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Review

An update on the mechanisms of action of the peroxisome proliferator-activated receptors (PPARs) and their roles in inflammation and cancer

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Abstract. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors and have been initially described as molecular targets for compounds which induce peroxisome proliferation. The interest of researchers for PPARs increased dramatically when these receptors were shown to be directly activated by a number of medically relevant compounds. These compounds include: the fibrate class of hypolidemic drugs, the thiazolidinediones, which are insulin sensitizers used as orally active antidiabetic agents, certain non-steroidal anti-inflammatory drugs (NSAIDs), and naturally occurring fatty acid-derived molecules. Rapidly, it was demonstrated that PPARs are key regulators of lipid homeostasis and provide a molecular link between nutrition and gene regulation. Recently, detailed studies of PPAR expression profiles in different tissues pointed to the roles these receptors play in inflammation control and cell proliferation. In this review we will focus on the new insights gained into these two areas and we will also discuss our current knowledge of the regulation of PPAR transcriptional activity by cofactors.

Key words. PPAR; nuclear receptor; lipid homeostasis; cofactor; inflammation; tumorigenesis; apoptosis.

The first PPAR era, from orphan receptors to receptors with functions in lipid metabolism

Peroxisome proliferators are a structurally diverse group of compounds which induce a dramatic increase in size and number of hepatic and renal peroxisomes as well as a concomitant increase in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β-oxidation cycle. Chemicals included in this group are the fibrate class of hypolidemic drugs, herbicides and phthalate plasticizers. The effects of these peroxisome proliferators were shown to be mediated by a member of the nuclear hormone receptor family, the peroxisome proliferator-activated receptor (PPAR). So far, three distinct PPARs, termed α, δ (also called β, NUC-1 or FAAR) and γ, each encoded by a separate gene and showing a distinct tissue distribution, have been identified in multiple species, including *Xenopus*, rodents and humans. Following heterodimerization with the retinoid X receptor (RXR) [1], the receptor for 9-*cis*-retinoic acid, PPAR binds to peroxisome proliferator response elements (PPREs), thereby governing the expression of many genes involved in lipid metabolism (reviewed in [2, 3]).

PPARα was the first PPAR to be identified [4] and is probably the only receptor that lives up to its name, since it is the PPAR subtype which is most effectively

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stimulated by peroxisome proliferators and which mediates the response to peroxisome proliferators in rodents [4, 5]. PPARα is expressed mainly in liver, kidney, heart and mouse brown adipose tissue [6]. In the liver, PPARα is responsible for regulating the oxidation of fatty acids and the detoxification of several xenobiotic compounds. Numerous studies have demonstrated that several genes involved in these metabolic pathways, such as the β- and ω-oxidation pathways, contain a PPRE in their promoter region and are under the transcriptional control of PPARα (reviewed in [3, 7]). Consistent with this observation, PPARα knockout mice, which are apparently healthy under basal conditions, are not able to induce genes involved in β- and ω-oxidation when treated with compounds which activate PPARα [5]. PPARα is activated by naturally occurring eicosanoids derived from arachidonic acid through the lipooxygenase pathway, such as leukotriene B4 (LTB4) and 8-*S*-hydroxyeicosatetranoic acid (8S-HETE) [8–10]. Moreover, fibrates, a class of hypolipidemic drugs widely used today in the treatment of hypertriglyceridemia, are synthetic PPARα ligands [8]. The lipid lowering effect of these fibrate drugs is caused by PPARα-mediated control of several genes involved in intra- and extracellular lipid metabolism [2, 3, 7].

