Inflamm. res. 49 (2000) 497–505
1023-3830/00/100497-9 $ 1.50+0.20/0

Inflammation Research

Review

Peroxisome proliferator-activated receptors (PPARs): Nuclear receptors at the crossroads between lipid metabolism and inflammation

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Received 2 December 1999; returned for revision 9 March 2000; accepted by M. J. Parnham 9 May 2000

Abstract. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor family. PPARs function as regulators of lipid and lipoprotein metabolism and glucose homeostasis and influence cellular proliferation, differentiation and apoptosis. PPARα is highly expressed in tissues such as liver, muscle, kidney and heart, where it stimulates the β-oxidative degradation of fatty acids. PPARγ is predominantly expressed in intestine and adipose tissue. PPARγ triggers adipocyte differentiation and promotes lipid storage. The hypolipidemic fibrates and the antidiabetic glitazones are synthetic ligands for PPARα and PPARγ, respectively. Furthermore, fatty acids and eicosanoids are natural PPAR ligands: PPARα is activated by leukotriene B4, whereas prostaglandin J2 is a PPARγ ligand. These observations suggested a potential role for PPARs not only in metabolic but also in inflammation control. The first evidence for a role of PPARα in inflammation control came from the demonstration that PPARα deficient mice display a prolonged response to inflammatory stimuli. It was suggested that PPARα deficiency results in a reduced β-oxidative degradation of these inflammatory fatty acid derivatives. More recently, PPAR activators were shown to inhibit the activation of inflammatory response genes (such as IL-2, IL-6, IL-8, TNFα and metalloproteases) by negatively interfering with the NF-κB, STAT and AP-1 signalling pathways. PPAR activators exert these anti-inflammatory activities in different immunological and vascular wall cell types such as monocyte/macrophages, endothelial, epithelial and smooth muscle cells in which PPARs are expressed. These recent findings indicate a modulatory role for PPARs in the control of the inflammatory response with potential therapeutic applications in inflammation-related diseases, such as atherosclerosis and inflammatory bowel disease.

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Key words: Transcription factors – Gene expression – Hypolipidemic drugs – Fatty acids

Introduction

Discovered in 1990 as key players in the response to peroxisome proliferators, work from numerous laboratories have identified Peroxisome Proliferator-Activated Receptors (PPARs) as regulators of lipid and lipoprotein metabolism, glucose homeostasis and cellular differentiation. Furthermore, recent observations indicate their implication in cancer development as well as in the control of the inflammatory response and inflammation-related disorders. In this article we will focus on the new insights indicating a role for PPARs in the metabolism of lipid-derived inflammatory mediators as well as their molecular action mechanism on the transcription of inflammatory response genes. These findings highlight their potential as therapeutic targets for the treatment of inflammation and inflammation-related disorders.

Molecular mechanism of action of the peroxisome proliferator-activated receptors

PPARs constitute a subfamily of the nuclear receptor family [1]. Three distinct PPARs, termed α, δ (also called β or NUC-1) and γ, each encoded by a separate gene and characterized by distinct tissue [2–4] and developmental [5] distribution patterns, have been described. PPARs are ligand-activated transcription factors which upon heterodimerization with the retinoic X receptor (RXR), recognize PPAR response elements (PPRE), located in the promoter of target genes [6]. PPREs consist of a direct repeat of the nuclear receptor hexameric AGGTCA recognition sequence separated by one or two interventing nucleotides (DR-1 and DR-2) [7, 8]. Within

this complex, PPAR binds to the 5′ extended half-site, while the RXR partner binds to the 3′ half site of the response element [7] (Fig. 1). PPARs can also repress gene transcription by negatively interfering with the NF-κB, STAT and AP-1 signalling pathways in a DNA-binding independent manner [9–13] (Fig. 2). Negative interference by PPARs with these signal transduction pathways is likely due to a combination of protein-protein interaction and cofactor squelching, as has been previously demonstrated for other members of the nuclear receptor family, such as the retinoic acid and glucocorticoid receptors [14]. PPARs interfere with the AP-1 and NF-κB signalling pathway by preventing the binding of AP-1 and NF-κB proteins to their target sequences [13, 15]. Furthermore, PPARs interact with c-*Jun* [16] as well as with p65 [17]. This trans-repression activity likely constitutes the mechanistical basis for the anti-inflammatory properties of PPARs.

