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Advances in understanding the regulation of apoptosis and mitosis by peroxisome-proliferator activated receptors in pre-clinical models: relevance for human health and disease

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Abstract

Peroxisome proliferator activated receptors (PPARs) are a family of related receptors implicated in a diverse array of biological processes. There are 3 main isotypes of PPARs known as PPARα, PPARβ and PPARγ and each is organized into domains associated with a function such as ligand binding, activation and DNA binding. PPARs are activated by ligands, which can be both endogenous such as fatty acids or their derivatives, or synthetic, such as peroxisome proliferators, hypolipidaemic drugs, anti-inflammatory or insulin-sensitizing drugs. Once activated, PPARs bind to DNA and regulate gene transcription. The different isotypes differ in their expression patterns, lending clues on their function. PPARα is expressed mainly in liver whereas PPARγ is expressed in fat and in some macrophages. Activation of PPARα in rodent liver is associated with peroxisome proliferation and with suppression of apoptosis and induction of cell proliferation. The mechanism by which activation of PPARα regulates apoptosis and proliferation is unclear but is likely to involve target gene transcription. Similarly, PPARγ is involved in the induction of cell growth arrest occurring during the differentiation process of fibroblasts to adipocytes. However, it has been implicated in the regulation of cell cycle and cell proliferation in colon cancer models. Less in known concerning PPARβ but it was identified as a downstream target gene for APC/β-catenin/T cell factor-4 tumor suppressor pathway, which is involved in the regulation of growth promoting genes such as c-*myc* and cyclin D1. Marked species and tissue differences in the expression of PPARs complicate the extrapolation of pre-clinical data to humans. For example, PPARα ligands such as the hypolipidaemic fibrates have been used extensively in the clinic over the past 20 years to treat cardiovascular disease and side effects of clinical fibrate use are rare, despite the observation that these compounds are rodent carcinogens. Similarly, adverse clinical responses have been seen with PPARγ ligands that were not predicted by pre-clinical models. Here, we consider the response to PPAR ligands seen in pre-clinical models of efficacy and safety in the context of human health and disease.

Introduction

The evaluation of the safety of drugs is a vital but complex process. Normally, candidate drugs are tested in a range of *in vivo* and *in vitro* pre-clinical models that serve to evaluate genotoxicity, general toxicity, reproductive toxicology and cardiovascular safety. *In vivo* studies use both rodent

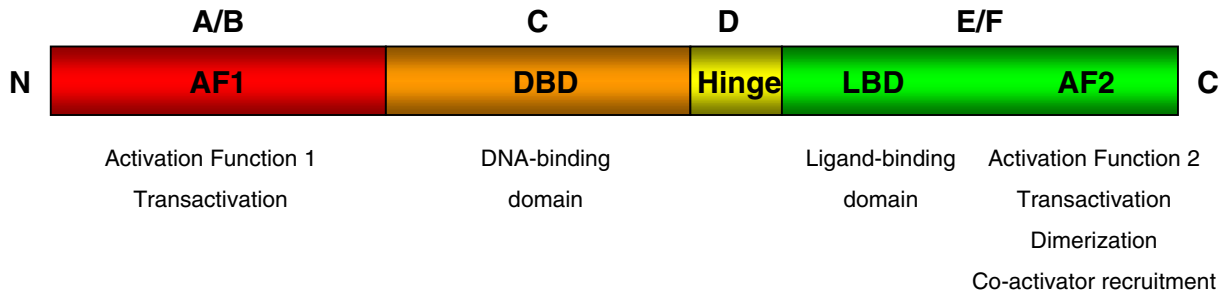

Figure 1
A schematic illustration of the domain structure of PPARs. The most conserved region is C, which consists of a highly conserved DNA-binding domain. The E/F domain is the ligand-binding domain, which contains the AF2 ligand-dependent activation domain. The amino-terminal A/B domain contains the AF1 ligand-independent activation domain. The D domain consists of a highly flexible hinge region.

and non-rodent animal dosing models depending on the endpoint and the compound characteristics. Although such models provide useful information, for some classes of compounds, the rodent models are poor predictors of human response, in some cases due to marked species differences in expression of the target receptors. For example, the family of peroxisome proliferator activated receptors (PPARs) display differences in expression and activation profiles between rodents and humans making the rodent models poor predictors of human response. However, this receptor family is an excellent drug target since the different isotypes PPARα, PPARβ and PPARγ play a central role in coordinating energy balance. Thus, PPARα ligands are hypolipidaemic and PPARγ ligands are insulin sensitizers with efficacy in type II diabetes. Here, we consider the response to PPAR ligands seen in pre-clinical models of efficacy and safety in the context of human health and disease.

Peroxisome proliferator-activated receptors: structure, ligands, expression and target genes

Structure

PPARs are ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily, together with the receptors for thyroid hormone, retinoids, steroid hormones and vitamin D. According to the recently proposed nomenclature of nuclear hormone receptors [1,2], PPARs form the group C in the subfamily 1 of the superfamily of nuclear hormone receptors, i.e., NR1C. PPARs occur in three different isotypes, namely PPARα (NR1C1), PPARβ (also called PPARδ, NUC-1 or FAAR), and PPARγ (NR1C3). These receptors have been found in various species such as cyclostoma [3], teleosts [3], amphibians [3], rodents [4] and humans [5–7]. There are three isoforms of PPARγ [8]; PPARγ1 and PPARγ3 are identical when fully translated and only differ in their splice variants, whereas PPARγ2 differs from the other isoforms in its N-terminus [9]. The PPAR nomenclature for PPARβ and PPARγ is a misnomer, since neither of these PPAR isotypes has been associated with peroxisome proliferation.