PPARγ was elegantly shown by Tontonoz et al. to be a key player in adipocyte differentiation [11, 12]. Indeed, infection of fibroblast [12] and muscle [13] cells with a retroviral vector expressing PPARγ could induce adipocyte differentiation. The PPARγ gene is transcribed into three PPARγ messenger RNA (mRNA) species, that is PPARγ1, PPARγ2 and PPARγ3, which are derived from alternative splicing and promoter usage ([14, 15], and L. Fajas and J. Auwerx, unpublished observations). Little is known about the expression pattern of PPARγ3, except that it appears to be the predominant PPARγ type in macrophages [16]. PPARγ1 seems ubiquitously expressed, whereas PPARγ2 expression is mainly confined to adipose tissue, underscoring the importance of the PPARγ2 form for adipocyte physiology [14, 17]. Although the mechanisms by which PPARγ activation drives adipogenesis are not fully elucidated, it involves most likely the regulation of adipocyte-specific gene expression [2, 18–20]. Indeed, PPARγ controls the expression of several crucial adipocyte genes, including lipoprotein lipase [21], acyl coenzyme A (CoA) synthase [22, 23], fatty acid transport protein [24, 25] and phosphoenol pyruvate carboxykinase [26], which are all involved in coordinating uptake, metabolism and storage of fatty acids (reviewed in [2, 19, 27]). Furthermore, PPARγ decreases the expression of the adipocyte-derived signaling molecule leptin, translating into an increase in energy intake and optimization of energy usage, and contributing further to PPARγ's adipogenic effect [28–31]. PPARγ is not only a crucial element in the control of adipocyte differentiation, but it also seems to be responsible for the modulation of programmed cell death in the adipocytes ([32], and A.-M. Lefebvre and J. Auwerx, unpublished results). Indeed, PPARγ activation seems to favor the formation of small adipocytes which tend to replace the large adipocytes normally constituting white adipose tissue [32, 33]. PPARγ can be activated by naturally occurring arachidonic acid metabolites derived from the cyclooxygenase pathway, such as ligand 15-deoxy-Δ12,14-prostaglandin J2 (15-deoxy-PGJ2) [34, 35] but also by synthetic ligands such as thiazolidinediones, which are insulin sensitizers used as orally active antidiabetic agents [36, 37] or certain nonsteroidal antiinflammatory drugs (NSAIDs) [38]. The high level of expression of PPARγ mRNA in adipose tissue suggests that the antidiabetic thiazolidinedione PPARγ ligands most likely exert their primary effect in this tissue and argue against an important direct transcriptional effect of these agents on the muscle, which expresses very little PPARγ under basal conditions. The insulin-sensitizing effects of these PPARγ agonists can be largely attributed to their effects on the redistribution of fatty acids between muscle and adipose tissue secondary to a decreased production of adipose tissue-signaling molecules, such as tumor necrosis factor (TNF)-α [39, 40], plasminogen activator inhibitor (PAI)-1 [41–44], leptin [29, 31, 45, 46] and free fatty acids [47, 48]. This relative fatty acid depletion in muscle could indeed cause an improvement in muscle glucose disposal according to Randle's hypothesis [48] (for a review see [49]).

The third PPAR, PPARδ, is expressed in a wide range of tissues including heart, adipose tissue, brain, intestine, muscle, spleen, lung and adrenal glands [6, 50]. Although the exact role of the delta subtype of PPAR is not known, our latest studies suggest that this PPARδ is also involved in lipid metabolism and affects more specifically high density lipoprotein (HDL) levels (M. D. Leibowitz and J. Auwerx, submitted). In fact, administration of PPARδ agonists to *db*/*db* mice resulted in a clear induction of HDL cholesterol levels, an effect clearly distinct from those of PPARα or PPARγ agonists in this animal model. Beside its putative role in lipoprotein metabolism, a recent study indicates that PPARδ could be implicated in another aspect of lipid metabolism, that is oligodendrocyte maturation and membrane sheet formation [51]. PPARδ is activated by eicosanoids such as (8S-HETE) [9, 10, 52] as well as ethyl esters of palmitic and oleic acids [53]. Synthetic PPARδ ligands are ETYA [9], a synthetic arachidonic acid analog, L-631,033 [or 4-(2-acetyl-6-hydroxyundecyl)cinnamic acid] [54], a fatty acid-like compound, and GW 2433 [55], a fibrate derivative.

Instead of giving a full overview of all aspects of PPARs, we will focus here on new insights gained recently into the roles played by PPARs in inflammatory processes and cell proliferation, and we will also discuss our current knowledge of the regulation of PPAR transcriptional activity by cofactors. For additional general information on PPARs, we refer to one of the previous reviews on this subject [2, 3, 56, 57].

