional cross-inhibitory relationship between PPAR α and STAT5b was described [41][42][43]. STAT5b is responsible for signal transduction from the IL-2 receptor [44]. IL-2 is a very important cytokine, crucial for both innate and adaptive immunity, being indispensable for NK cell proliferation and maturation, as well as promoting the development, differentiation, and proinflammatory response of both Th1 and Th2 cells [44][45].

2.3. PPAR α and Inflammatory Lipid Mediators

Another important mechanism of the anti-inflammatory action of PPAR α involves the catabolism of lipid mediators, such as leukotriene B $_4$ (LTB $_4$). The elegant study by Devchand and colleagues [46] revealed that LTB $_4$ is a potent and specific PPAR α ligand that induces expression of PPAR α -transactivated genes of the peroxisomal β -oxidation pathway, namely, acyl-CoA oxidase, which is a rate-limiting enzyme of LTB $_4$ catabolism. PPAR α ^{-/-} mice subjected to a topical application of 5-LOX-inducing inflammatory agent and LTB $_4$ showed signs of tissue inflammation much longer (by about 30–40%) than wt mice, which were able to clear LTB $_4$ from circulation much faster [46]. This experiment illustrates the importance of PPAR α in the resolution of inflammation. This role of PPAR α is necessary for regulation of the innate immune response, because proinflammatory lipid mediators, such as LTB $_4$, are not only strong chemotactic agents for neutrophils and other leukocytes, but they also facilitate PMNs extravasation and diapedesis at the local site of inflammation and increase vascular permeability in this region [47][48]. By restricting LTB $_4$ duration, PPAR α alleviates three out of four inflammation symptoms (heat, flushing, and edema). Moreover, PMNs are not only recipients of LTB $_4$ signals, but they are also activated to its production via a positive autocrine feedback loop [49]. Therefore, the PPAR α -regulated LTB $_4$ clearance protects from an overexaggerated inflammatory response and its transition from acute to destructive chronic state. The other eicosanoids, the products of either COX, i.e., prostaglandins PGD $_1$, PGD $_2$, PGA $_1$, and PGA $_2$, or 5-LOX product 8-(S)-HETE, also activate PPAR α [50], which opens the possibility of modulating their impact on the cells with PPAR α expression, whether in immunocompetent cells, such as monocytes/macrophages that express high levels of this receptor, or in the inflamed tissue. Such an activity contributes to tissue protection from inflammatory damage and facilitates regeneration.

2.4. PPAR α Crosstalk with Pattern Recognition Receptors

Vertebrates take advantage of the PRR functions and employ them to sense all sorts of factors that induce tissue homeostatic imbalance. The PRR receptors are activated by the numerous compounds comprising specific structural entities referred to as the microbial-associated molecular patterns (MAMPs) or the Damage-associated molecular patterns (DAMPs). Several types of PRRs are broadly present in both immune and nonimmune cells, and their activation sparked by contacts with microorganisms, viruses, and some fragments of damaged cells or an alteration in the functioning of cell components (e.g., cytoskeleton or mitochondria malfunction or endoplasmic reticular stress) is the main trigger of the innate immunity response [51]. The PRRs can be divided into four main subfamilies: the Toll-like receptors (TLRs), the nucleotide-binding oligomerization domain (NOD)-leucine-rich repeat (LRR)-containing receptors (NLRs), the retinoic acid-inducible gene 1-like receptors (RLRs), and the C-type lectin receptors (CLRs) [52]. Nevertheless, some other cellular proteins can serve as PRRs in certain situations, e.g., the glycolytic enzyme, hexokinase II, which is able to spot the microbial sugar, N-acetylglucosamine, when this building block of peptidoglycan happens to be present in the cytoplasm [53]. In this section, we address the question of how PPAR α may be involved in the MAMP and DAMP recognition process in various tissues and cells.

The noteworthy information on TLR and PPAR α crosstalk comes from the studies on PPAR α knockout (KO) mice and cells derived from these animals. The colonic macrophages from KO mice did not produce the regulatory IL-10, but secreted IL-6, IL-1 β , and IL-12, potent inducers of Th1 and Th17 differentiation. Moreover, innate immune ILC3 cells isolated from the colon of PPAR α KO mice produce lower levels of IL-22 compared with those from WT mice, which results in the impaired secretion of antimicrobial peptides and commensal dysbiosis. This indicates that PPAR α regulates the ILC3 effector functions, which are important for both fighting infections and sustaining tolerance to commensal microbiota. The absence of PPAR α affects the species composition of the microbiome and leads to increased representation of segmented filamentous bacteria (SFB). All these facts render the KO mice prone to gut inflammation development and are indirect proof of the critical role of PPAR α activation in gut immunological homeostasis [19].

It is well known that interactions between the microbiota and intestinal cells engage Toll-like receptors [54], e.g., SFB regulate the process of Th17 differentiation in the intestine via activation of TLR5 by flagellin [55], and TLR4 ligand LPS from Gram-negative bacteria stimulates Th17 differentiation in vitro [56]. It seems that these events can be modulated by PPAR α ligands. Accordingly, it was shown that macrophages from PPAR α knockout mice are characterized by higher expression levels of mRNA for proinflammatory cytokines IL1 β and IL6, as well as for COX-2 and NF- κ B (p65) upon TLR4 ligand stimulation (LPS 50 ng/mL, 5 h), as compared to wild-type cells. It seems that PPAR α deficiency speeds up LPS-induced inflammatory responses in murine macrophages [21]. Another study on PPAR α KO mice indicated that PPAR α was essential for the anti-inflammatory effect of acute exercises. Its absence induced overexpression of proinflammatory cytokines in LPS-treated macrophages isolated from mice 24 h post exercise [57].

