Biology and therapeutic applications of peroxisome proliferator-activated receptors

Running title: **PPAR biology in medicine**

Number of pages: 66

Number of figures: 2

Number of tables: 8

SUMMARY

Peroxisome proliferator-activated receptors (PPARs) are ligand dependent transcription factors. The three mammalian PPARs are key regulators of fatty acid and lipoprotein metabolism, glucose homeostasis, cellular proliferation/differentiation and the immune response. PPARs are therefore important targets in the treatment of metabolic disorders such as insulin resistance and type 2 diabetes mellitus, and are also of interest in relation to chronic inflammatory diseases such as atherosclerosis, arthritis, chronic pulmonary inflammation, pancreatitis, inflammatory bowel disease, and psoriasis. Recent advances have attributed novel functions to PPARs in blood pressure regulation, neuroinflammation, nerve-cell protection, inflammatory pain reduction, and the hypothalamic control of metabolism. The abundant pleiotropic actions of PPARs suggest that PPAR agonists have enormous therapeutic potential. However, current PPAR-based therapies often have undesired side effects due to the concomitant activation of PPARs in non-target cells. There is therefore growing interest in the development of cell-specific PPAR agonists and improvement of the clinical use of PPAR ligands. This review gives an overview of PPAR functions and discusses the current and potential medical implications of PPAR ligands in various pathologies, ranging from metabolic disorders to cardiovascular disease, chronic inflammation, neurodegenerative disorders and cancer.

Keywords: nuclear receptors – PPAR – transcription – metabolism – inflammation – cardiovascular disease – neuroinflammation – cancer

1. INTRODUCTION

1.1. Members of the PPAR family

Peroxisome proliferator-activated receptors (PPARs) were initially identified in the early 1990s as the mediators of peroxisome proliferation [1]. They belong to the nuclear hormone receptor (NR) superfamily, the largest group of eukaryotic transcription factors (TFs), and regulate a wide range of biological processes through the control of gene expression. PPARs play a central role in regulating the storage and catabolism of dietary fats via complex metabolic pathways, including fatty acid oxidation (FAO) and lipogenesis [1]. They also have important roles in the regulation of glucose metabolism, metabolic control, cell proliferation/differentiation, and the immune response [1]. PPARs are therefore important targets in the treatment of metabolic disorders [2] and are of interest for the treatment of chronic inflammatory diseases [3, 4].

Three mammalian PPARs have been identified, and are referred to as PPARα (NR1C1), PPARδ/β (NR1C2), and PPARγ (NR1C3). Although each PPAR isotype is encoded by a separate gene, they share a high degree of amino acid sequence homology, resulting in some degree of cross reactivity [5]. The expression pattern of each PPAR in adult animals is tissue-specific. PPARα is highly expressed in metabolically active tissues, including liver, kidney, and brown adipose tissue. In hepatocytes, PPARα controls FAO, ketogenesis, lipoprotein assembly, and gluconeogenesis, and suppresses amino acid catabolism and the inflammatory response [6]. PPARα is also expressed in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs), where it plays anti-inflammatory roles [7] and is implicated in the control of vascular tone [8]. PPARδ/β has been detected in all tissues examined, with higher levels in brain, adipose tissue, pancreatic islets, and skin. It plays a variety of roles in lipid metabolism, FAO and energy dissipation, and inflammation [1, 9]. The best-characterized function of PPARδ/β is its important role in the control of cell proliferation, differentiation and survival, especially in keratinocytes [10]. PPARγ is widely expressed, with abundant expression in intestine, liver, kidney, adipose tissue, and vascular and immune cells, including lymphocytes and macrophages [11, 12]. PPARγ has two splice variants: PPARγ1 is expressed in various cell types, including vascular cells and leukocytes, whereas PPARγ2 is expressed exclusively in adipocytes. PPARγ is an essential modulator of fat cell differentiation and lipid storage in white adipose tissue, and of energy dissipation in brown adipose tissue [1]. In addition, it contributes to insulin sensitivity [2] and plays important anti-inflammatory roles in macrophages and other tissues [13].