Cofactors for the PPARs

Lately, crucial new insights into the molecular mechanisms of transcriptional activation were gained owing to the discovery and characterization of a new functional class of proteins called 'cofactors'. Such cofactors have been reported to interact directly with nuclear receptors and can either repress (corepressors) or enhance (coactivators) their transcriptional activities. The molecular mechanisms through which cofactors modulate the activity of nuclear receptors are not yet clearly understood. Initially it was thought that cofactors could simply bridge transcription factors with the basic transcription machinery. This is indeed the case for cofactors such as p300, a coactivator which is also a component of TATA-binding protein complexes [58], or CBP, a p300 homologous protein, which has been shown to be associated with the RNA polymerase II via RNA helicase A [59]. Although this bridging function is definitely important, it recently became clear that these cofactors also carried several enzymatic activities, suggesting that they could control gene expression by specifically modifying chromatin and DNA structure. There are also numerous examples of enzymatic activities which are given below. For instance, SUG-1 is a DNA-helicase [60], TIF1α is a protein kinase [61], members of the SRC-1 family as well as p300 and CBP can acetylate histones [62–67] and other proteins of the transcription complex such as TFIIEβ and TFIIF [68], and the two corepressors SMRT and NCoR occur in a complex with histone deacetylase activity [69]. Classically it is suggested that in absence of any ligand, nuclear receptors may bind to corepressors which extinguish the nuclear receptor transcriptional activity and can even confer to the nuclear receptor a role in active gene repression. Ligand binding induces a conformational change in the nuclear receptor that results in dissociation of corepressors and binding of coactivators. The receptor/coactivator complex can then activate gene transcription (for reviews see [70, 71]). An important number of putative cofactors have been shown to interact with PPARs, but a firm role in the regulation of the transcriptional activity of PPAR has not always been established [72–83] (see table 1). We will limit this discussion to cofactors which have been shown to be genuine coactivators or corepressors for PPARs, for example cofactors which have been shown not only to bind to PPARs but also to modulate their transcriptional activity.

CBP and p300 are two related cofactors that were originally identified as CREB (cAMP-responsive binding protein) [84] and E1A [85] interacting factors (see also [86] and [87] for reviews). CBP/p300 are widely expressed [88] and coactivate numerous transcription factors [89–91], including several nuclear receptors such as the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the retinoic acid receptor (RAR), the retinoid X receptor (RXR), the thyroid hormone receptor (TR) and the vitamin D receptor (VDR) [73, 91–93]. In addition, CBP/p300 interact with the LBDs of PPARγ [76] and PPARα [73] in a ligand-dependent manner. Whereas it is not yet established whether this interaction enhances the transcriptional activity of PPARγ, PPARα transcriptional activity is clearly stimulated by p300/CBP. We have recently observed that the association between p300 and PPARγ was complex. Indeed, the two molecules actually interact through multiple domains in each protein. Most notably, the N-terminal region of PPARγ can dimerize with p300 in the absence of ligand, and this association results in enhancement of the constitutive AF-1 transcriptional activity of the receptor [93a]. We hypothesize that the presence of cofactors such as p300 could enhance the ligand-independent transcriptional activity of PPARs in vivo, which could thereby modulate the expression of several genes in the absence of any agonist. This could perhaps explain the high level of basal activity observed in PPAR cotransfection assays.

The steroid receptor coactivator (SRC)-1 was first characterized as a progesterone receptor (PR) coactivator [80] but later on was also isolated in a yeast two-hybrid screening on the basis of its interaction with the PPARγ LBD [94]. Although some contradictory results have been published, the interaction between PPAR and SRC-1 appears to be ligand-dependent, a property that allowed G. Krey et al. to develop an in vitro screening method for selection of PPAR agonists [52]. Like p300/CBP, SRC-1 is ubiquitously expressed [88, 94] and is not a PPAR-specific coactivator, as it has been shown to also interact with transcription factors not belonging to the nuclear receptor family [95–100].

The PPAR binding protein (PBP) has been isolated on the basis of its interaction with the LBD of PPARγ in a yeast two-hybrid screen of a mouse liver complementary DNA (cDNA) library [79]. PPARγ and PBP are constitutively associated both in vitro and in vivo, but the presence of a ligand enhances this interaction. PBP coactivates PPARγ transcriptional activity only modestly, but a truncated form bearing only the receptor-binding domain acts as a dominant-negative repressor,

Table 1. List of PPAR cofactors.