PPARs are typically organized in main structural and functional domains (Fig. 1): A/B, C, D, and E/F [10,11]:

The amino-terminal A/B region encodes a ligand-independent transcriptional activation domain (activation function-1) that is active in some cell types. The region is poorly conserved between the three PPAR isotypes. It has been shown that its phosphorylation state contributes to the modulation of PPARα and γ activity, by affecting the receptor/ligand affinity: insulin enhances transcriptional stimulation by human PPARα *via* phosphorylation of the conserved MAP-kinase sites Ser12 and Ser21 in the A/B domain [12,13], whereas MAP-kinase mediated phosphorylation of Ser112 of mouse PPARγ2 lowers transcriptional activity [14,15].

The ligand binding domain (LBD), or E/F domain of PPARs, is responsible for ligand-binding and converting PPARs to an active form that binds DNA and modulates gene expression. The interaction of PPARs with their ligands, because of the conformational changes that are induced especially involving the transactivation domain (activation function-2, AF-2) located in the C-terminal α-helix, allows recruitment of co-activators, such as the steroid receptor coactivator-1 [16,17], the CREB-binding protein CBP/P300 [18], the tuberous sclerosis gene 2 product [19], the PPAR binding protein [20], PGC-1 [21], PGC-2 [22], Ara70 [23], and the release of corepressors, such as the nuclear receptor corepressors (or RXR-interacting protein 13) and the silencing mediator for retinoid and thyroid hormone receptors [18,24,25]. When co-transfected into cell lines, COUP-TFI [26] and COUP-TFII (also called ARP-1) [27] block PPAR action by binding specific DNA sequences in PPAR target genes called peroxisome proliferator responsive elements (PPREs). In addition, the E region is also important in nuclear localization and dimerization of the receptor. Indeed, dimerization is essential for the activity of PPARs, as it is for most of the other members of the nuclear hormone receptor superfamily. They heterodimerize with 9-*cis* retinoid X receptor (RXR), forming a complex that is able to bind, *via* a **central DNA binding domain (C domain)**, to PPREs.

The **C domain** is highly conserved, with its two zinc finger-like structure and its α-helical DNA binding motifs, as often found in various transcription factors. The whole PPRE consensus sequence (TGACCT X TGACCT) fits a DR1 pattern (DR for direct repeat, 1 for one spacing base between the two consensus motifs TGACCT) [28]. These elements bind PPAR-RXR heterodimers with PPAR occupying the 5' extended half site and RXR the 3' half site [29]. PPAR-RXR heterodimers were shown to compete with hepatocyte nuclear factor-4 (HNF-4) homodimers for binding to DR1 elements, resulting in decreases in transcription of apolipoprotein C-III and transferrin genes [30,31]. The first PPRE sequences were identified by promoter analysis of the peroxisome proliferator (PP)-responsive gene, acyl-CoA oxidase (ACO) [32,33]. A number of studies point to the importance of the sequences flanking the PPREs for maintaining the optimal conformation of the PPAR-RXR heterodimers on the PPREs [34,35]. These flanking sequences may provide an extra level of specificity to different nuclear receptors that recognize the DR1 element [36].

The D region encodes a flexible hinge region, thought to allow independent movement of the LBD relative to the DNA binding domain.

PPAR ligands: identification, interaction with PPARs and specificity

PPAR ligands can be both synthetic, such as peroxisome proliferators, hypolipidaemic drugs, anti-inflammatory or insulin-sensitizing drugs, or endogenous, most of them being fatty acids or their derivatives.

Among the group of synthetic ligands, fibrates are hypolipidaemic drugs used in the treatment of hyperlipidemia. Most of them preferentially activate PPARα. Others are industrial compounds [37]. The insulin-sensitizing thiazolidinedione (TZD) class of compounds is selective for PPARγ [38], with an affinity (K_ds) ranging from 40 nM (rosiglitazone) to several micromolars (troglitazone). These two compounds have been approved for the treatment of type II diabetes in humans. They efficiently reduce both insulin resistance and triglyceride plasma levels. Although their main effects are not mediated by PPARs, some non-steroidal anti-inflammatory drugs, such as indomethacin, flufenamic acid, ibuprofen or fenoprofen, activate both PPARα and PPARγ, which may contribute to their anti-inflammatory properties [39]. Recently, the L165041 compound has been identified as being the first PPARβ-selective synthetic agonist [40].

Fatty acids have been discovered to bind to all three PPAR isotypes, demonstrating that they are not only energy storing molecules, but also "hormones" controlling nuclear receptor activities and consequently gene expression. Among the three isotypes, PPARα is not only the one that exhibits a high affinity for fatty acids, but is also the best characterized in terms of ligand specificity. It has been shown to have a clear preference for binding of long chain unsaturated fatty acids, such as the essential fatty acids linoleic, linolenic and arachidonic acids, at concentrations that correlate with circulating blood levels of these fatty acids. Fatty acid derivatives, such as the inflammatory mediators leukotriene B4 and 8(S)-hydroxy-eicosatetraenoic acid, were also identified as relatively high-affinity ligands for PPARα [41]. In the case of PPARγ, a metabolite of the eicosanoid prostaglandin G2, 15-desoxy-$\Delta^{12,14}$-PGJ2

(15d-PGJ2) is the most potent natural ligand described so far, with reported K_ds varying from 325 nM to 2.5 μM. Polyunsaturated fatty acids, such as 18:2, 18:3 and 20:4, seem to be the most efficient PPARβ natural ligands.

Tissue expression distribution

Each of the three PPAR isotypes is expressed in a distinct, tissue-specific pattern. PPARα is highly expressed in liver, heart, proximal tubules of kidney cortex, skeletal muscle, intestinal mucosa and in brown adipose, tissues that are metabolically very active [42]. PPARγ is most highly expressed in white and brown adipose tissue, large intestine and spleen [43,44]. In contrast to PPARα and PPARγ, which are abundantly expressed in just a few tissues, PPARβ is expressed in virtually all tissues at comparable levels [45,46]. Furthermore, there is no sex-specific expression of the three PPAR isotypes as analyzed in rats [47].

