EUROSTERONE MEETING

Peroxisome proliferator-activated receptors in inflammation control

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. PPARα is highly expressed in liver, skeletal muscle, kidney, heart and the vascular wall. PPARγ is predominantly detected in adipose tissue, intestine and macrophages. PPARs are activated by fatty-acid derivatives and pharmacological agents such as fibrates and glitazones which are specific for PPARα and PPARγ respectively. PPARs regulate lipid and lipoprotein metabolism, glucose homeostasis, cell proliferation and differentiation, and apoptosis. PPARα controls intra- and extracellular lipid metabolisms whereas PPARγ triggers adipocyte differentiation and promotes lipid storage. In addition, PPARs also modulate the inflammatory response. PPAR activators have been shown to exert anti-inflammatory activities in various cell types by inhibiting the expression of proinflammatory genes such as cytokines, metalloproteases and acute-phase proteins. PPARs negatively regulate the transcription of inflammatory response genes by antagonizing the AP-1, nuclear factor-κB (NF-κB), signal transducer and activator of transcription and nuclear factor of activated T-cells signalling pathways and by stimulating the catabolism of proinflammatory eicosanoids. These recent findings indicate a modulatory role for PPARs in inflammation with potential therapeutical applications in chronic inflammatory diseases.

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Introduction

Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily which are ligand-activated transcription factors (Issemann & Green 1990). To date, three different PPAR subtypes have been identified: PPARα, PPARβ (NUC-1 or PPARδ) and PPARγ. PPARs are activated by natural ligands such as fatty acids, eicosanoids and oxidized fatty acids (Kliewer *et al.* 1995, Devchand *et al.* 1996, Forman *et al.* 1997, Nagy *et al.* 1998, Delerive *et al.* 2000*a*). Furthermore, the lipid-lowering fibrates and the anti-diabetic glitazones are synthetic ligands for PPARα and PPARγ respectively (Lehmann *et al.* 1995, Forman *et al.* 1997). PPARs regulate gene expression by binding with retinoid X receptor (RXR) as a heterodimeric partner to specific DNA sequence elements termed PPAR response elements (PPRE) (Fig. 1) (Tugwood *et al.* 1992). PPREs consist of a direct repeat of the nuclear receptor hexameric AGGTCA recognition sequence separated by one or two nucleotides (DR-1 and DR-2) (Ijpenberg *et al.* 1997, Gervois *et al.* 1999). PPARs have been reported to be involved in lipid and lipoprotein metabolism, glucose homeostasis, cell proliferation and differentiation, and apoptosis (for review see Desvergne & Wahli 1999). It has recently been demonstrated that PPARs may also play a role in the control of the inflammatory response. In this review, we will focus on the new insights indicating the implication of PPARα and PPARγ in inflammation control and discuss our current understanding of the molecular mechanisms by which they regulate the expression of inflammatory response genes.

PPARα in inflammation: from bench to bedside

The first evidence indicating a potential role for PPARs in the inflammatory response was the demonstration that leukotriene B4 (LTB4), a proinflammatory eicosanoid, binds to PPARα and induces the transcription of genes involved in ω- and β-oxydation which leads to the induction of its own catabolism (Devchand *et al.* 1996). Using the mouse ear-swelling test, these authors showed that the duration of the inflammatory response is prolonged in PPARα-deficient mice in response to LTB4 (Devchand *et al.* 1996). Several recent studies have been

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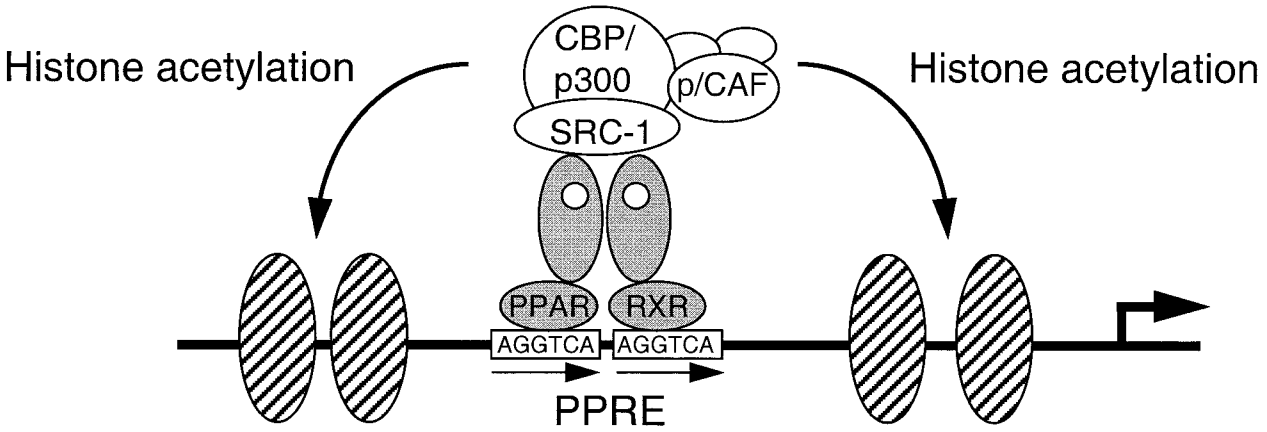