Tissue distribution and regulation of the peroxisome proliferator-activated receptors

Tissue distribution of PPARs

An important determinant for the physiological functions of nuclear receptors, such as PPARs, is their tissue distribution patterns and expression levels. PPARα is mostly present in tissues characterized by high rates of fatty acid catabolism, such as liver, kidney, heart and muscle [2, 18], whereas PPARγ is not only highly expressed in adipose tissue [19] but is also detected in mammary gland and a number of other tissues [5, 20]. In addition, PPARs are expressed in immunological and vascular wall cell types: PPARα and PPARγ are expressed in primary cultures of endothelial [13, 15, 21–23] and smooth muscle cells [11, 24] and in monocyte/macrophages [9, 10, 25, 26]. Whereas PPARα is present in isolated human monocytes and its expression increases during the differentiation process, PPARγ is not detectable in human monocytes but is strongly induced upon differentiation [9]. In addition, the expression of PPARα and PPARγ in the subendothelial region and in the lipid core of atherosclerotic lesions, where they colocalize with specific markers of macrophages, smooth muscle cells and foam cells, has been described [15, 22, 26–28]. The third member of the PPAR family, PPARδ is expressed in a wide range of tissues including heart, adipose tissue, brain, intestine, muscle, spleen lung and adrenal glands [2, 5].

Regulation of PPAR expression by cytokines

Although PPAR expression is under the control of a wide variety of factors, more recently it has been demonstrated that different inflammatory cytokines, including TNFα, interleukin (IL)-1 α and β, IL-6 and leukemia inhibitory factor decrease PPARγ expression in mature rat adipocytes, an effect which was reversed after treatment with different glitazones [29]. By contrast, in monocytes and macrophages, IL-4, an interleukin which exerts an anti-inflammatory effect through macrophage inactivation, induces PPARγ1 expression [30]. In addition, in human macrophages, pro-inflam-

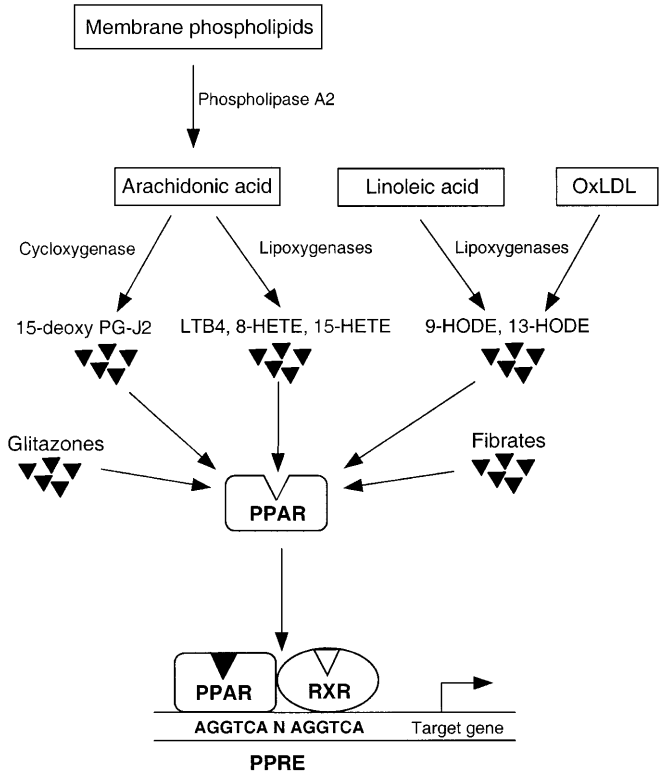

Fig. 1. Peroxisome proliferator-activated receptors: ligands and transcriptional activation. Upon activation, PPARs heterodimerize with the 9-cis retinoic acid receptor and bind to response elements (PPRE) located in the promoter of target genes thus regulating their transcription. Synthetic ligands and natural activators derived from fatty acids through the cycloxygenase and lipoxygenase pathways are represented.