The fact that some tissues express more than one PPAR isotype raises the question of PPAR-specific PPRE recognition. Assessment of the relative DNA-capabilities of the three PPAR isotypes to 16 native PPREs led to the classification of PPREs into three functional groups: strong, intermediate and weak elements, which correlates with the level of PPRE conformity to the consensus element [29]. Surprisingly, the number of identical nucleotides in the core DR1 region is rather homogeneous across the different elements, and it is mainly the number of identities in the 5'-flanking nucleotides, rather than the *stricto sensu* core DR1, which determines the binding strength of a given PPRE. In all cases, PPARγ binds more strongly than do PPARα and PPARβ and is thus less dependent on well-conserved 5'-flanking extension. In contrast, conservation of the 5'-flank is particularly essential for PPARα binding and therefore contributes to isotype specificity. The PPAR DNA-binding activity is also modulated by the isotype of the RXR heterodimeric partner. Binding of PPAR:RXR to strong elements is reinforced when RXRγ is the partner, whereas heterodimerization with RXRα is more favorable for binding to weak elements.

PPAR target genes

PPARα is a central regulator of hepatic lipid metabolism as well as participant in genes involved in bile acid synthesis [48]. The first identified PPARα target genes code for several enzymes involved in the β-oxidation pathway, namely acyl-CoA oxidase [49], bifunctional enzyme [50] and thiolase [51]. The activation of long-chain fatty acid into acyl-CoA thioester by the long-chain fatty acyl-CoA synthetase is likely to be regulated by PPARα [52].

PPARα also participates in the control of fatty acid transport and uptake, by stimulating the genes encoding the fatty acid transport protein (FATP), the fatty acid translocase (FAT/CD36) and the liver cytosolic fatty acid-binding protein (L-FABP) (Fig. 2) [53]. The metabolism of triglyceride-rich lipoproteins is modulated by PPARα-dependent stimulation of the lipoprotein lipase gene, which facilitates the release of fatty acids from lipoprotein particles, and the down-regulation of apolipoprotein C-III [54]. Furthermore, PPARα up-regulates apolipoprotein A-I and A-II in humans, which leads to an increase in plasma high-density lipoprotein (HDL) cholesterol. Additional PPARα target genes participate in mitochondrial fatty acid metabolism [55,56], in ketogenesis [57] and in microsomal fatty acid ω-hydroxylation by cytochrome P450 ω-hydroxylases that belong to the CYP4A family [58,59]. Among the key lipid metabolizing extra-hepatic genes activated by PPARα is lipoprotein lipase, involved in the degradation of triglycerides [60]. Hepatic lipogenesis and phospholipid transport (MDR2, ABCB4) are regulated by fibrates [61]. Several bile acid synthetic genes are regulated by PPARα. Sterol 12α-hydroxylase (CYP8B1), responsible for modulating the cholic acid: chenodeoxycholic acid ratio, is a PPARα target gene [62]. Interestingly, the first committed step in bile acid synthesis, CYP7A1, is repressed by PPARα [63,64].

There are also PP-responsive genes that have a link to cell cycle control although no PPREs have been found in these genes to date. Induction of the oncogenes c-*Ha-ras*, *jun* and c-*myc* by PP has been reported and the ability to induce these genes correlates well with tumor-promoting potential [65–68]. For example, Wy-14,643, clofibrate, ciprofibrate and DEHP were inducers of c-*fos*, c-*jun*, *junB* egr-1, and NUP475 whereas the noncarcinogenic PP dehydroepiandrosterone was ineffective [67]. In addition, an immediate early gene (IEG) critically involved in lipid metabolism, tumor promotion and inflammation, cyclooxygenase-2, is also regulated by PP [66]. IEG are key genes involved in regulating the cell cycle and are characterized by rapid response to mitogens as well as serum and cycloheximide inducibility [69]. Recently, a novel IEG involved in neuronal differentiation, rZFP-37, was characterized as a PP-regulated gene in rodent liver [70]. These regulatory genes are critical in the progression of the cell cycle, particularly the G_1 to S transition. For example, PP-induced expression of growth regulatory genes precedes entry of the cell in S phase [67]. In addition, alterations in CDK1, CDK2, CDK4, cyclin D1 and cyclin E have been reported following exposure to PP [67,68,71].

Because expression of PPARγ is highest in adipose tissue, the search for PPARγ target genes has concentrated on adipocytes. The two markers of terminal adipocyte differentiation – aP2, a fatty acid-binding protein, and phosphoenolpyruvate carboxykinase, an enzyme of the glyceroneogenesis pathway – are indeed regulated by PPARγ [72]. Similarly, PPARγ also regulates the expression