Figure 1 Mechanism of transcriptional activation by PPARs. p/CAF, p300/cyclic AMP-responsive element binding protein (CRES) binding protein-associated factor.

aimed at delineating the cellular and molecular mechanisms explaining the control of the inflammatory response by PPARα. In primary aortic smooth muscle cells which express substantial amounts of PPARα, it was demonstrated that PPARα ligands inhibit interleukin (IL)-1β-induced IL-6 secretion as well as 6-keto-prostaglandin (PG) $F_{1\alpha}$ production. In addition, PPARα agonists have been reported to decrease cytokine-induced genes, such as expression of vascular cell adhesion molecule-1 and tissue factor in endothelial cells and monocytes respectively (Marx *et al.* 1999, Neve *et al.* 2001). Subsequently, it was shown that PPARα acts by down-regulating the transcription of these genes (Staels *et al.* 1998, Delerive *et al.* 1999*a*). *In vivo* evidence for an anti-inflammatory action of PPARα in the vascular wall came with the demonstration that aortas from PPARα-deficient mice displayed an exacerbated inflammatory response to lipopolysaccharide stimulation (Delerive *et al.* 1999*a*). Furthermore, fibrates did not affect LPS-induced IL-6 transcription in PPARα-deficient mice, demonstrating that the anti-inflammatory activities of these agonists require PPARα expression *in vivo*. In addition, Poynter & Daynes (1998) reported that PPARα-deficient splenocytes produced, in response to lipopolysaccharide (LPS) stimulation, two to three times more IL-6 and IL-12 than splenocytes from wild-type mice. Finally, fibrates were shown to repress the expression of a number of acute-phase proteins in liver, such as fibrinogen, in a PPARα-dependent manner (Kockx *et al.* 1999). Taken together, these observations provide evidence that PPARα plays a role in the inflammatory response at the vascular, splenic and hepatic level.

Studies addressing the molecular mechanisms of this anti-inflammatory action demonstrated that PPARα negatively interferes with the inflammatory response by antagonizing the nuclear factor-κB (NF-κB) signalling pathway (Poynter & Daynes 1998, Staels *et al.* 1998, Delerive *et al.* 1999*a*, Marx *et al.* 1999). In fact, a bidirectional antagonism between the PPARα and NF-κB signalling pathways exists (Delerive *et al.* 1999*a*). PPARα overexpression inhibits NF-κB-driven gene transcription and co-transfection of increasing amounts of p65 led to a dose-dependent inhibition of a PPAR response element (PPRE)-driven promoter construct. Glutathion-S-transferase (GST) pull-down assays revealed that PPARα physically interacts with p65 via its Rel homology domain which mediates homo- and heterodimerization and interaction with inhibitor of NFκB (IκB) (Delerive *et al.* 1999*a*). Since PPARα-mediated inhibition of NF-κB-driven gene transcription becomes more and more important upon longer exposure to PPARα ligands, we speculated that a complementary mechanism might exist. NF-κB activity is tightly controlled by the degradation of IκBα which sequesters inactive NF-κB dimers in the cytoplasm. Interestingly, PPARα activators were found to induce IκBα mRNA and protein expression in primary smooth muscle cells and hepatocytes (Delerive *et al.* 2000*b*). IκBα induction by fibrates again requires PPARα expression. Surprisingly, IκBα induction did not affect p65 nuclear translocation but was associated with reduced NF-κB DNA-binding activity (Delerive *et al.* 2000*b*). Western blot analysis revealed that IκBα protein induction occurs mainly in the nucleus which may provide an explanation for the reduced NF-κB-binding activity (Delerive *et al.* 2000*b*). The induction of IκBα by fibrates in cytokine-activated cells should therefore result in an acceleration of NF-κB nuclear deactivation. In line with this observation, the increase of IκBα protein after treatment with PPARα activators would lead to a halt in p65-mediated gene activation, thereby reducing the duration of the inflammatory response. This is consistent with a previous report in which PPARα ligands were shown to affect the duration of the inflammatory response in a PPARα-dependent manner (Devchand *et al.* 1996). In view of these results, we propose a model in which