Since they are ligand-dependent TFs, the activation of transcription by PPARs depends on ligand binding and the interaction of coregulators. PPARs heterodimerize with retinoid X receptor (RXR) and regulate the transcription of target genes through binding to specific response elements, which consist of a direct repeat of the NR hexameric DNA core recognition motif separated by a single nucleotide (DR-1). Ligands that bind to and activate PPARs are chemically unrelated molecules, including a variety of fatty acids, phospholipids, eicosanoids and prostaglandin (PG) metabolites, as well as synthetic compounds [14]. Upon binding these ligands, the PPAR molecule undergoes a conformational change that stabilizes its interaction with RXR, allowing the recruitment of a set of cofactors and consequently stimulating the transcription of target genes. PPARs act in two ways, by transactivation and by transrepression. Transactivation is the principle mechanism via which PPARs exert their metabolic effects, whereas transrepression is the dominant mechanism underlying the anti-inflammatory effects of PPARs [15].

1.2. Endogenous PPAR ligands

PPARs are bound and activated by several naturally occurring fatty acids and their metabolites, derived mostly from arachidonic acid as products of the lipooxgenase (LOX) and cyclooxygenase (COX) pathways. PPARs have therefore been suggested to act as sensors of overall lipid status. Polyunsaturated fatty acids activate all three PPAR isotypes with relatively low affinity (binding constants in the micromolar range), whereas fatty-acid derivatives show more binding selectivity. Thus, the different endogenous fatty acid derivatives, which are COX-derived eicosanoids and PGs, and LOX-derived hydroperoxy products (HETE, HODE) and leukotrienes (LT), selectively bind and activate specific PPAR isotypes. For example, 15-deoxy-$\Delta^{12,\ 14}$-prostaglandin J_2 (15dPGJ$_2$), 15-keto-prostaglandin E_2 (15kPGE$_2$), 13-hydroxyoctadeca-9, 11-dienoic acid (13-HODE) and 15-hydroxy-eicosatetraenoic acid (15-HETE) are all natural ligands of PPARγ. Endogenous ligands for PPARα include the phospholipid 16:0/18:1-GPC (1-palmitoyl-2-oleosyl-sn-glycerol-3-phosphocholine) and possibly leukotriene B_4 (LTB$_4$), while PPARδ/β ligands include lysophosphatidic acid, prostacyclin (PGI$_2$), and prostaglandin E_2 (PGE$_2$). Because of their hydrophobic nature, PPAR ligands are probably delivered to their receptor in the nucleus by cytoplasmic fatty-acid-binding proteins (FABPs), though this mechanism has not been demonstrated experimentally.

1.3. Synthetic PPAR agonists

Great efforts have been made to develop drugs targeting PPARs, and synthetic agonists of PPARα and PPARγ are already commonly used in clinical practice (Figure 1). Fibrate agonists of PPARα, such as fenofibrate and gemfibrozil, are antiatherosclerotic and hypolipidemic agents that induce hepatic lipid uptake and catabolism. Fibrates have been used clinically to treat hyperlipidemias for more than 40 years, and have been shown to exert their triglyceride (TG) lowering effect through their action on PPARα [16]. More recently, synthetic PPARγ agonists, the thiazolidinediones (TZDs; troglitazone and the currently-used drugs rosiglitazone and pioglitazone), have been used successfully to treat non-insulin-dependent type 2 diabetes mellitus (T2DM). TZDs stimulate pre-adipocyte differentiation [17] and induce insulin sensitization [1] (Figure 2). Genetic and pharmacological studies have revealed that PPARδ/β ligands have potential in the treatment of metabolic disorders, and a number of small molecule agonists of PPARδ/β have been clinically evaluated for the treatment of patients with hyperlipidaemia, insulin resistance (IR) and obesity [3]. However, despite the proven benefits of targeting PPARs, there are concerns about the safety of these treatments (reviewed in [18]). These safety concerns include potential carcinogenicity (based on findings in rodents), increased plasma creatinine and homocysteine, signs of myopathy and rhabdomyolysis (a condition in which damaged skeletal muscle tissue breaks down rapidly), fluid retention, peripheral edema, weight gain, and a potential increased risk of cardiac failure. These concerns have led to the development of new PPAR agonists. These include novel specific PPARγ ligands such as metaglidasen, FMOC-Leu, nTZDpa, SPPARM12 and T131, and dual PPARα/γ agonists such as tesaglitazar, muraglitazar, ragaglitazar, imiglitazar and MK-767. The clinical potential of these new PPAR agonists remains to be determined [18]. PPARδ/β ligands were developed more recently and some of these compounds are currently undergoing clinical trials (e.g. GW0742 and GW501516) [18, 19].