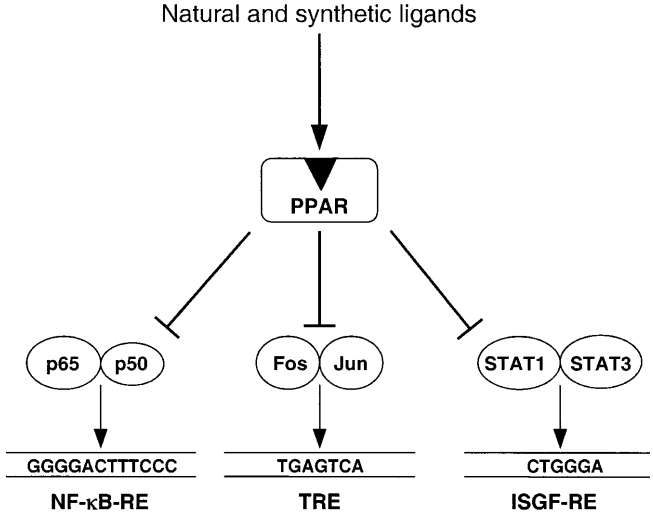

Fig. 2. Mechanism of transcriptional repression by peroxisome proliferator-activated receptors. PPARs repress gene transcription by negatively interfering with the NF-κB, AP-1 (Fos/Jun) and STAT signalling pathways in a DNA-binding independent manner. TRE: TPA-response element. ISGF-RE: interferon stimulated gene factor response element.

matory mediators derived from oxidized LDL (9- and 13-HODE) increase PPARγ mRNA levels [25].

Synthetic and natural ligands of peroxisome proliferator-activated receptors

PPARs are activated by a number of pharmacological compounds, as well as by fatty acids and fatty acid-derived molecules. PPARα is activated by naturally occuring eicosanoids derived from arachidonic acid through the lipoxygenase pathway, such as 8-S-hydroxyeicosatetraenoic acid (8S-HETE) and leukotriene B4 (LTB4) [31–33] and by OxLDL-derived oxidized phospholipids [34]. Moreover, fibrates, a class of first-line drugs in the treatment of hypertriglyceridemia and combined hyperlipidemia, are synthetic ligands for PPARα [32]. PPARγ can be activated by arachidonic acid-metabolites derived from the cycloxygenase and lipoxygenase pathways, such as 15-deoxy-Δ-12,14-prostaglandin J2 (PG-J2) and 15-HETE [35–37]. Recent findings have revealed a crucial role of 12/15-lipoxygenase in the generation of endogenous PPARγ ligands [30]. In addition, fatty acid-derived components of oxidized low density lipoproteins (OxLDL), such as 9-hydroxyoctadecadienoic acid (9-HODE) and 13-hydroxyoctadecadienoic acid (13-HODE) are natural ligands for PPARγ [37] (Fig. 1). Finally, the antidiabetic glitazones, currently used as insulin sensitizers, are synthetic high affinity ligands for PPARγ [38].

In addition to fibrates and glitazones, other pharmacological compounds have been identified as PPAR activators. Inhibition of cycloxygenase by NSAIDs (Non Steroidal Anti-Inflammatory Drugs) constitutes a clinical approach for the treatment of inflammatory states. Lehmann et al. [39] have demonstrated that certain NSAIDs, including indomethacin and ibuprofen, are activators of PPARγ acting in the micromolar range. These data are consistent with the observation that indomethacin can promote terminal adipocyte differentiation of various preadipocyte cell lines in vitro [40]. The molecular basis underlying this adipogenic action could thus be mediated via activation of PPARγ, a transcription factor with a pivotal role in adipogenesis. In addition, certain NSAIDs are also ligands for the PPARα form [39]. Several NSAIDs have marked effects on peroxisome activity in rodent hepatocytes when used either in vitro or in vivo [41, 42] and it appears likely that these effects are mediated by PPARα activation.