Cofactor	Isolated with	Interaction in vitro		Interaction in cells		Effect on nuclear receptor transcriptional activity	Interaction with other receptors	Reference
		without ligand	with ligand	without ligand	with ligand			
CBP/p300	CBP = CREB Binding Protein [84] p300 = E1A associated factor [85]	+	++	+	++	activation	AR, ER, PR, RAR, RXR, TR, VDR	73, 91–93, [141]
PBP	Yeast two-hybrid, bait: mPPARγ LBD, library: mouse liver cDNA.	+	++	+	++	activation	PPARα, RAR, RXR, TR	79
PGC-1	Yeast two-hybrid, bait: mPPARγ LBD, library: mouse brown fat cell cDNA	++	++	+	++	activation	RAR, ER	77
RIP140	Yeast two-hybrid, bait: PPARα LBD, library: human liver cDNA	–	++	++	++	inhibition	PPARγ, RXR, TR	83
SMRT	Yeast two-hybrid, bait: hRXR LBD, library: HeLa cell cDNA	++	?	++	?	repression	TR, RAR,	101, 102
SRC-1	Yeast two-hybrid, bait: mPPARγ LBD, library: mouse liver cDNA	++	++	++	++	activation	PR, PPARα, PPARδ, TR	95–100

CBP, CREB-binding protein; PBP, PPARγ-binding protein; PGC-1, PPARγ coactivator-1; RIP140, receptor interacting protein 140; SMRT, silencing mediator for retinoid- and thyroid-hormone receptors; SRC-1, steroid receptor coactivator; AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; TR, thyroid hormone receptor; VDR, vitamin D receptor; m, mouse; h, human.

suggesting that PBP is a genuine coactivator for PPARγ. Nevertheless, PBP does not seem to be a specific coactivator for PPAR, since it can interact with several other nuclear receptors and is expressed in a wide range of tissues. In order to evaluate its importance specifically for PPARγ transcriptional activity, it would be of interest to assay PBP expression levels also in tissues where PPARγ is of physiological importance, such as adipose tissue, colon and macrophages.

The PPAR gamma coactivator (PGC)-1 was isolated on the basis of its interaction with PPARγ in a yeast two-hybrid screen of a mouse brown fat cell cDNA library [77]. PGC-1 has also been reported to interact with the TR. Interestingly, the interaction between PGC-1 and PPARγ is ligand-independent both in vitro and in vivo. PGC-1 is expressed in brown fat, heart, kidney and brain, all tissues where PPARγ might be of physiological importance. Furthermore, PGC-1 expression is induced upon cold exposure in brown fat and skeletal muscle, and when it is ectopically expressed in white adipose cells, PGC-1 activates expression of the uncoupling protein (UCP)-1, a key mitochondrial enzyme of the respiratory chain. These observations suggest that PGC-1 plays a role in linking nuclear receptors to the transcriptional program of adaptive thermogenesis.

The receptor interacting protein (RIP)-140 has been isolated on the basis of its interaction with the LBD of PPARα in the yeast two-hybrid system [83]. Although the in vitro interaction between RIP140 and PPAR is ligand-dependent, the two molecules can constitutively associate in a cellular context. In cotransfection experiments RIP140 inhibits PPAR transcriptional activity. In vitro RIP140 can compete with coactivators such as SRC-1 for binding to nuclear receptors, a mechanism that may also occur in vivo and that could explain its inhibitory action on PPAR transcriptional activity.

The silencing mediator for retinoid- and thyroid-hormone receptors (SMRT) has been isolated on the basis of its interaction with the RAR and the TR in absence of ligand in a yeast two-hybrid screen of a HeLa cell cDNA library [101, 102]. SMRT is a corepressor and inhibits RAR- and TR-dependent gene transcription in the absence of their respective ligands. In the presence of ligands, SMRT dissociates from these receptors, which then recruit coactivators. Lavinsky et al. showed that SMRT may also be involved in PPARγ-mediated gene transcription [74]. Indeed, EGF enhances PPARγ and SMRT interaction in whole-cell extracts from epidermal growth factor (EGF)-treated CV-1 cells. Furthermore, antibodies directed against SMRT can relieve the mitogen-activated protein (MAP) kinase-dependent inhibition of PPARγ transcriptional activity [74]. The PPARγ/SMRT complex has also been shown to bind to DNA, but the interaction detected is very weak, and the

PPAR/RXR complex did not seem to show any repression activity [78]. Interestingly, microinjection of antibodies directed against SMRT could relieve SMRT corepression of PPAR activity, whereas antibodies directed against NCoR, another important nuclear receptor corepressor, were ineffective [74]. Nevertheless, it is still not clear at present whether PPARs exert any constitutive repression on gene expression in vivo.