PPARs translate nutritional, pharmacological and metabolic stimuli into changes in gene expression and are activated by various fatty acid metabolites and several drugs used in the treatment of metabolic disorders. In this review we describe some of the pleiotropic functions of PPARs and the potential medical implications of modulating these actions.

2. CLINICALLY RELEVANT BIOLOGICAL FUNCTIONS

2.1. PPAR ligands in glucose and lipid metabolism

2.1.1. Major metabolic benefits of PPAR activation: overview

A major metabolic effect of PPARα activators is a decrease in plasma TGs and an increase in high density lipoprotein (HDL)-cholesterol, concomitant with increased fatty acid utilization [20]. PPARα therefore improves overall lipid homeostasis and secondarily protects against lipotoxic injury associated with IR [21, 22]. Deletion of PPARα in mice protects against IR, though it has no effect on high fat diet (HFD)-induced IR development and β-cell function, and also disturbs hepatic lipogenesis [23]. A possible role of PPARα has also been shown in starvation-induced changes in substrate utilization in muscle [22].

PPARδ/β ligands increase FAO in skeletal muscle and also improve glucose disposal, thereby reducing hyperglycemia and supporting the resolution of IR by forced fatty acid catabolism [24]. PPARδ/β activators also increase glucose disposal in skeletal muscle [19] and improve glycemic control [25]. Mice lacking PPARδ/β show glucose intolerance, increased hepatic gluconeogenesis and an inflammatory Kupffer-cell phenotype [25, 26].

TZDs, the clinically proven synthetic ligands of PPARγ, normalize a wide range of metabolic abnormalities associated with IR [2]. The cellular mechanisms underlying metabolic benefits of TZDs are increased muscle glucose uptake, reduced hepatic gluconeogenesis, and increased lipid deposition in adipose tissue TG stores [17, 27, 28]. These effects reduce circulating glucose levels and prevent the ectopic accumulation of lipid metabolites, which would exacerbate IR [20]. TZDs also improve insulin signaling, increase insulin release in response to hyperglycemia, and protect pancreatic β-cells [29]. Activation of PPARγ also reduces the secretion of inflammatory cytokines and increases the plasma level of adiponectin, the most important anti-diabetic adipokine [30], which secondarily mitigates IR in liver and skeletal muscle [31, 32]. In addition, TZDs promote the differentiation of adipocyte precursors into mature adipocytes, thereby expanding fat storage and reducing hyperlipidemia [17]. Accordingly, ablation of PPARγ in metabolically important tissues, such as skeletal muscle and adipose tissue, induces IR [33, 34] (Table 1). Overexpression of PPARγ in adipose tissue normalizes glycemic control in insulin-resistant mice [35]. Activation of PPARγ in other cell types, such as macrophages, ECs and neurons, is also required for TZD effects [36-38]. Systemic deletion of PPARγ is normally embryonically lethal; however, some mice survive, showing IR and lipodistrophy [39, 40]. In these mice, TZDs improve glucose homeostasis via a PPARγ-independent increase in β-cell mass in males and adipose tissue growth in females [41, 42]. Paradoxically, in mice, PPARγ haploinsufficiency or inhibition of PPARγ/RXRα heterodimers diminishes the development of diet-induced IR [43, 44] (Table 1). Similarly, the human Pro12Ala polymorphism of the PPARγ allele is associated with a decreased risk of T2DM [45]. The underlying mechanism may be the reduced adipogenesis in PPARγ deficiency, which prevents the development of obesity-related IR [43, 44]. However, reduced leptin levels have also been detected in PPARγ heterozygous mice [46], and Pro12Ala carriers show a higher-than-normal rate of obesity [47], factors which would be expected to promote IR development.

2.1.2. Mechanism of action: effects of PPAR ligands on glucose uptake

Transmembrane transport of glucose is a rate-limiting step in cellular glucose utilization. The process is mediated by glucose transporter (GLUT) proteins, which belong to the family of membrane-bound facilitative hexose carriers. Most cells express the insulin-independent GLUT-1, which is required for the maintenance of basal glucose uptake. In skeletal muscle, liver cells, adipocytes and heart muscle cells, insulin stimulates glucose uptake by increasing the synthesis and cell membrane targeting of GLUT-4, the major insulin-sensitive glucose transporter [48].