Peroxisome proliferator-activated receptors: nuclear receptors with functions in the metabolism of lipid mediators of inflammation

Fibrates are clinically used hypolipidemic drugs, which efficiently decreased plasma triglyceride levels and increase HDL cholesterol concentrations [43]. Using PPARα-deficient mice, the role of this receptor in HDL and triglyceride metabolism, as well as in hepatic regulation of apolipoprotein and fatty acid β-oxidation enzyme expression was unequivocally demonstrated [44, 45]. PPARα mediates the triglyceride-lowering action of fibrates by increasing lipoprotein lipase gene expression in a PPRE-mediated manner [46] and decreasing apo CIII levels [47], thus resulting in an enhanced lipolytic activity. By contrast, the antidiabetic agents glitazones, which are PPARγ ligands, decrease plasma triglyceride and free fatty acids levels by enhancing their catabolism via the induction of lipoprotein lipase gene expression in adipose tissue [48]. Several studies have demonstrated that in liver, PPARα regulates the oxidation of fatty acids. Numerous genes involved in these metabolic pathways, such as the β and ω-oxidation pathways present a PPRE in their promoter region and are under the transcriptional control of PPARα [6].

In addition to their effects on extra-cellular lipid metabolism, PPARs act also as regulators of cellular fatty acid uptake and control of their intracellular fate. Intracellular fatty acid concentrations are partly determined by a regulation of import and export system that is controlled by proteins such as fatty acid transport protein (FATP) [49] and fatty acid translocase (FAT/CD36) [25, 50]. It has been reported that the expression of long chain fatty acid transporters is induced in a tissue-dependent fashion in liver by PPARα and in adipose tissue by PPARγ activators [49, 51]. Once inside the cell, fatty acids must penetrate into the cellular organite, where their metabolism takes place. The expression of Acyl-CoA synthetase (ACS), an important enzyme for the fatty acid esterification, preventing their efflux from cells, is enhanced by fibrates in liver and kidney [49, 52]. Carnitine palmitoyltransferase type I (CPT-I), a key enzyme in mitochondrial fatty acid catabolism, contains a PPRE in its promoter region and is regulated by PPARα activators [53, 54]. Taken together, these observations indicate that PPARα controls fatty acid uptake, activation into acyl-CoA esters and degradation via the peroxisomal and mitochondrial β-oxidation pathways [6]. In addition to their effects on plasma fatty acid and triglyceride levels, these actions of PPARα may result in an enhanced degradation of lipid-derived inflammatory mediators through the β-oxidation pathways. In support for this hypothesis comes the observation that inflammation provoked by arachidonic acid or its derivative LTB4 is prolonged in mice with a target disruption of the PPARα gene [33]. Binding of the inflammatory mediator LTB4 to PPARα results in the activation of PPARα-mediated transcription of enzymes implicated in ω- and β-oxidation in liver. Via such feed-back mechanism, LTB4 and other fatty acid-derived compounds may induce their own catabolism through stimulation of PPARα. As a result of the activation of the β-oxidation pathways by PPARα, degradation of these fatty acids will result in the termination of an inflammatory status.

Peroxisome proliferation-activated receptors and inflammation control

Besides their crucial role in β-oxidation of fatty acids and arachidonic acid metabolites, PPARs also exert direct anti-inflammatory activities. The first evidence suggesting a potential implication of PPAR in inflammation came from the observation of an antagonism between PPARγ and the proinflammatory cytokine tumor necrosis factor alpha (TNFα) [55, 56]. In adipose tissue, TNFα inhibits adipogenesis via the downregulation of adipogenic factors such as C/EBPα and PPARγ, whereas intravenous injection of TNFα

into rats resulted in a decreased hepatic expression of PPARα [57]. Reduced PPARγ gene expression could represent an important component of the mechanism by which TNFα exerts its anti-adipogenic effects [55]. Interestingly, obesity states are associated with increased production of inflammatory cytokines, such as TNFα, in adipose tissue. Studies in obese rats showed that treatment with the synthetic and natural PPARγ ligands rosiglitazone and PG-J2 reduces TNFα expression levels in retroperitoneal and mesenteric white adipose tissues [58]. Taken together these data indicate an anti-inflammatory action of PPARs in adipose tissue.