Although several cofactors that interact with PPARs have already been identified, our knowledge of their mechanism of action is still in its infancy. So far, none of the cofactors described for nuclear receptors seem to be specific for the PPAR subclass of receptors or a particular PPAR subtype. Understanding how these cofactors interact will require in addition to structural studies the careful analysis of PPAR transcriptional activity in purified reconstituted transcription systems. Furthermore, it will be necessary to test whether the roles of these various cofactors are actually redundant. The recent observations made on the mode of action of RIP140 suggest that some of them are mutually exclusive when interacting with the same receptor. These observations also point to the importance of the stoichiometry of the different components involved in the nuclear receptor transcription complex. It will thus be of interest in the future to better characterize the expression profiles of the various cofactors as well as to gain more insight into the regulation of their respective promoters.

PPARs and inflammation

Besides their structural function and key role in energy homeostasis, lipids are important signaling molecules and are key components of several second messengers (reviewed in [103]). PPARs can be considered as one of the key tertiary messengers mediating certain of the transcriptional effects of lipid second messengers.

Most of the information available on a potential role of PPARs in inflammation relates to PPARγ. The importance of PPARγ in inflammatory processes was first suggested by some studies in adipose tissue, where a general antagonism exists between the activities of the proinflammatory cytokine tumor necrosis factor (TNF)-α on the one hand and PPARγ on the other hand. The expression of TNF-α in adipose tissue is highly interesting. In fact, TNF-α is a potent inhibitor of adipocyte differentiation, and exposure of 3T3-L1 adipocytes to TNF-α results in lipid depletion and a complete reversal of adipocyte differentiation [104]. An important mechanism by which TNF-α exerts this antiadipogenic action is via the downregulation of the expression of adipogenic factors such as C/EBPα [104–106] and PPARγ [104, 107, 108]. Interestingly, obesity characterized by increased adipose tissue mass is associated with increased amounts of TNF-α in adipose tissue. Although the exact role of high TNF-α levels in obesity in unclear, the increase in TNF-α might constitute a regulatory mechanism aimed at limiting further increase in adipose tissue mass. This increase in TNF-α in obesity is also believed to interfere with insulin-signaling pathways [39, 109, 110] and to contribute to the insulin resistance characteristic of the obese state [40]. Consistent with the opposing effects of PPARγ and TNF-α on adipose tissue, treatment of obese rats with PPARγ agonists, such as Rosiglitazone (BRL 49,653) or 15-deoxy-PGJ2, reduces the expression levels of TNF-α in the retroperitoneal and mesenteric white adipose tissues, contributing to weight gain [32]. PPARγ activation furthermore blocks the inhibitory effects of TNF-α on insulin signaling [109] as well as TNF-α-induced glycerol and free fatty acid (FFA) release [111]. Very interestingly, this antagonism between PPARγ and TNF-α is not restricted to the control of adipocyte differentiation and has been recently observed in inflammatory processes linked to the development of atherosclerosis (see below).

Recently several articles suggested that PPARγ is involved in the differentiation of monocytes into macrophages. In particular PPARγ would accelerate the conversion of monocytes to macrophage foam cells, which are the initial abnormality in the primitive atherosclerotic lesion. These cells are thought to influence the progression of atherosclerosis by several additional mechanisms such as the stimulation of low density lipoprotein (LDL) oxidation and secretion of proinflammatory cytokines. PPARγ is expressed in low levels in human peripheral blood monocytes [112] as well as in murine peritoneal [16] and lymph node macrophages [113]. Relative to undifferentiated resting monocytes, PPARγ expression increases along the macrophage differentiation process which can be induced by exposing the cells either to granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte colony stimulating factor (M-CSF), 1,25-dihydroxyvitamin D3 or phorbol myristate acetate (PMA) [16, 113]. Activation of the PPARγ/RXR heterodimer furthermore enhances macrophage differentiation [113]. Interestingly, exposure of human monocytes or monocytic cell lines to oxidized LDL (oxLDL) but not regular LDL also induces PPARγ expression [16, 113]. Moreover, PPARγ directly induces the transcription of the oxLDL receptor CD36, also called FAT, through a PPAR responsive element (PPRE) in the CD36 gene promoter, thereby establishing a positive feedback mechanism for monocyte activation (fig. 1) [113]. Exposure of monocyte/macrophages to oxLDL not only induces PPARγ expression, but owing to the CD36 facilitated uptake, the oxLDL also provides the