PPARα can decrease cardiac GLUT-4 levels and glucose uptake during ischemia, possibly by an indirect mechanism [49]. Interestingly, GLUT-1 overexpression and consequent increased glucose uptake and utilization reduces PPARα transcript levels [50, 51]. Reduced PPARα expression leads to a metabolic shift of substrate preference toward glucose instead of fatty acids, although the beneficial effect of low PPARα activity and excess GLUT-1–mediated glucose uptake is disputed [50-52].

PPARδ/β ligands also improve glucose homeostasis [19, 25]; however, there is still no consensus about whether they affect glucose transport [24]. In rat skeletal muscle, PPARδ/β activation has no acute effect on glucose uptake [53], although a PPARδ/β ligand (NNC61-5920) increases glucose disposal to muscle in diabetic rats [54]. Similarly, in human skeletal muscle cells and C2C12 cells, PPARδ/β-dependent glucose uptake has been shown [19, 55]. A recent study showed that PPARδ/β-RXRγ heterodimers increase GLUT-1 expression in mouse skeletal muscle [56]. Glucose utilization by muscle cells can thus be improved by PPARδ/RXRγ-mediated enhancement of glucose transport through GLUT-1.

TZDs induce GLUT-4 mRNA expression in adipose tissue and muscle [57], thus promoting glycogen synthesis [58]. Accordingly, PPARγ suppression reduces GLUT-1 and GLUT-4–mediated glucose uptake [59]. A non-TZD-type PPARγ agonist (GI-262570) also increases the transcript levels of GLUT-1 and GLUT-4 in diabetic rat heart, and increases the capacity of the myocardium to oxidize glucose [60]. The TZD pioglitazone increases GLUT-4 protein levels in diabetic rat liver and muscle [61]. In rat adipocytes and CHO-K1 cells PPARγ represses the activity of the GLUT-4 promoter, and this repression is augmented by the natural ligand 15d-PGJ_2 and alleviated by RSG [57]. A similar role of PPARγ has been established in cardiac muscle cells [62]. PPARγ is also required for the enrichment of GLUT-1 and GLUT-4 in the plasma membrane in response to insulin [63] or arachidonic acid [64], without affecting GLUT-4 synthesis [65]. Adiponectin is capable of increasing the effect of insulin on GLUT-4 expression and recruitment to the plasma membrane [66]. Since administration of PPARγ ligands increases adiponectin levels in diabetic rodents [67] and human patients [68], PPARγ may also stimulate GLUT-4 expression through this indirect mechanism.

PPARγ also affects glucose utilization in the kidney, by stimulating GLUT-1-mediated glucose uptake by podocytes [69]. This effect is impaired in diabetic renal disease [69, 70], since podocytes in the inflamed kidney are defective for the docking of GLUT-1 and GLUT-4 rich transport vesicles to the plasma membrane [70, 71].

The expression of the fructose transporter GLUT-5 is increased in skeletal muscle in T2DM and in adipose tissue in obesity [72]. Fructose stimulates hepatic lipogenesis, promotes non-alcoholic steatotic hepatitis (NASH) and T2DM development, and also increases insulin levels [73]. A clinical study shows that pioglitazone treatment of T2DM patients decreases muscle GLUT-5 mRNA and protein levels, mitigating IR [74]. Importantly, glucose uptake by GLUT-2 functions as a glucose sensor in pancreatic β-cells and increases insulin release. In β-cells, RSG upregulates the expression of GLUT-2, thus stimulating the release of insulin in response to increased blood glucose levels [75].

PPARγ ligands thus increase insulin availability by increasing β-cell responsiveness, without affecting the basal insulin secretion rate [29]. Apart from this mechanism, PPARγ ligands also exert anti-apoptotic effects on pancreatic cells and mitigate oxidative and lipotoxic damage to insulin-secreting cells in T2DM [40].