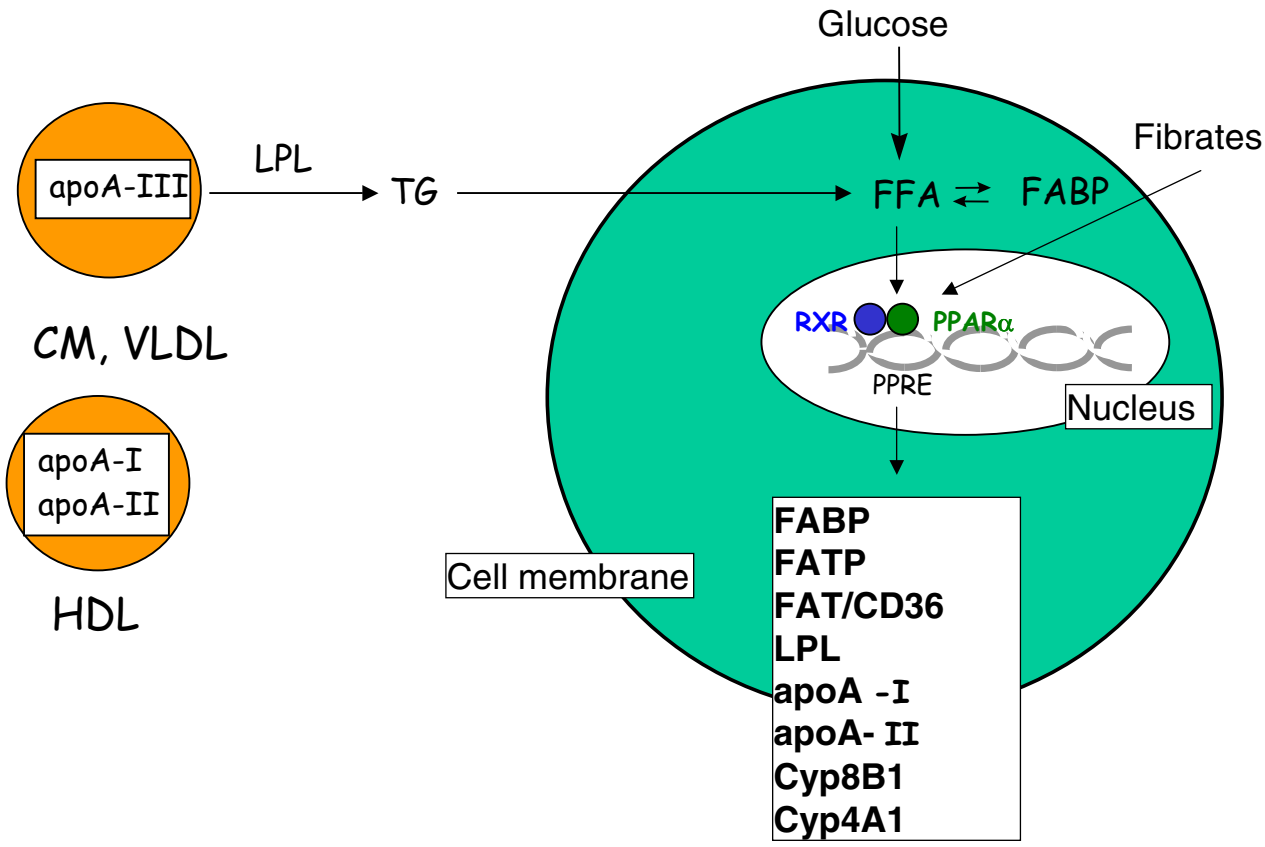

Figure 2
PPARα plays a central role in lipid transport and metabolism as well as in the response to xenobiotics. PPARα is since activated by a diverse array of ligands, including natural and synthetic compounds. The natural ligands free fatty acids (FFA) originate either from the catabolism of chylomicrons (CM), very-low-density lipoproteins (VLDL) or high-density lipoproteins (HDL) *via* the lipoprotein lipase (LPL), or from the degradation of glucose. They are also released in the cell from the fatty acid binding protein (FABP). Activated PPARα heterodimerizes with RXR and binds to PPRE to drive expression of target genes.

of the genes coding for lipoprotein lipase, fatty acid transport protein, and the fatty acid translocase [53]. Recently, the idea of a link between PPARγ and the insulin signaling has been reinforced by the finding that the c-*Cbl*-associated protein, a signaling protein interacting with the insulin receptor, could be encoded by a potential PPARγ target gene [73].

Probably because of its ubiquitous expression, it has been hard to anticipate a function for PPARβ. However, some of its target genes have been identified. For example, PPARβ can promote cellular lipid accumulation in macrophages by increasing the expression of genes that are involved in lipid uptake and by repressing key genes implicated in lipid metabolism and efflux [74].

Regulation of mitosis and apoptosis by PPARs in pre-clinical models

PPARα

PPARα ligands such as Wy-14,643, ciprofibrate and clofibrate are known to produce peroxisome proliferation and liver tumors in rats and mice [75,76]. However, since PP belong to the class of carcinogens whose mode of action does not involve direct damage to DNA, there have been several theories to explain how non-mutagenic chemicals such as PP [77] result in liver cancer. Most notably, the link between a xenobiotic's ability to alter differentiation, proliferation and apoptosis with the emergence of tumors has been well established (Fig. 3) [78]:

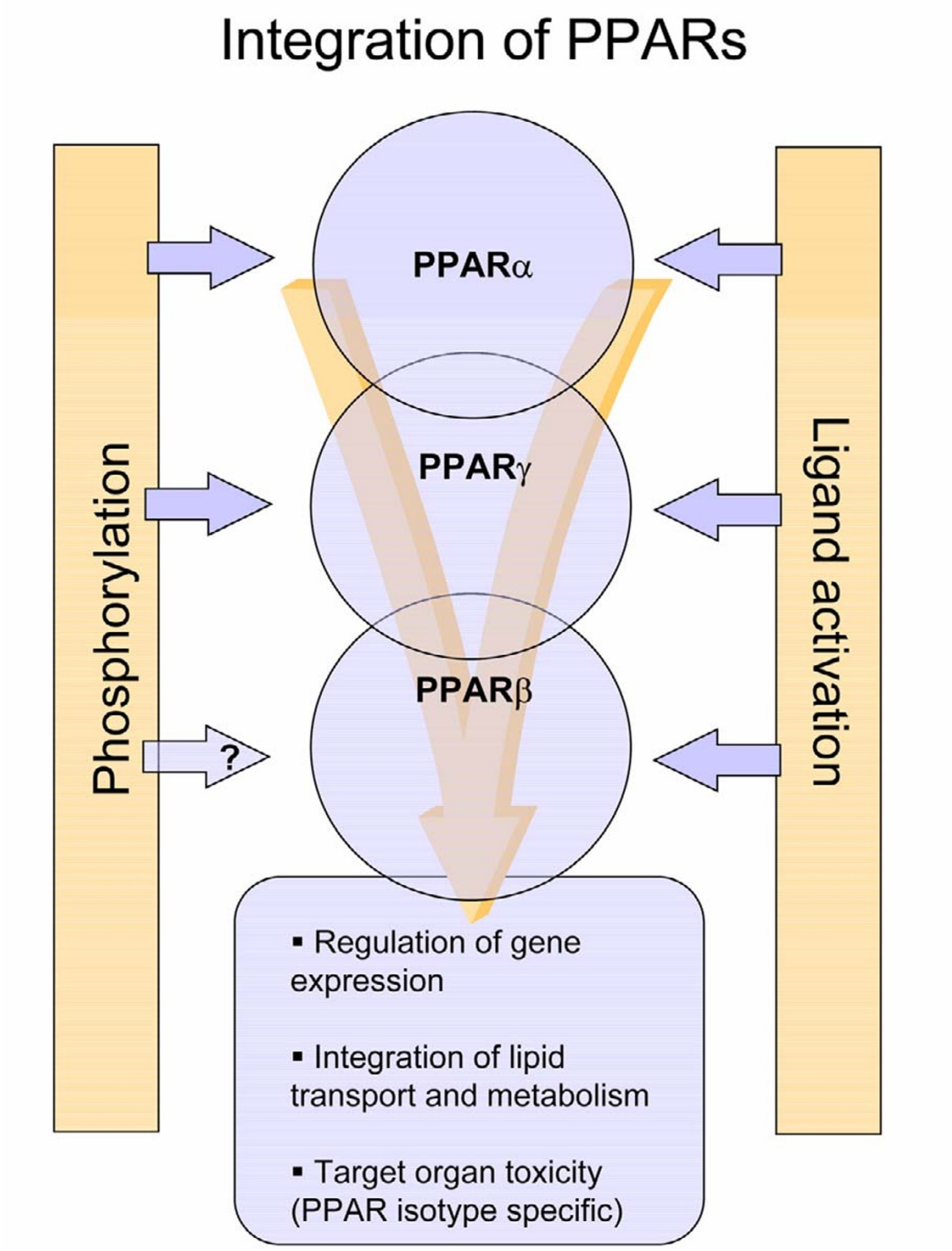

Figure 3
The different PPAR isoforms have different functions and activation profiles but share the ability to be activated by natural or synthetic ligands. In addition, the activity of PPARα and PPARγ is modulated by phosphorylation providing the opportunity for cross-talk between the nuclear hormone receptor and kinase families of regulatory molecules.

Role of PPARα activation on mitosis

The process of peroxisome proliferation-induced hepatocarcinogenesis is dependent on PPARα [79]. Mice lacking this receptor are totally resistant to Wy-14,643-induced liver tumors [51]. Remarkably, the mice that lack PPARα do not display the typical pleiotropic response when challenged with the PP, such as peroxisome proliferation, abnormal lipid homeostasis [80] and transcriptional activation of target genes [51]. Importantly, PPARα-null mice do not exhibit enhanced cell proliferation as evident by hepatomegaly, incorporation of bromodeoxyuridine into DNA, and expression of proteins involved in progression of the cell cycle, like the proliferating cell nuclear antigen PCNA [71]. These data clearly demonstrate that PPARα is a key contributor for the process of peroxisome proliferation, hypertrophy, cell proliferation and hepatocarcinogenesis. However, even though PPARα regulates PP-mediated cell proliferation, it is unclear whether this function is direct or indirect.

PP have mitogenic effects when given directly to primary hepatocytes in culture [81]. However, others have suggested that Kupffer cells are responsible for the mitogenic effects of PP on hepatocytes, presumably *via* an interleukin [82] or tumor necrosis factor α (TNFα)-dependent mechanism [83]. Kupffer cells represent about 2% of the liver mass and share many properties with macrophages such as secretion of the cytokines TNFα, interleukin-1 (IL-1), IL-2 and IL-6 [84]. In support of the hypothesis that Kupffer cells are required for the proliferation of hepatocytes, Rose et al. [85] showed that inhibition of Kupffer cell activity by dietary glycine and methylpalmitate inhibited Wy-14,643-induced hepatocyte proliferation. Furthermore, the hepatocyte growth response to PP can be prevented by antibodies to TNFα [83,86] or TNFα receptor 1 (TNRF1) [87]. More recent studies have revealed that hepatocytes cultured in the absence of Kupffer cells do not exhibit cell proliferation when treated with Wy-14,643 or nafenopin [88,89], and this response can be restored by returning the Kupffer cells to purified hepatocytes.

In support of the role of TNFα as a key mediator in the stimulation of hepatocellular proliferation, recent findings suggest that down-regulation of the iron-binding protein lactoferrin (LF) upon PP treatment may play a role in initiating the growth response [90]. Indeed, LF may putatively be able to regulate liver expression of TNFα, and possibly other pro-inflammatory cytokines. Following PP exposure, the down-regulation of LF expression would result in increased levels of TNFα, which, in turn, would mediate some or all the growth changes associated with PP. These increased levels would occur by bioactivation or release of preexisting TNFα protein from hepatic Kupffer cells rather than by increase in TNFα expression as no changes in TNFα mRNA levels were detected following PP treatment [91].

IL-1α was shown to be able to induce DNA synthesis in mouse hepatocytes, even in the presence of the anti-TNFR1 antibody, suggesting that IL-1α acts independently rather than by elaborating TNFα [87]. However, the mandatory roles of TNFα and interleukins in the regulation of mitosis in the liver have recently been questioned. Indeed, mice lacking TNFα [92,93] respond to Wy-14,643 no differently than wild-type animals in terms of stimulation of hepatocyte proliferation. Moreover, cell proliferation can be still triggered by PP in the liver of IL-6 null transgenic mice [94,95]. Perhaps multiple cytokines are required to elicit the mitogenic response to PP. Alternatively, a cytokine that has not yet been characterized might be responsible for hepatocyte proliferation. Mitogen-activated protein (MAP) kinase pathways contribute to the transmission of extracellular signals, resulting in the direct or indirect phosphorylation of transcription factors and subsequent alterations in gene expression [96]. The MEK (MAP kinase kinase) and extracellular signal regulated kinases (ERK) pathway primarily responds to cellular proliferation signals, while the p38 MAP kinases and c-*Jun* N-terminal kinases are modulated by cytokines, growth factors and a variety of cellular stress signals [97]. Inhibition of either enzyme in hepatocytes using specific inhibitors prevented PP-induced increase in S-phase [98], suggesting a role of MAP kinase activity in PP-regulated cell proliferation. The activation of both p38 and ERK has been shown to lead to the release of TNFα and IL-6 by macrophages and other cell types [99,100]. Therefore, one of the functions of MAP kinase signaling pathway may be to regulate the levels of cytokines or interleukines, thereby controlling cell mitosis in the liver. As mentioned before, PPARα activation also leads to increase in S-phase. It has therefore been suggested that PPARα activation would rely upon p38 MAP kinase-induced phosphorylation [101]. In support of this assumption, Barger et al. [102] showed that transcription of PPARα target genes was induced upon PP exposure in a P38 MAP kinase dependent manner. Moreover, a ligand-independent transcriptional activation domain in PPARα has been shown to contain MAP kinase sites [103]. Activation of the MEK-ERK pathway seems to be a prerequisite for the growth response of rodent liver cells to PP [65,98,104], suggesting that PP may be using both stress and growth pathways. Induction of oxidative stress by PP [85,105] may also play a role in the activation of MAP kinase pathways. In particular, p38 MAP kinase has been associated with oxidative stress [106] and has been reported to be constitutively active in mouse liver [107].