PPARs and monocyte/macrophages

Both PPARα and PPARγ are expressed in differentiated human macrophages [9]. Although PPARγ has been suggested to promote monocyte-macrophage differentiation [25], it is unlikely that it is involved in the first steps of the differentiation process since PPARγ seems to be absent from isolated human monocytes [9]. Nevertheless, PPARs regulate monocyte/macrophage physiology, as well as their response to inflammatory stimuli within the arterial wall [9, 10, 26, 59]. Ricote et al. [10] reported that PPARγ is markedly upregulated in murine activated macrophages and that natural and synthetic PPARγ ligands inhibit the induction of inducible nitric oxyde synthase (iNOS), gelatinase B (MMP-9) and scavenger receptor A gene transcription. Promoter studies have revealed that PPARγ inhibits the transcriptional activity of these genes by interfering with the AP-1, NF-κB and STAT1 transcription factors [10]. Furthermore, Jiang et al. [59] have shown that incubation of human monocytes with the natural PPARγ ligand PG-J2 or with synthetic agonists, inhibits the production of proinflammatory cytokines, including TNFα, IL-1β, and IL-6. All these processes seem to be mediated at the transcriptional level, since PPARγ activators could inhibit TNFα promoter activity [59]. However, one caveat with respect to the interpretation of these studies is the fact that the most pronounced effects are observed with PG-J2, which may not be very selective for PPARγ and may also act through PPAR independent mechanisms [60, 61]. When more selective ligands, such as rosiglitazone are employed, extremely high concentrations are needed to obtain similar effects. This suggests that additional pathways may be involved in the responses to eicosanoids. In fact, recents observations indicate that PG-J2 exerts anti-inflammatory activities in a PPARγ-independent manner through the inhibition of IκB kinase [62, 63]. Additional evidence for a protective role of PPARs in the inflammatory response comes from experiments performed in activated RAW 264.7 murine macrophages [64], where natural PPARγ activators including PG-J2 and the synthetic PPARα ligand Wy14,643 reduce nitrite accumulation. By contrast, natural PPARα ligands LTB4 and 8(S)-HETE stimulate nitrite accumulation in these cells, indicating that they have proinflammatory properties [64]. Again, synthetic and natural ligands have distinct effects, which may be due to the low specificity of natural activators compared to the more selective synthetic compounds. In the same line, PG-J2 has been shown to suppress iNOS promoter activity and expression in a PPARγ-independent manner in murine and rat microglial cells and astrocytes [61]. These observations call for caution when interpreting results obtained using these natural fatty acid derivatives with respects to the role of PPARγ in their actions.

PPARs in atherosclerosis and vascular wall cell types

Atherosclerosis is a long-term process which involves recruitment and activation of different cell types, including monocyte/macrophages, endothelial cells, smooth muscle cells and T-lymphocytes in the intima of the arteries, thus leading to a local inflammatory response [65]. A role for PPARs in atherosclerosis is suggested by clinical observations indicating that fibrate treatment lowers progression of atherosclerotic lesions in humans, as well as in animal models [66–68]. In addition, the PPARγ activator troglitazone inhibits smooth muscle cell proliferation and decreases the intima and media thickness in human carotid arteries [69]. Recent studies on PPAR expression patterns have demonstrated that these transcription factors are expressed in cells within human and murine atherosclerotic lesions colocalizing with macrophages, smooth muscle and foam cells [26–28].

In the vascular wall, PPARs interfere with chemo-attraction and cell adhesion of monocytes, T-lymphocytes and eosinophils. In human endothelial cells, glitazones inhibit the expression of monocyte-chemoattractant protein-1 (MCP-1) at the transcriptional level [70], one of the key factors initiating the inflammatory process of atherogenesis (Fig. 3). In addition, these compounds inhibit the expression of the chemokine RANTES in a human lung epithelial cell line [71]. PPAR activators furthermore inhibit cytokine-induced vascular cell adhesion molecule-1 (VCAM-1) [15, 72], an adhesion molecule critical for leukocyte recruitment to atherosclerotic lesions (Fig. 3). The reduction of VCAM-1 expression by PPARα activators occurs at the transcriptional level, at least in part by inhibiting NF-κB activity [15]. Since VCAM-1 and MCP-1 are involved in monocyte recruitment to early atherosclerotic lesions, these findings suggest that PPARs inhibit early processes in atherosclerotic lesion development (Fig. 3). In endothelial cells, both PPARα and PPARγ ligands repress thrombin-induced expression of endothelin-1 (ET-1), a potent vasoconstrictor peptide and inducer of smooth muscle cell proliferation [13, 73]. PPAR agonists exert their activities on ET-1 expression by negatively interfering with AP-1 DNA binding activities [13].