2.1.3. Control of fuel utilization by PPAR ligands

2.1.3.1. PPARα and PPARδ/β ligands increase fatty acid oxidation

PPARα potentiates fatty acid catabolism in liver, skeletal muscle and heart, and is the molecular target of the lipid-lowering fibrates (e.g. fenofibrate and gemfibrozil; Figure 1). PPARα activation increases hepatic uptake and the esterification of free fatty acids by stimulating expression of fatty acid binding protein (FABP) and acyl-CoA synthetase (EC 6.2.1.1). In skeletal muscle and heart, PPARα increases mitochondrial free fatty acid uptake, cholesterol efflux, and the resulting FAO through stimulation of muscle-type carnitine palmitoyltransferase-I (EC 2.3.1.21) [54, 76, 77]. PPARα stimulates the hepatic expression of lipoprotein lipase (LPL) and inhibits apolipoprotein C-III expression, which leads to reduced plasma levels of TG-rich lipoproteins [78]. A concomitant increase in plasma HDL cholesterol is a consequence of PPARα-mediated overexpression of apolipoprotein A1 and apolipoprotein A2 [78]. PPARα ligands also reduce the levels of very low density lipoprotein (VLDL) apoB-100 by enhancing clearance and reducing its production [51, 78]. The major metabolic effects of PPARα ligands can be used to mitigate atherogenic dyslipidemia (concomitant hypertriglyceridemia, hypercholesterolemia and low HDL levels), a comorbidity of IR, T2DM and obesity [78]. Administration of TZDs increases liver expression of PPARα [79], raising the interesting question of whether dual PPARα and PPARγ activation yields additive metabolic benefits. Recent and ongoing clinical studies show that the dual PPARα and PPARγ agonists muraglitzar and aleglitazar have the potential to simultaneously treat hyperglycemia and dyslipidemia in patients with T2DM (Figure 1) [80, 81]. However, muraglitzar and other PPARα/γ dual agonists, such as tesaglitazar and ragaglitazar, have been noted to increase several cardiovascular risk factors and are carcinogenic [82]. Characteristic TZD side effects such as edema and weight gain have not been observed in recent clinical trials of aleglitazar; however, other potential unwanted effects, such as bone homeostasis changes, have not been measured [83].

Although the main target of PPARα is lipid metabolism, it also affects liver glucose handling. Transcriptional activation of hepatic cytosolic phosphoenolpyruvate carboxykinase (PEPCK), which is required for hepatic gluconeogenesis, can be increased by PPARα [84]. During fasting or in T2DM, liver PPARα is activated, which up-regulates hepatic PEPCK and glucose-6-phosphatase (G6Pase, EC 3.1.3.9), a key enzyme responsible for liver glucose production. PPARα activation thus contributes to increased hepatic glucose output [85]. In diabetic mice, the increased PPARα expression in liver might account for increased gluconeogenesis [86]. Interestingly, the PPARα agonists statins can raise adiponectin levels [31], suggesting that they might indirectly improve insulin sensitivity.

Studies in PPARα knockout mice have yielded conflicting findings, showing either a protective [87] or neutral [88] effect of PPARα ablation on IR development (Table 2). Although PPARα activation changes substrate preference in mitochondrial oxidation from glucose to fatty acids, consequently increasing gluconeogenesis [85], the improved FAO can secondarily attenuate IR [89]. The excess amount of fatty acids in the blood stream causes IR and also mitigates insulin release from β-cells [4]. These events are reduced by the lipid-lowering effect of PPARα [89].

Obesity downregulates adipose tissue PPARδ/β expression, and accordingly, administration of PPARδ/β ligands improves whole-body insulin responsiveness, lowers plasma lipid levels and reduces body adiposity [90].

PPARδ/β activation induces expression of lipid and glucose homeostasis genes in liver and adipose tissue; for example, the insulin-signaling gene 3-phosphoinositide-dependent protein kinase 1 (PDK1; also known as PDPK1), stearoyl-CoA desaturase 1 (EC 1.14.19.1), the scavenger receptor CD36, and LPL [54]. Major effects of PPARδ/β are stimulation of lipolysis and FAO and reduction of TG content in adipose tissue and liver [90]. By sensing VLDL, PPARδ/β might also be important for the control of TG levels [20].