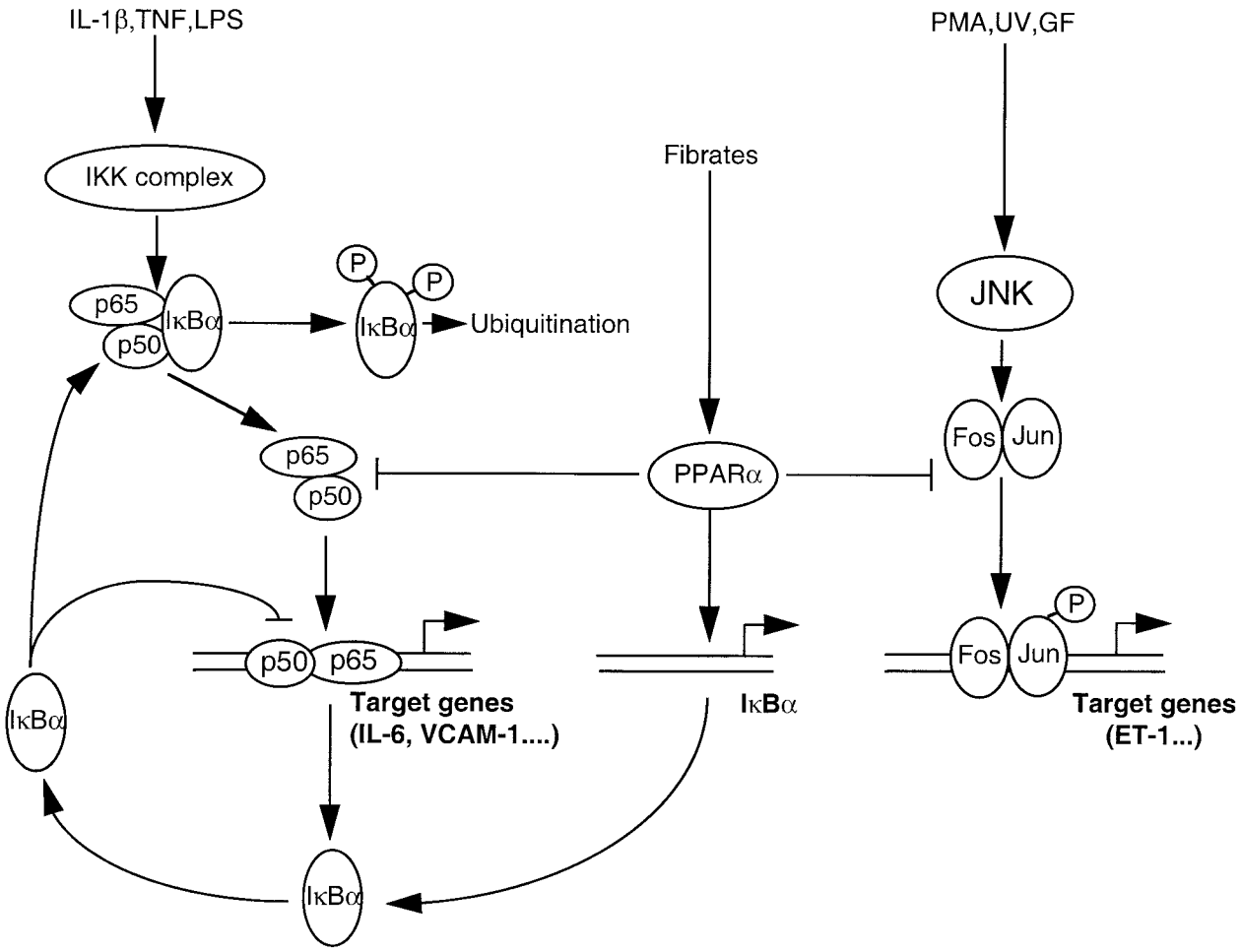

Figure 2 Mechanisms of PPARα-mediated inhibition of the AP-1 and NF-κB signalling pathways. P, ; UV, ; GF, ; ET-1, endothelin-1.