cells with two new PPARγ ligands, that is 9- and 13-hydroxyoctadecadienoic acids, both oxidative metabolites of linoleic acid [114]. Consistent with this theory, high amounts of PPARγ were observed in human [16, 115] or mouse [113] atherosclerotic lesions, where PPARγ expression colocalized with oxLDL accumulation [16, 115]. The strong expression of PPARγ in macrophage foam cells as well as the important amounts of 9- and 13-hydroxyoctadecadienoic acids present in oxLDL in atherosclerotic lesions suggest that such a mechanism could indeed occur in vivo, but further in vivo studies are necessary to define the exact role of PPARγ in atherosclerosis and plaque formation [116].

This role of PPARγ in macrophage differentiation, foam cell formation and induction of macrophage gene expression appears to contradict the earlier observations that PPARγ agonists might inhibit macrophage activation and limit the production of cytokines. Indeed, treatment of monocytes with high doses of either the natural PPARγ ligand 15-deoxy-PGJ2 or with PPARγ synthetic agonists inhibits production of TNF-α, interleukin (IL)-1β and IL-6 [117]. Also, treatment of macrophages with natural or synthetic PPARγ agonists induces a resting phenotype and downregulates the nitric oxide synthase [118, 119], gelatinase B and scavenger receptor A genes [118]. All these processes seem to be mediated by a direct transcriptional effect of PPARγ since in transient transfection experiments synthetic PPARγ agonists could inhibit the TNF-α promoter-driven expression of a luciferase reporter gene [117]. PPARγ activation would actually inhibit the activities of the nuclear factor-κB (NF-κB), activation protein-1 (AP-1), and STAT transcription factors, three

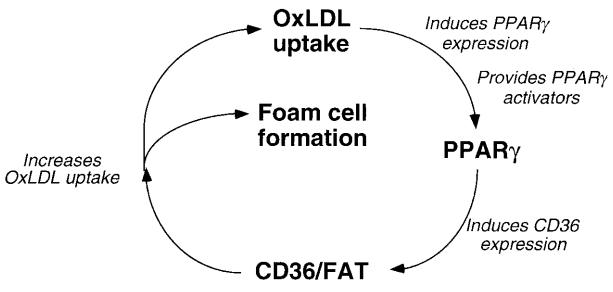

Figure 1. oxLDL and PPARγ promote macrophage differentiation. Exposure of monocytes/macrophages to oxLDL induces PPARγ expression and provides the cells with PPARγ ligands, that is 9- and 13-hydroxyoctadecadienoic acids. PPARγ then enhances the expression of several genes involved in fatty acid uptake and storage, as well as the CD36 gene that codes for an oxLDL receptor, thereby establishing a positive feedback loop leading to foam cell formation.

important factors that regulate cytokine gene expression by binding to their promoters [118]. The potential weakness of these studies is that significant effects in macrophages were only obtained when using high concentrations of PPARγ agonists. In classical dose-response curves, it was shown that these concentrations apparently do not match the concentrations which are necessary to activate PPARγ. This suggests that additional pathways to PPARγ might be involved in these processes.

Another link between PPARγ and inflammatory processes is the fact that the naturally occurring PPARγ ligand 15-deoxy-PGJ2 is a product of the cyclooxygenase pathway. Inhibition of cyclooxygenases by NSAIDs constitutes a common clinical approach for treatment of inflammatory processes. Recently, several lines of evidence suggested that some of the actions of NSAIDs might not only be mediated through inhibition of cyclooxygenase but also through activation of PPARs. Indeed, Lehmann et al. have shown that some NSAIDs are bona fide activators of PPARγ (and PPARα) [38]. The doses required for PPARγ agonist activity are in the micromolar range, and exceed those required for in vivo inhibition of cyclooxygenases. However, high doses of NSAIDs are often required in vivo for the treatment of inflammatory processes. It could therefore be hypothesized that certain of the therapeutic effects of NSAIDs might be due to a PPARγ-mediated suppression of cytokine synthesis. A more careful analysis of the agonist activity of each of these NSAIDs needs to be performed before a general conclusion can be drawn, as some of these compounds are both PPARγ and PPARα activators, whereas others do not bind to PPARs and yet have good antiinflammatory properties.