In skeletal muscle cells some of the key PPARδ/β target genes are the pyruvate dehydrogenase kinases (PDKs, EC 2.7.11.2) [91]. Skeletal muscle contains two PDK isoforms, PDK2 and PDK4 [92], and increased PDK4 expression leads to reduced carbohydrate oxidation and a switch toward lipid utilization in muscle [24]. The main effect of PPARδ/β activation in muscle is therefore to increase lipid oxidation. Exercise-induced fatty acid utilization by muscle in rats is increased by treatment with the PPARδ/β agonist GW610742 [93, 94], possibly as a consequence of PPARδ/β-dependent PDK4 expression. Consistent with this possibility, fasting-induced PDK4 expression is unaltered in PPARα-deficient skeletal muscle [95] but it is abolished in muscle lacking PPARδ/β [96]. In addition to enhanced expression of PDK4 and consequent inhibition of glucose oxidation, PPARδ/β activation also increases the transcription of genes involved in fatty acid uptake (CD36) and oxidation (carnityl palmitoyl transferase, CPT1) [96]. The primary roles of PPARδ/β in muscle are the adaptation to fasting and the switch from glucose utilization to lipid oxidation [24]. Beneficial effects of PPARδ/β on whole-body glucose homeostasis may rely in this effect, since increased FAO improves lipid metabolism. However, a recent report shows that the effect of PPARδ/β ligands is species specific [54]. Treatment of diabetic rats with the PPARδ/β ligands NNC61-5920 or GW501516 increases mRNA expression of CPT1, PDK4, and uncoupling protein 3 (UCP-3) in muscle, but despite this, plasma and muscle TG levels are increased [54]. In diabetic mice, the same ligands improve the plasma lipid profile, glucose tolerance and insulin action in muscle. Hepatic effects of PPARδ/β ligands do not differ between mice and rats [54].

2.1.3.2. PPARγ ligands improve insulin signaling and promote glucose utilization

Activation of PPARγ improves insulin receptor signaling [97]. Administration of TZDs increases the expression of insulin receptor and several components of the insulin signaling pathway in adipocytes, such as IRS-1, IRS-2, and the p85 regulatory subunit of PI3-K [98, 99]. In skeletal muscle of diabetic mice, TZD treatment increases the transcription of the insulin receptor, IRS-1 and IRS-2 [100]. A similar effect has been shown with a PPARα/γ dual agonist [101]. TZDs also restore tyrosine phosphorylation of the adipocyte insulin receptor, and improve downstream signaling by decreasing IRS-1 Ser-307 phosphorylation [97]. Increased activation of this insulin signaling pathway facilitates GLUT-4 translocation to the plasma membrane, thereby further stimulating insulin-induced glucose uptake and promoting glucose storage as glycogen. Insulin receptor activation and TZDs can affect gene expression synergistically in adipocytes, and insulin stimulates PPARγ-mediated transactivation [102]. PPARγ is transiently phosphorylated by insulin stimulation [102] and this might affect the DNA binding and transcriptional activity of PPARγ [103].

TZDs inhibit gluconeogenesis in the liver [28, 101] and kidney [104], and normalize glycogen synthesis in muscle [105]. Liver gluconeogenesis is dependent on the expression of PEPCK (EC 4.1.1.49), and TZDs are known to inhibit PEPCK expression in hepatocytes [106]; however, this inhibitory effect might be PPAR-independent [104]. Since T2DM is characterized by excessive hepatic gluconeogenesis, combined administration of TZDs with the gluconeogenesis inhibitor metformin has a clinical impact [107]. In adipocytes, PEPCK is responsible for glyceroneogenesis, and the gene encoding PEPCK is a PPARγ target. Increased expression of PPARγ2 and its

heterodimerization partner RXRα activates the PEPCK enhancer [108], and RSG treatment in diabetic rodents increases PEPCK expression [100, 109]. PPARγ response elements (gAF1/PCK1 and PCK2) have been identified upstream of the gene, and PCK2 is required for PEPCK expression and responsiveness to RSG [110]. Interestingly, gAF1/PCK1 is essential for glucocorticoid inhibition of PPARγ-induced PEPCK gene expression in adipocytes [110].

A recent study shows that the insulin sensitizing effects of PPARγ require the action of inducible 6-phosphofructo-2-kinase (iPFK2, EC 2.7.1.105) [111]. This enzyme is highly expressed in adipose tissue, where it is considered a master regulator of nutrient metabolism [112, 113]. Ablation of iPFK2 is embryonically lethal [114] and HFD-fed iPFK2 heterozygous mice show severe IR and increased inflammatory cytokine production in adipose tissue that cannot be reversed by TZD administration [112].

In adipose tissue and liver of diabetic mice, TZD treatment increases the transcription of genes involved in lipid uptake and catabolism, such as FABP, apolipoprotein 1A, LPL (EC 3.1.1.34), uncoupling factor 1 (UCP-1), acyl coenzyme-A-oxidase (EC 1.3.3.6) and other β-oxidation enzymes [100]. In muscle cells, genes of glycolytic enzymes, such as glucokinase (EC 2.7.1.2), 6-phosphofructo-1-kinase (EC 2.7.1.11) and pyruvate carboxylase (EC 6.4.1.1), which links glycolysis to the citric acid cycle, are moderately increased by PPARγ activation [100]. As a net result of TZD administration, carbohydrate utilization is increased in skeletal muscle, while liver and adipose tissue function as metabolic sinks for lipids.