PPARα negatively interferes with NF-κB transcription activity by forming inactive complexes with p65 and by inducing IκBα, the major inhibitor of NF-κB signalling (Fig. 2). Chromatin immunoprecipitation experiments revealed that the glucocorticoid receptor antagonizes NF-κB transcriptional activity by interfering with phosphorylation of the serine-2 of the carboxy-terminal domain of the RNA polymerase II without affecting NF-κB DNA-binding activities, although the glucocorticoid receptor strongly interacts with p65 (Nissen & Yamamoto 2000). It would be of interest to determine whether such a mechanism is also operative for PPARα using the same technical approach. However, we cannot exclude the existence of additional mechanisms. For instance, PPARα was reported to play a major role in the control of the cellular redox status (Poynter & Daynes 1998). Moreover, Klucis *et al.* (1984) reported that administration of PPARα activators results in a drastic increase of the activity of catalase, an antioxidant enzyme. Finally, catalase activity and expression were found to be increased in endothelial cells upon fibrate treatment (C Furman, E Teissier, B Staels & P Duriez, unpublished observations) (data not shown). A potential involvement of catalase in the control of NF-κB-driven transcription by PPARα activators is under investigation in our laboratory.

Promoter analysis revealed that PPARα controls IL-6 transcription by negatively interfering not only with NF-κB but also with AP-1 transcriptional activities (Delerive *et al.* 1999*a*). GST pull-down experiments as well as electrophoretic mobility shift assays demonstrated that PPARα activators reduce AP-1 DNA-binding activity by physically interacting with the amino-terminal domain of c-Jun (Delerive *et al.* 1999*a*,*b*) (Fig. 2). Since most of the proinflammatory genes are under the control of the AP-1 and NF-κB signalling pathways, it is likely that PPARα agonists regulate a wide spectrum of genes involved in inflammatory disorders.

One of the most relevant indications regarding a role of PPARα agonists in inflammation control comes from

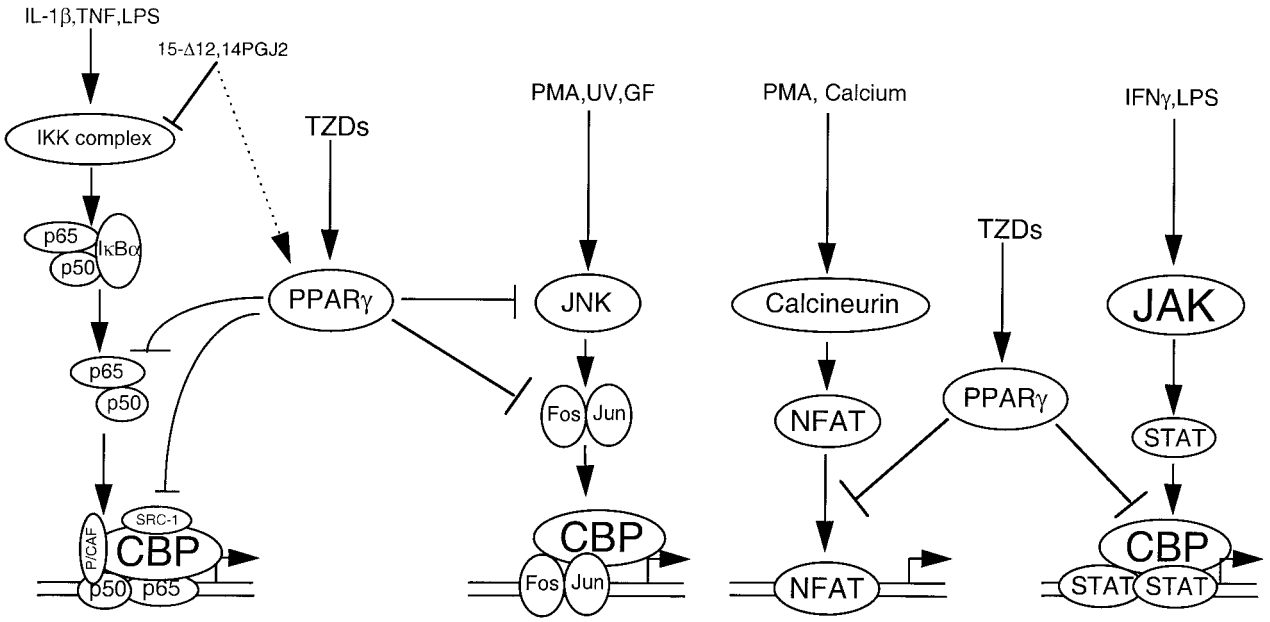

Figure 3 Hypothetical model of PPARγ-mediated inhibition of the inflammatory response genes. PPARγ antagonizes the AP-1, NF-κB, STAT and NFAT signalling pathways. TZDs, thiazolidinediones; JAK, Janus kinase.