Recent evidence also seems to suggest a potential role for PPARα in inflammatory processes. Devchand et al. demonstrated that lipid mediators such as leukotriene B4 (LTB4) may control a generalized inflammatory response by binding and activating PPARα [8]. In mice with a targeted mutation of the PPARα gene, inflammation due to either arachidonic acid or its derivative LTB4 is prolonged compared with wild-type mice. These investigators explained this effect by the binding of LTB4 to PPARα and consecutive activation of PPARα-dependent transcription [8, 9]. In the liver, PPARα activation results in an increase in the expression of enzymes involved in the ω- and the β-oxidation pathways, hence stimulating the catabolism of proinflammatory lipid mediators such as LTB4 [120, 121]. Thus, LTB4 and other fatty acid lipid mediators activate their own degradation through stimulation of the transcriptional activity of PPARα, hence limiting the inflammatory response which they induce [8]. This negative feedback mechanism that controls LTB4

turnover is of importance in inflammatory processes whose duration needs to be tightly controlled in order to avoid inflammatory tissue injury. A few unresolved issues with this theory are the variable affinity with which LTB4 has been shown to bind and to transactivate PPARα [8, 9] and the fact that reduction of inflammation depends on PPARα activity in the liver and involves an efficient shuttling of the lipid mediator between different cell systems.

More recently, studies performed either in monocytes [119] or smooth muscle cells [122] suggested that PPARα could also influence inflammation in the vascular wall, although the data are still very controversial. In contrast to PPARγ agonists, PPARα agonists stimulate nitrite accumulation in murine macrophages, indicating that they could enhance nitric oxide synthase activity and hence have proinflammatory properties in these cells [119]. Smooth-muscle cells (SMCs) in which PPARα is present [122, 123] may also play a role in the atherosclerotic process. In these cells, IL-1-induced production of IL-6 and prostaglandin as well as cyclooxygenase-2 expression were inhibited in a dose-dependent manner by addition of PPARα activators [122]. It was suggested that similar to PPARγ in macrophages [118], PPARα regulates cytokine production in SMCs by interfering with different signaling pathways, inhibiting the NF-κB, AP-1 and signal transducer and activator of transcription (STAT) activities [122]. These results obtained in vitro were invoked to explain the transient decrease in plasma IL-6 and acute-phase protein concentrations in patients treated with fibrates [122]. Further long-term clinical studies are, however, necessary in order to establish whether PPARα activation will result in a transient or more permanent reduction of inflammatory activity. Furthermore, these results do not fit with those obtained in liver, where peroxisome proliferators can increase TNF-α production [124] and activate NF-κB activity [125–127]. Whether these opposite results reflect tissue-specific actions of PPARs will have to be determined.

It is clear that drugs and dietary agents that modify body lipid levels and PPAR expression or activation may have a broad influence on inflammatory processes. Epidemiological studies in subjects consuming high amounts of fish oil, such as the Inuit and Eskimo populations, demonstrated wide-ranging effects of fatty acids in the diet on immune functions and atherosclerosis (see [128] for reviews).

PPARs, cancer and cell cycle

It is well established that PPARγ is a factor capable of promoting differentiation or transdifferentiation of cells. For instance, infection of fibroblast [12] and muscle [13] cells with a retroviral vector expressing PPARγ could induce adipocyte differentiation. Interestingly, the phenotype induced following the activation of PPARγ is often adipocyte-like. A striking example was provided by the fact that PPARγ ligands have also been shown to promote differentiation of monocytes into macrophage foam cells which are characterized by fat accumulation [113] (fig. 2). Differentiation of preadipocytes into adipocyte cells occurs only after a prior and permanent exit from the cell cycle [129]. The exit from the cell cycle is due to changes in the activities of several factors involved in regulation of the cell cycle. It is noteworthy that the DNA-binding and transcriptional activity of the cell growth-promoting E2F/DP transcription factors is inhibited following PPARγ activation. This decrease in E2F/DP activity is attributable to an increase in the phosphorylation of these proteins that results from the downregulation of PP2A protein phosphatase expression [130]. This observation suggests that PPARγ not only controls the expression of genes involved in the acquisition of a differentiated phenotype but also that PPARγ plays an active role in the process of cell cycle withdrawal.