Role of PPARα activation on apoptosis

Many PPs such as nafenopin were shown to suppress both spontaneous apoptosis [108–111] and that induced by diverse stimuli including transforming growth factor-β1 (TGFβ1) [112]. The PP-induced suppression of apoptosis can be reproduced in cultured rodent hepatocytes with high concentrations of TNFα [83], suggesting that TNFα may play a role in permitting or mediating such an inhibition. In line with this assumption, removal of TNFα-producing Kupffer cells from hepatocyte cultures abolishes the decrease in apoptosis typically observed with hepatocytes exposed to PPs [88]. Suppression of apoptosis is restored when the Kupffer cells are added back to the hepatocyte cultures. Furthermore, *in vitro* experiments using a dominant negative repressor of PPARα activity suggested that PPARα mediates the PP-induced suppression of apoptosis [113]. This was later confirmed in experiments using PP-stimulated hepatocytes from PPARα null transgenic mice [110,114]. TNFα has been found to be still capable of suppressing apoptosis in cultured PPARα null mice in the absence of PPs and PPARα, suggesting that TNFα is clearly a downstream effector on apoptosis suppression compared to PPs or PPARα. In the presence of the protein synthesis inhibitor cycloheximide, the response of hepatocytes to TNFα is reversed, with a clear induction of cell death [87]. This finding perhaps explains the pleiotropic response of rodent liver to TNFα. Depending on the signaling context, this cytokine may induce or may suppress hepatocyte apoptosis.

PP-induced suppression of hepatocyte apoptosis was shown to rely upon the activation of the MEK/ERK signalling pathway [104] as well as the p38 MAP kinase pathway [115]. The response to PP is also dependent upon the transcription factor NFκB since a dominant negative form of the upstream kinase Iκ that activates NFκB prevents the suppression of apoptosis in response to PP [116].

Recent findings showed that the liver from aged rats is exceedingly sensitive to the anti-apoptotic effect of PPARα agonists [117]. This high sensitivity could be related to the remarkably higher levels of the anti-apoptotic protein Bcl-2 in aged livers than in livers of young, adult, and middle-aged animals. Interestingly, the PPARα agonist Wy-14,643 significantly diminished elements of the pro-apoptotic machinery (*e.g.*, Bax, caspases, and fas) in the aged liver.

In summary, suppression of apoptosis induced by PP may prevent the removal of damaged or excess cells that would normally be eliminated, these cells then remaining as targets for further mitogenic stimulation and DNA mutations [118].

PPARγ

Role of PPARγ activation on mitosis

PPARγ is involved in the induction of cell growth arrest occurring during the differentiation process of fibroblasts to adipocytes. Differentiation of 3T3-L1 cells into adipocytes necessitates withdrawal from the cell cycle in addition to the coexpression of PPARγ and C/EBP, and involves phosphorylation of the retinoblastoma susceptibility gene product Rb [119]. However, activation of PPARγ in Rb-/- mouse embryo fibroblasts is sufficient to induce adipocyte terminal differentiation and thus the link between PPARγ and Rb phosphorylation remains to be established [120].

PPARγ ligands may protect the vasculature against injury. Inhibition of cell growth is among others one mechanism involved in this process. The antiproliferative effects of PPARγ ligands on vascular smooth muscle cells are mediated by targeting critical cell cycle regulators, including Rb and $p27^{Kip1}$, that regulate the progression of cells from G1 phase into S phase to conduct DNA synthesis [121]. PPARγ ligands have been recently shown to suppress development of atherosclerosis in LDL receptor-deficient mice [122].

Ligand activation of PPARγ results in the inhibition of proliferation of various cancer cells. Primary human liposarcoma cells, which express high levels of PPARγ, can be stimulated to undergo cell cycle arrest and terminal differentiation by treatment with PPARγ and RXR-specific ligands [123]. Activation of PPARγ also induces a reduction in growth rate and clonogenic capacity of human breast cancer cells in culture. In one breast cancer cell line, which expresses high levels of PPARγ, the resistance to TZD was associated with a high MAP kinase activity, which might explain a low PPARγ activity due to phosphorylation of the A/B region of the receptor [124].

Human colon tumor cell lines express PPARγ and respond to diverse PPARγ agonists with a reduced rate of growth and an increased degree of differentiation. Morphological maturation, defined by an increased cytoplasmic-to-nuclear ratio, was observed concomitantly with changes in gene expression consistent with a transition to a more differentiated state [125]. PPARγ-selective targets included genes linked to growth regulatory pathways (regenerating gene IA), colon epithelial cell maturation (GOB-4 and keratin 20), and immune modulation (neutrophil-gelatinase-associated lipocalin) [126]. Drg-1 (differentiation-related gene-1), a putative suppressor gene in human colorectal cancer, and PTEN, a tumor suppressor gene which modulates several cellular functions, including cell migration, survival, and proliferation, were found to be controlled at least in part by PPARγ agonists in colon cancer cell lines [127,128].