PPARs are also involved in the formation and function of foam cells. Nagy and collaborators [37] described a metacrine regulatory pathway in which OxLDL and the oxidized fatty acids therein may promote foam cell formation and macrophage gene expression through PPARγ activation [37]. The OxLDL-derived 9- and 13-HODE activate PPARγ in monocytes and monocytic cell lines resulting in a PPRE-mediated induction of the expression of the OxLDL receptor CD36, thus initiating a positive feed-back loop for monocyte activation and foam cell formation [25] (Fig. 3). Besides their effects on CD36 regulation, in differentiated human macrophages PPAR ligands furthermore induce the expression of CLA-1/SR-BI, a scavenger receptor implicated in cholesterol efflux [28]. In addition, PPARs induce macrophage lipoprotein lipase expression, but reduce its enzyme

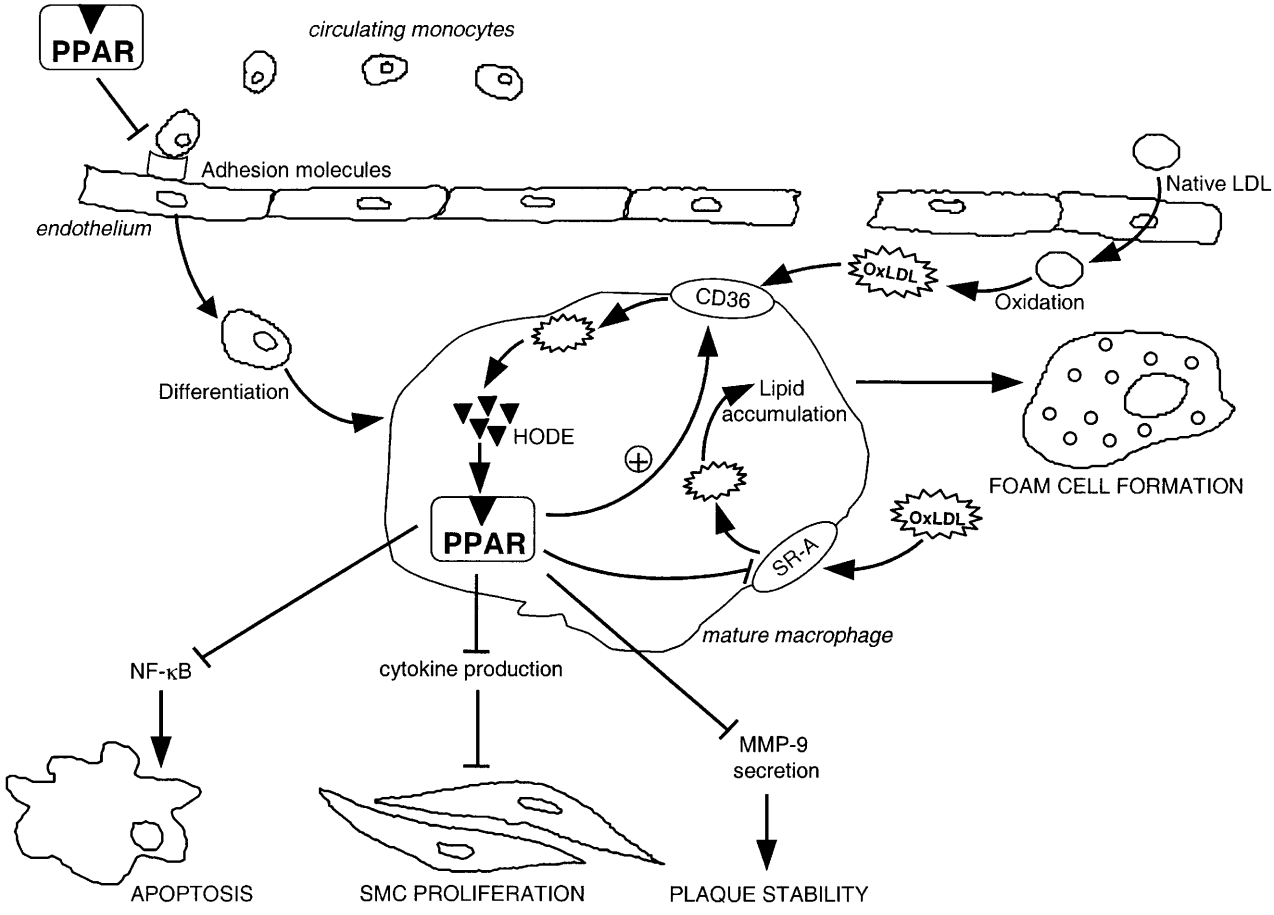

Fig. 3. PPARs control macrophage functions during atherosclerosis development. PPAR activation controls the expression of genes implicated in monocyte adhesion, lipid accumulation (such as CD36 and SR-A), apoptosis, vascular inflammation (cytokines) and plaque stability (MMP-9), thus modulating atherosclerotic lesion development.

activity [74]. Taken together these observations indicate a role of PPAR activators in macrophage cholesterol and fatty acid homeostasis with likely consequences in foam cell formation and atherosclerosis progression.

In macrophages, PPARγ activators also reduce the secretion and gelatinolytic activity of the metalloproteinase MMP-9, also referred to as gelatinase B [24, 26]. This enzyme, which is secreted in response to inflammatory cytokines found in atheroma, plays a pivotal role in the degradation of extracellular matrix, with consequences in atherosclerotic plaque rupture and thrombosis (Fig. 3). These observations support the previously reported results indicating that PPARγ agonists inhibit the induction of MMP-9 promoter activity [10].

PPARs also regulate smooth muscle cell function. In human aortic smooth muscle cells, fibrates prevent IL-1-induced secretion of IL-6 and 6-keto-$PGF_{1\alpha}$. These drugs act by inhibiting the expression of inducible COX-2 at the transcriptional level through a negative regulation of NF-κB activity [11]. In rat vascular smooth muscle cells, troglitazone inhibited the degradation of iNOS mRNA [75]. However, since no expression of PPARγ was