clinical trials. The influence of PPARα activators on plasma cytokine levels as well as on acute-phase proteins was determined in patients with angiographically established atherosclerosis (Staels *et al.* 1998). Fibrate treatment for 4 weeks (200 mg daily) reduced IL-6, C-reactive protein and fibrinogen levels in patients with coronary artery disease (Staels *et al.* 1998). Another group reported independently that fenofibrate treatment for 1 month resulted in a significant reduction of plasma interferon-γ (IFNγ) and tumour necrosis factor-α (TNFα) levels in patients with hyperlipoproteinaemia type IIb (Madej *et al.* 1998). These two reports demonstrate that PPARα activators decrease inflammation in patients, thus indicating a potential use of PPARα agonists in the treatment of chronic inflammatory diseases.

Is there a role for PPARγ in inflammation?

A growing body of evidence suggests that PPARγ may also play a role in inflammation. PPARγ ligands were shown to inhibit TNFα, IL-6 and IL-1β expression in monocytes (Jiang *et al.* 1998); inducible nitric oxide synthase (iNOS), matrix metalloprotease-9 (MMP-9) and scavenger receptor-A expression in macrophages (Ricote *et al.* 1998); IFN-inducible protein 10, monokine induced by inteferon gamma, inteferon gamma inducible T-cell alpha chemoattractant and endothelin-1 expression in endothelial cells (Delerive *et al.* 1999*b*, Marx *et al.* 2000); IL-2 in T lymphocytes (Yang *et al.* 2000) and IL-8 in colonic epithelial cells (Su *et al.* 1999). Huang *et al.* (1999) demonstrated that IL-4 induces the generation of endogenous ligands for PPARγ through activation of the 12/15-lipoxygenase pathway in macrophages, providing a molecular basis for IL-4-mediated down-regulation of iNOS expression. PPARγ ligands inhibit the expression of these genes at the transcriptional level. However, one caveat with respect to the interpretation of these studies is the fact that the most pronounced effects were observed with 15-deoxy-Δ12,14-PGJ2 which is not a very selective PPARγ ligand. Moreover, when high affinity PPARγ ligands such as rosiglitazone are used extremely high concentrations (>200 kDa) are required to obtain anti-inflammatory activities (Jiang *et al.* 1998, Ricote *et al.* 1998). These pharmacological discrepancies suggested that 15-deoxy-Δ12,14-PGJ2 may act through PPARγ-independent pathways. Several recent reports indeed demonstrated that, in the absence of PPARγ expression, 15-deoxy-Δ12,14-PGJ2 also negatively regulates the inflammatory response (Petrova *et al.* 1999, Vaidya *et al.* 1999). Two groups demonstrated independently that 15-deoxy-Δ12,14-PGJ2 represses NF-κB activation by inhibiting the IKB-kinase (IKK) complex activity (Castrillo *et al.* 2000, Rossi *et al.* 2000) thereby preventing IκBα degradation. Straus *et al.* (2000) showed that, in addition to inhibiting IKK activity, 15-deoxy-Δ12,14-PG-J2 probably reduces NF-κB binding by alkylating p50/p65 dimers (Straus *et al.* 2000). 15-deoxy-Δ12,14-PGJ2 appears thus to inhibit NF-κB activation at different levels and may thus exert its activities in both a PPARγ-dependent and -independent manner.

The molecular mechanisms by which PPARγ regulates inflammatory response genes are not fully understood (Fig. 3).