Human colorectal carcinoma cells implanted in nude mice were shown to grow more slowly in mice treated with troglitazone [125,129]. On the other hand, two independent studies performed in mice bearing a mutation in the adenomatous polyposis coli tumor suppressor gene (APC^{min}) showed an increase in tumors or polyps in the colon after these mice were fed a diet containing a PPARγ agonist for 8 or 5 weeks [130,131]. The discrepancy with the above mentioned results obtained with colon cancer cell lines does not seem to be attributable to the genetic defect that causes the tumors in mice, since some of these lines also bear this specific mutation [125,132]. Interestingly, recent studies with mice heterozygous for PPARγ have shown that heterozygous loss of PPARγ causes an increase in β-catenin levels and a greater incidence of colon cancer when animals are treated with azoxymethane [133]. However, mice with preexisting damage to APC, a regulator of β-catenin, develop tumors in a manner insensitive to the status of PPARγ. These data show that PPARγ can suppress β-catenin levels and colon carcinogenesis but only before damage to the APC/β-catenin pathway. This finding suggests a potentially important use for PPARγ ligands as chemopreventative agents in colon cancer.

Troglitazone showed a potent dose-dependent effect on the growth inhibition of six hepatocellular carcinoma (HCC) cell lines [134]. The growth inhibition was linked to the G1 phase cell cycle arrest through the up-expression of the cyclin-dependent kinase inhibitors, p21 and p27 proteins, and the hypophosphorylation of retinoblastoma protein. Unfortunately, no PPARγ knock-out transgenic mice are available since deletion of the PPARγ gene in mice results in embryonic lethality at approximately day 10 of gestation due to placental insufficiency [135].

Role of PPARγ activation on apoptosis

PPARγ ligands have been implicated in inducing apoptosis in a number of cell types. For example, rosiglitazone (at low concentrations, in the range of its Kd value of 20 nM) was able to increase the number of TUNEL-positive cells and to increase activation of caspase-3 in human monocyte-derived macrophages [136]. Similarly, TZDs triggered apoptosis in cultured astrocytes [137] or in B lymphocytes [138]*via* PPARγ. 15d-PGJ2 can also trigger the apoptosis of endothelial cells *via* a PPAR-dependent pathway [139]. Part of the effectiveness of the PPARγ agonists troglitazone and 15d-PGJ2 in the rat adjuvant arthritis model of human rheumatoid arthritis is *via* inducing apoptosis in synoviocytes [140]. PPARγ ligands also induce apoptosis in human hepatocellular and esophageal carcinoma cells [134,141].

The mechanism underlying the induction of apoptosis is not clear, but evidence suggests that TZDs could interfere with the anti-apoptotic NFκB signaling pathway. The induction of apoptosis by PPARγ is increased by costimulation with TNFα-related apoptosis-inducing ligand (TRAIL), a member of the TNF family [142]. It has not been determined whether a similar NFκB inhibition might be responsible for the observed TRAIL-induced pro-apoptotic effects of TZDs, which enhances apoptosis in tumor cells. To date, no reports are available on ligand-induced apoptosis in liver with high PPARγ expression levels.

The inhibition of cell growth observed in human breast cancer cells treated *in vitro* with ligands for PPARγ and retinoic acid receptor is accompanied with a profound decrease of Bcl-2 gene expression and a marked increase in apoptosis [143]. Troglitazone induced apoptosis in six HCC by caspase-dependent (mitochondrial transmembrane potential decrease, cleavage of poly [adenosine diphosphate ribose] polymerase, 7A6 antigen exposure, Bcl-2 decrease, and activation of caspase 3) and caspase-independent (phosphatidylserine externalization) mechanisms [134].

PPARβ

Role of PPARβ activation on mitosis

PPARβ was identified as a downstream target gene for APC/β-catenin/T cell factor-4 (TCF-4) tumor suppressor pathway, which is involved in the regulation of growth promoting genes such as c-*myc* and cyclin D1. Indeed, PPARβ expression was elevated in human colorectal cancer cells and was down-regulated upon restoration of APC expression in these cells [144]. This down-regulation appeared to be direct as the promoter of PPARβ contains β-catenin/TCF-4-responsive elements, and PPARβ promoter reporters were repressed by APC as well as stimulated by mutants of β-catenin (resistant to the inhibitory effect of APC). Genetic disruption of PPARβ also decreased the tumorigenicity of human colon cancer cells transplanted in mice, thus suggesting that PPARβ contributes to the growth-inhibitory properties of the APC tumor suppressor [145]. In other experiments with vascular tissues, PPARβ was found up-regulated during vascular lesion formation and promoted post-confluent cell proliferation in vascular smooth muscle cells (VSMC) by increasing the cyclin A and CDK2 as well as decreasing $p57^{kip2}$ [146].

Role of PPARβ activation on apoptosis

PPARβ plays an antiapoptotic role in keratinocytes *via* transcriptional control of the Akt1 signaling pathway [147]. Both 3-phosphoinositide-dependent kinase-1 and integrin-linked kinase are target genes of PPARβ. The up-regulation of these genes together with the down-regulation of PTEN led to an increase of Akt1 activity in keratinocytes and suppressed apoptosis induced by growth factors deprivation in cell culture.

Relevance to human health

Cancer

Role of PPARα

Although rodents are sensitive to the hepatocarcinogenic effects of PP, there is little evidence that humans are at increased risk of liver cancer, even after chronic exposure. The hypolipidemic drugs gemfibrozil and clofibrate have been used in the clinic for 15 and 30 years, respectively, and epidemiological studies do not reveal a statistically significant increase in cancer up to 8 years after initiation of therapy [148]. Livers from humans and monkeys given fibrate drugs showed no evidence of peroxisome proliferation [149–152]. Human and marmoset hepatocyte cultures, in contrast to rats, are unresponsive to treatment to MEHP [153].