detected in this cellular model, the results suggest that troglitazone acts in a PPARγ-independent manner. By contrast, in rat aortic smooth muscle cells which express PPARγ, PG-J2 and 9-HODE induced the expression of type II-secreted phospholipase A_2 (type II-$sPLA_2$) in which a PPRE has been identified in the promoter [76], an enzyme implicated in the hydrolysis of phospholipids, thus generating lipid inflammatory mediators such as lysophosphatidic and arachidonic acids. Since it has been reported that type II-$sPLA_2$ increases lipoxygenase-induced HODE production from LDL [77], this observation raises the possibility that type II-sPLA2-induced HODE synthesis constitutes a positive autocrine loop in the aorta during inflammatory states.

PPARs and the regulation of hemostatic factors and acute phase proteins

Acute coronary events are provoked by a dysbalance of pro- and anti-thrombotic factors. Recently, Marx et al. [22] reported that treatment of human saphenous vein endothelial cells with natural fatty acid-derived PPARγ activators (PG-J2, 9 and 13-HODE) increases the expression of plasminogen activator inhibitor type 1 (PAI-1), a member of the serine protease inhibitor family which limits fibrinolysis and promotes thrombosis. However, troglitazone and pioglitazone, synthe-

tic PPARγ ligands, down-regulate PAI-1 expression in human umbilical vein endothelial cells (HUVEC) [78]. Furthermore, troglitazone markedly reduced blood levels of PAI-1 in patients affected by the polycystic ovary syndrome [79]. The discrepancy between both studies may be related to differences in cell type or to the higher-mentionned problems of interpretation of results obtained using less specific natural ligands, compared to synthetic ligands. When the influence of PPARα activators on PAI-1 production was tested in cynomolgus monkey hepatocytes no correlation between the inhibition of PAI-1 production and PPARα transactivation activity was observed [80]. In human endothelial cell lines low concentrations of clofibric acid and bezafibrate increase PAI-1 transcription and secretion, whereas fenofibric acid and gemfibrozil markedly decrease PAI-1 [81]. Clinical studies reported that gemfibrozil and bezafibrate increase plasma PAI-1 levels [82], whereas ciprofibrate did not modify its plasma concentrations [83]. Clearly, the role of PPARs in the regulation of PAI-1 expression requires further studies.