TLR ligands can regulate PPAR α activity, and PPAR α agonists influence the expression of TLRs, as well as proteins involved in signaling from TLRs in various cells of both immune and nonimmune types. Becker et al. studied the involvement of LPS in the regulation of PPAR α in murine lungs and showed that 24 h on from a prolonged LPS challenge (daily intranasal administration of 1 μ g LPS for 4 consecutive days), a profound inhibition of PPAR α mRNA expression took place [58]. LPS, peptidoglycan, and flagellin (ligands of TLR4, TLR1/2, and TLR5, respectively) strongly suppressed PPAR α activity in rat astrocytes acting at the mRNA and protein expression level [59]. On the other hand, it was shown that fenofibrate, a pharmacological PPAR agonist, significantly inhibited the TLR4, MYD-88, and NF- κ B mRNA expression, as well as TNF α production, in murine melanoma B16F10 LPS-stimulated cells [60]. The strong relationship between TLR4 and the PPAR α signaling pathway was also clearly demonstrated in a model of endotoxin-induced uveitis. This study suggested that fenofibrate can also attenuate LPS-induced cytokine production, inhibit NF- κ B signaling, and suppress TLR4 expression in retinal pigment epithelial cells. Simultaneously, LPS could act as a direct PPAR α antagonist in a PPAR α reporter cell line [61]. All these experimental data point to a subtle tuning and complicated interplay between activation of PPAR α and the TLR signaling pathway, which is needed for the homeostatic balance between triggering and resolution of the inflammatory response in tissues.

2.5. PPAR α and the Regulation of Inflammasomes

The inflammasomes, the complex molecular platforms formed in the cytoplasm (mainly in macrophages, but also in other nonimmune cells, such as endothelial and epithelial cells encountering various DAMPs and MAMPs), are now considered the key element of innate immunity. They are the multiprotein complexes composed of cytoplasmic sensors (mainly NLR family members), adaptive proteins (apoptosis-associated speck-like protein, ASC, or PY-CARD), and effectors (such as cysteine proteinase precursor or pro-caspase-1). In the case of some nonconventional inflammasomes, pro-caspase-1 is substituted by pro-caspase-11 in murine cells and pro-caspase 4/5 in human cells. The complex formation enables the proteolysis of pro-IL1 β and pro-IL18 and the release of active cytokines into the cell microenvironment and bloodstream, which drives local or systemic inflammation [62]. Alternatively, the inflammasome formation induces a chain of events leading to pyroptosis—the special type of a programmed cell death connected to an inflammatory state. The molecular mechanisms contributing to inflammasome activity are not yet completely understood, but it is believed that the process of their formation requires two subsequent signals, e.g., LPS binding to TLR4 on the cell membrane as the primary signal and K⁺ efflux, cytosolic release of lysosomal cathepsins, or mitochondria-derived factors and reactive oxygen species generation as the secondary signal [63]. The regulation of inflammasome activation can occur at both signals on the post-transcriptional and post-translational levels [64].

It was shown in some animal models that PPAR α activation can profoundly suppress the inflammasome-induced tissue injury, thereby contributing to the resolution of inflammation. This can be partially attributed to the downregulation of TLR expression by PPAR α and interference with the primary step of inflammasome activation. However, in PPAR α KO mice with lung inflammation caused by *Pseudomonas aeruginosa* introduction, a significant increase in expression of NLRP-3, ASC-1, and caspase-1, as compared with infected wt mice, was observed [65]. This indicates that PPAR α expression background is also important for the supply of inflammasome building blocks.

Acute liver injury is a disease strongly connected with NLRP3 inflammasome activity. In the context of this pathology, Brocker et al. proposed a mechanism connecting fasting, PPAR α , and the reduction in liver inflammation and injury. They showed that the long noncoding RNA gene Gm15441 contained a PPAR α -binding site within its promoter, and the Gm15441 RNA expression was activated by PPAR α ligand Wy-14643. Gm15441 suppressed its antisense transcript, encoding thioredoxin-interacting protein (TXNIP). This subsequently decreased TXNIP-stimulated NLRP3 inflammasome activation (**Figure 2d**) [66].

Moreover, it was shown that OEA, an endogenous bioactive lipid and a natural ligand of PPAR α , prevented tissue damage in the onset of LPS/d-galactosamine (d-Gal)-induced acute liver injury. OEA administration increased PPAR α expression in murine liver subjected to LPS/d-Gal

treatment. In turn, the liver protein levels of IL-1 β and NLRP3 inflammasome components, NLRP3 protein and pro-caspase-1, were enhanced after LPS/d-Gal injection in mice. The increase in these proteins was alleviated by OEA addition to the diet [67]. The OEA anti-inflammatory effects were also evident in dextran sulfate sodium (DSS)-induced mice colitis, and the effect was mediated by the inhibition of NLRP3, NF- κ B, or MyD88-dependent pathways [68].

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Keywords

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