There are several possibilities that could account for lack of peroxisome proliferation in human liver compared to rats and mice. Even though functionally active, the human PPARα is expressed at only about 10% of that in mouse liver [154], and extracts from human liver contain little PPARα that can bind to PPRE [155]. Recently, mutant forms have been described in some human liver samples: hPPARα8/14 is a truncated receptor that results from aberrant splicing of the PPARα mRNA [154]; hPPARα6/29 is a full length receptor that binds to PPRE, yet cannot be activated by PPs [113]. However, screening of a sample of the human population for the presence of hPPARα6/29 revealed that this form is rare. An alteration of the PPRE sequence in the human acyl-CoA oxidase gene might also explain the relative human unresponsiveness to PPARα ligands [156]. Finally, species-specific responses to some synthetic PPARα ligands, as analyzed in *Xenopus*, mouse and human PPARα have also been observed [157,158]. These dramatic differences in PPARα expression and activity or in PPRE structure may account for the absence of indicators of PP response in human liver, including peroxisome proliferation and cell proliferation/apoptosis suppression [148]. Different levels of expression of PPARα may have differential effects on gene expression. The PPARα activity induced by these drugs in humans could be sufficient to mediate hypolipidaemia but too low to trigger transcriptional induction of genes involved in peroxisome proliferation and adverse effects [159]. As well as being resistant to peroxisome proliferation, human hepatocytes are also resistant to PP-mediated induction of mitosis and suppression of apoptosis [148,160]. Because the rodent hepatocarcinogenesis following PP exposure is mediated by PPARα, the current evidence suggests that humans exposed to these compounds are not likely to develop liver tumors.

Anecdotically, PPARα agonists have been reported to suppress the growth of a human hepatoma cell line [161]. A massive apoptosis was observed in the AH-130 hepatoma, a poorly differentiated tumor, maintained by weekly transplantations in rats, upon exposure to clofibrate. Similar results were obtained with HepG2 cells. The mechanisms by which clofibrate induces apoptosis are still unclear. Since the peroxisome proliferator-activated receptor was expressed at a very low level and was not stimulated by clofibrate in the AH-130 hepatoma cells, its involvement seems unlikely. Phospholipids and cholesterol were significantly decreased, suggesting an inhibition of the mevalonate pathway and, therefore, of isoprenylation of proteins involved in cell proliferation.

Role of PPARγ

Recent evidence suggests that PPARγ ligands could have an anti-tumor effect in humans as these compounds decrease cell growth and induce apoptosis in several malignant human cell types, including HCC [134], breast adenocarcinoma [124,143] and colon adenocarcinoma [125]. In addition, loss-of-function mutations in PPARγ were identified in a subset of human colorectal tumors, supporting a role for PPARγ as a tumor suppressor of colorectal carcinogenesis [162]. In agreement with a potential role of PPARγ ligands for the treatment of cancer, troglitazone treatment was found active in the treatment of advanced liposarcoma [163]. On the other hand, although some recent findings have suggested a potentially important use for PPARγ ligands as chemo-preventative agents in colon cancer [133], the PPARγ ligand troglitazone was not found active in the treatment of metastatic colorectal cancer during a phase II clinical trial [164]. The potential beneficial effect of PPARγ ligands in the treatment of human HCC has not yet been tested.

Role of PPARβ

A link exists between PPARβ and human cancer *via* the APC tumor repressor gene. In the majority of human colorectal cancers, APC is inactivated by deletions, thus giving rise to increased levels of β-catenin/TCF-4 mediated transcriptional activity. PPARβ is, beside c-*myc* and cyclin D1, one of the target genes regulated by this transcription complex and thus may contribute to cell proliferation in cancer. Epidemiological studies have shown a decrease risk of colorectal carcinoma deaths associated with the use of the non-steroidal anti-inflammatory drug (NSAID) aspirin. Moreover, in individuals with familial adenomatous polyposis, an inherited predisposition to multiple colorectal polyps, the NSAID sulindac can reduce both the size and the number of colorectal tumors. Interestingly, sulindac was shown to bind and antagonize PPARβ leading to increased apoptosis in colon cancer cells [144]. Thus PPARβ may be a critical intermediate in the tumorigenesis pathway of the APC gene and may be a molecular target of the effect of NSAID in colorectal cancer.

Hepatic toxicity induced by the PPARγ agonist troglitazone

Troglitazone is an antidiabetic agent, which has been reported to cause severe hepatic injury in certain individuals. The mechanism underlying this rare but severe adverse drug reaction associated with troglitazone is not clear. Results obtained with HepG2 cells suggest that troglitazone induces apoptotic hepatocyte death, which may be one of the factors of liver injury in humans [165]. As hepatocytes in some diabetes type II patients contain higher level of PPARγ level, this could be related to an increased risk of troglitazone-induced hepatotoxicity in these patients [166].

Other pathologies

PPARγ agonists have been proposed as therapeutic targets against inflammation and atherosclerosis in humans. Indeed, PPARγ agonists, which decrease cytokine secretion as TNFα, IL-1, IL-6 in macrophages, and which increase apoptosis in macrophages and synoviocytes [140], could potentially be used to treat rheumatoid arthritis [167]. PPARγ agonists, which protect against the proliferation of vascular smooth muscle cells after vascular injury in animal models may have a similar effect in humans [121].

Conclusions

The regulation of apoptosis and mitosis by PPAR ligands in rodent models is complex but much has been done in the last 10 years towards understanding the pathways involved. For the rodent liver, the mode of action of PPARα ligands is understood sufficiently to permit us to conclude that this is not relevant to humans. However, the genes that are activated by PPARα ligands to regulate apoptosis and mitosis remain to be determined.

For other modes of action, the pathways are less clear, limiting the usefulness of rodent models of clinical toxicity. However, the advent of new technologies such as proteomics, genomics and pharmacogenetics is allowing more innovative approaches to these difficult issues.

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