In clinic, administration of fenofibrate to patients with mild hyperlipidemia resulted in decreased plasma concentrations of IL-6. Furthermore, fenofibrate significantly lowered plasma levels of fibrinogen and C-reactive protein (CRP) which are established risk factors for cardiovascular disease and whose production is controlled by cytokines [11]. Furthermore, in patients with hyperlipoproteinemia type IIb, fenofibrate treatment decreased plasma TNFα and IFNγ levels [84]. Taken together, these data indicate that PPARα activators exert anti-inflammatory activities in humans in vivo.

PPARs in epithelial cells and inflammatory bowel diseases

In contrast to human smooth muscle cells [11], fatty acid metabolites and NSAIDs, including PG-J2 and indomethacin, as well as the PPARα ligand Wy14,643 induce COX-2 transcription in epithelial cells (mammary and colon) [85]. One possible explanation for the differences observed between epithelial and smooth muscle cells may be related to differences in origin. Alternatively, PPAR activators may inhibit COX-2 activation through negative interference with NF-κB activation [11] and induce its expression through a classical PPRE-mediated mechanism [85]. The predominant response could be tissue-specific, but may also depend on kinetics, since trans-repression occurs immediately, whereas induction via a PPRE may be slower. Regulation of COX-2 by PPARγ agonists has also been studied in colon cancer models [86]. Activation of PPARγ did not affect COX-2 expression either in mouse adenomas in vivo or in human colon carcinoma cell lines although colon tumor formation was induced. Thus, PPARγ activators could alter colon epithelial cell function in a COX-2 independent manner, whereas PPARα agonists could induce transcription of COX-2 in epithelial cells. In patients affected by Crohn's disease, which present a mesenteric adipose tissue hypertrophy, adipocyte PPARγ and TNFα expression levels are elevated [87]. These results suggest that confined increased PPARγ concentrations could lead to mesenteric fat hypertrophy, resulting in an enhanced synthesis of TNFα and a local inflammatory reaction [87]. More recently, PPARγ activators have been shown to inhibit the epithelial inflammatory response in an animal model of colitis [88]. In colon cancer cell lines, PG-J2 and rosiglitazone inhibit IL-1β-induced expression of IL-8, likely by preventing NF-κB activation via an IκB-α-dependent mechanism. Although the authors did not exclude the possibility that a component of the anti-inflammatory effect of PPARγ ligands could be mediated via the systemic immune system, they concluded that PPARγ activators protect against inflammatory bowel disease.

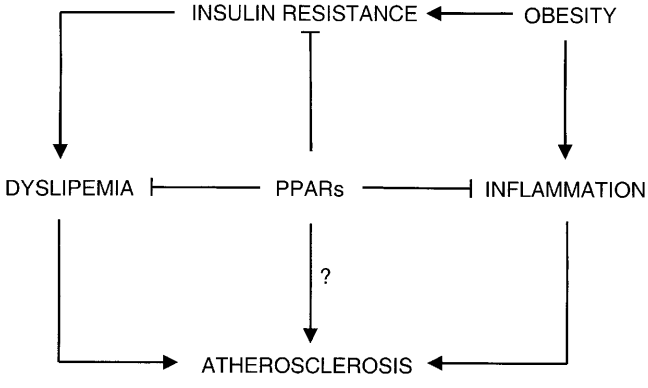

Fig. 4. Role of peroxisome proliferator-activated receptors (PPARs) in metabolic and inflammation-related disorders. PPARs are negative regulators of insulin resistance, dyslipemia and inflammatory response, with likely consequences in atherosclerosis development.

Conclusion

Our knowledge of the physiological functions of the PPAR transcription factors has enormously progressed in the last three years. Known at the beginning as regulators of lipid and lipoprotein metabolism, more recently PPARs have been identified as important players in the metabolism of lipid-derived inflammatory mediators and in inflammation-related pathologies, such as atherosclerosis and inflammatory bowel disease. These observations indicate that PPARs could mediate the modulation of immune cell activation by pharmacological and nutritional products.

Acknowledgements. We thank members of the B. Staels laboratory for critical reading of the manuscript and helpful discussions. Support of grants from the Fondation pour la Recherche Médicale (to GC), the Laboratoires Fournier, ARCOL and the European Community (grant QLRT-1999-01007) is kindly acknowledged.

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