Using transient transfection experiments, Ricote *et al.* (1998) demonstrated that PPARγ inhibits scavenger receptor-A, iNOS and MMP-9 expression by antagonizing the AP-1, signal transducer and activator of transcription (STAT) and NF-κB pathways. In a recent paper, it was demonstrated that, similar to that reported for PPARα (Delerive *et al.* 1999*a*), PPARγ inhibits NF-κB-driven transcription by physically interacting with both p65 and p50 (Chung *et al.* 2000). Using endothelin-1 promoter as a model, we demonstrated that PPARγ inhibits AP-1 transcriptional activity by reducing AP-1 DNA binding (Delerive *et al.* 1999*b*). This inhibition is likely due to a direct interaction between PPARγ and c-Jun as previously reported for PPARα (Delerive *et al.* 1999*a*). Law *et al.* (1996) reported that glitazones inhibit c-Fos transcription in vascular smooth muscle cells, resulting in a reduction of cell proliferation and migration. The same group demonstrated that glitazones inhibit angiotensin II but not TNFα-mediated extra-cellular signal-regulated kinase 1/2 activation in vascular smooth muscle cells (Goetze *et al.* 1999*a*,*b*). We also demonstrated, in a model of cardiac ischemia reperfusion, that rosiglitazone significantly reduces c-Jun-NH_2-terminal kinase (JNK) activation *in vivo* (N Khandoudi, P Delerive, B Staels & A Bril, unpublished observations). Previous reports suggested that nuclear receptors may regulate AP-1 activation by modulating JNK function (Caelles *et al.* 1997, Srivastava *et al.* 1999). However, little is known about the molecular mechanism of kinase inhibition by nuclear receptors.

Li *et al.* (2000*b*) recently proposed a model for PPARγ-mediated inhibition of iNOS transcription. In this model, PPARγ would inhibit STAT1, AP-1 and NF-κB transcriptional activities by targeting CBP through direct interaction with its N-terminal domain and via SRC-1-like bridge factors (Li *et al.* 2000*b*). Such a model of competition for limiting amounts of co-activators to inhibit transcriptional activation has already been proposed for other nuclear receptors (Kamei *et al.* 1996, Göttlicher *et al.* 1998, Sheppard *et al.* 1998). However, recent reports do not support this model of transrepression (De Bosscher *et al.* 2000, McKay & Cidlowski 2000).

Finally, Yang *et al.* (2000) showed that PPARγ activation results in a reduction of IL-2 secretion in T lymphocytes. Using electrophoretic mobility shift assays and immunoprecipitation experiments, these authors demonstrated that this inhibition was due to a ligand-dependent interaction between the transcription factor nuclear factor of activated T-cells (NFAT) and PPARγ (Yang *et al.* 2000). Further studies will be required to elucidate the precise molecular mechanisms of PPARγ-mediated NF-κB, AP-1 and STAT1 transcriptional inhibition.

Having established a role for PPARγ in inflammation *in vitro*, a number of groups carried out *in vivo* studies to assess the potential use of glitazones as anti-inflammatory drugs (Wiesenberg *et al.* 1998, Su *et al.* 1999, Thieringer *et al.* 2000). Using a mouse model of inflammatory bowel disease, Su *et al.* (1999) demonstrated that glitazones markedly reduce colonic inflammation. In a mouse model of atherosclerosis, Li *et al.* (2000*a*) demonstrated that glitazones reduce TNFα and gelatinase B gene expression in the aortic root. In contrast to these data, other reports indicated that IL-6 and TNF levels were not affected by glitazone treatment in *db/db* mice in response to LPS challenge (Thieringer *et al.* 2000). These authors also showed that PPARγ ligands, even if used at high concentrations, were ineffective in reducing cytokine levels in monocytes and macrophages (Thieringer *et al.* 2000), raising significant doubts about the potential utility of PPARγ ligands as anti-inflammatory drugs. In a chronic autoimmune model, rosiglitazone was again inactive in reducing the development and the progression of arthritis (Wiesenberg *et al.* 1998). These apparently conflicting results may reflect the heterogeneity of the different animal models used in these various studies. Additional *in vivo* studies are necessary to determine whether glitazones possess anti-inflammatory activities *in vivo*.

Conclusion

Even though PPARs are considered as master regulators of energy homeostasis, their role no longer seems to be restricted to controlling lipid storage and usage. PPARs may mediate the modulation of the inflammatory response by nutritional and pharmacological stimuli. From a nutritional point of view, additional studies will be necessary to determine whether the beneficial effects of certain dietary fatty acids on immune response are PPAR-mediated and whether PPAR activation will result in a permanent or transient reduction of the inflammatory status. From a pharmacological point of view, clinical studies with the recently launched glitazones should allow determination as to whether these drugs, similar to PPARα ligands, exert anti-inflammatory activities *in vivo* in humans. Our current knowledge, derived mainly from *in vitro* data, allows us to speculate that PPAR ligands may indeed be useful for the treatment of chronic inflammatory diseases such as atherosclerosis and rheumatoid arthritis.

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