PPARγ has been shown to drive the differentiation process of adipocytes and colon cells to its terminal point, that is apoptosis ([32], and A.-M. Lefebvre and J. Auwerx, unpublished results). Furthermore, in cells from different lineage, such as liposarcoma [131], human breast cancer [132, 133] and human prostate cancer cells [134], PPARγ ligands were also shown to inhibit growth and at least for breast and prostate cancer cells to induce apoptosis [132, 134]. These observations suggest that induction of terminal differentiation by PPARγ agonists may represent a promising therapeutic approach to certain human malignancies. Nevertheless, the Evans's laboratory and our group independently demonstrated that activation of PPARγ can also promote the development of colon tumors in C57BL/6J-APC^{Min}/+ mice, a clinically relevant model for both human familial adenomatous polyposis and sporadic colon cancer [135, 136]. Hence, the action of PPARγ on cell cycle, differentiation and apoptosis seems to depend on the cell type and/or the contingence of mutational events that predispose tissues to cancer development. It will be of interest to study the role played by cofactors in these phenomena and whether mutations or modulation in expression of coactivators or corepressors could be responsible for PPARγ-dependent tumor formation, as seems to be the case for the ER and the amplified in breast cancer (AIB)-1 coactivator [137].

In contrast to PPARγ whose role in cell proliferation and cancer received attention only recently, it has been known for a long time that PPARα is involved in the induction of hepatic, pancreatic and testicular cancers in rodents (see [3] and [5] and references herein). So far,

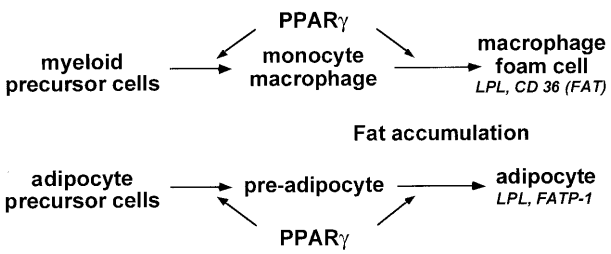

Figure 2. similar role for PPARγ in macrophage and adipocyte differentiation.

a role for PPARα in hepatocarcinogensis in humans has never been demonstrated [138]. Nevertheless, it has been shown that peroxisome proliferators, such as nafenopin, could suppress liver cell apoptosis in vitro [139], and a recent paper demonstrates that this effect of nafenopin can be abrogated when a naturally occurring human PPARα variant which acts as a dominant negative regulator of PPARα-mediated gene transcription is present [140]. These observations suggest that PPARα activation could be responsible for tumor development. As exemplified by the action of PPARγ in $APC^{Min}/+$ mice, it is possible that PPARα promotes tumor development in humans only under some pathological circumstances. In general, treatment with PPARα activators of patients predisposed to cancer development should be achieved with sufficient care.

Conclusion

Even though one of the main actions of the PPARs consists of control of lipid metabolism, their role no longer seems restricted to mere regulation of lipid storage and usage in view of the broad involvement of lipids in cell signaling. As a consequence of the role of lipid mediators in inflammatory processes, PPARs are susceptible to mediate the modulation of immune cell activation by nutritional and pharmacological stimuli. If a major role for PPARs in tumor development is confirmed, PPARs may also provide a link between nutrition and certain types of cancers. However, further studies will be required to establish a correlation between nutrition, PPAR activation, and inflammation or cancer. The characterization of specific PPAR cofactors should also provide future clues for understanding the specific actions of PPARs in various tissues. If the specific action of PPAR in different tissues is due to the recruitment of specific cofactors, it will be of interest to develop new molecules that are able to interfere with the interactions between PPARs and cofactors and to modulate a restricted range of PPAR target genes.

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