PPARγ is expressed in the nervous system and appears to affect brain glucose utilization [38, 115]. Neurons have been classically considered to be insulin-insensitive, although the translocation of GLUT-3 to the neuronal cell membrane is increased by insulin [116] and special glucosensor neurons have been identified in the hypothalamus [117]. Activation of PPARγ enhances oxidative glucose metabolism of neurons and aerobic glycolysis and lactate release in astroglia [118]. Recent studies show that brain PPARγ is also required for the insulin-sensitizing effects of TZDs [38, 119].

2.1.3.3. Reducing inflammation and IR: another benefit of PPARγ and PPAR δ/β ligands

Adipose tissue dysfunction, which is commonly associated with obesity, is a major effect of IR development. In response to nutrient overload, visceral adipose tissue (VAT) releases free fatty acids and resistin, which contribute to IR and also decrease the production of adiponectin. In adipose tissue dysfunction, adipocytes and adipose tissue macrophages (ATMs) secrete a wide variety of inflammatory cytokines, such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1α (IL-1α), interleukin-18 (IL-18) and tumor necrosis factor-α (TNF-α) [4]. Under physiological conditions, resident ATMs express anti-inflammatory genes such as arginase-1 (Arg1) and interleukin-10 (IL-10) [4]. However, in diet-induced obesity, ATMs express high levels of inflammatory genes, leading to a subclinical inflammatory state that compromises insulin responsiveness [4]. The pro-inflammatory ATM phenotype is associated with increased lipid accumulation, and obesity progression thus promotes inflammatory cytokine production in adipose tissue [120].

Differentiation of monocytes into macrophages is associated with increased PPARγ expression, and PPARs also determine the acquisition of the inflammatory (M1) or anti-inflammatory (M2) macrophage phenotypes [4]. Activation of PPARγ has been related to differentiation of monocytes into M2-type macrophages in humans and mice [4]. Studies with macrophage-specific deletion of PPARγ show that inflammatory M1 macrophage polarization is increased by PPARγ deficiency during obesity progression, which leads to the development of IR [36, 121]. In the

absence of PPARγ, M1 inflammatory macrophages also invade adipose tissue and skeletal muscle, further aggravating insulin responsiveness [36]. In the liver, PPARδ/β might play a similar role, since deletion of PPARδ/β in Kupffer-cells leads to proinflammatory phenotype acquisition and IR [26]. Administration of TZDs reduces the macrophage inflammatory phenotype and thus ameliorates IR [36]. PPARδ/β ligands may play a similar role by mitigating proinflammatory Kupffer-cell activation [26], in addition to the beneficial effects of PPARδ/β activation on glucose metabolism [25]. Activation of PPARδ/β in adipocytes prevents IL-6-induced desensitization of the insulin signaling pathway, thereby protecting adipose tissue from IR [122]. Administration of PPARδ/β ligands also mitigates inflammatory gene expression in other tissues [123-125], demonstrating that the anti-inflammatory effects of PPARδ/β are not confined to macrophages.

2.1.3.4. Future challenges and perspectives on the use of PPAR ligands to treat metabolic disorders

Following the early success of TZDs in T2DM management, side effects of these ligands (such as unwanted weight gain, water retention and edema, cardiac events and reduced bone mineral density) led to the withdrawal of RSG (market name Avendia) from the European markets, and its use with caution in the USA [126]. Another TZD, pioglitazone (Actos) is still used to treat T2DM [127]. Moreover, many efforts have been made to find new PPAR ligands and to test clinical settings in which the metabolic benefits of PPAR activation (insulin sensitization with reduction of body adiposity) could be combined with mitigation of the side effects. To date, promising results have been obtained with PPARδ/β-PPARα dual agonists (e.g. bezafibrate and tetradecylthioacetic acid) and the combined administration of PPAR ligands (e.g. GW501516/fenofibrate or TZDs/fenofibrate combinations) [82]. Recent clinical studies show that dual activation of distinct PPAR isotypes has clinical potential [32]. Design of selective PPARγ modulators (SPPARMs) and specific PPARγ/RXR activators is today a subject of intense research. Nutrients or modified lipids that are low-affinity agonists of PPARs have also attracted interest for the selective targeting of PPAR-related metabolic pathways [32].

Recent findings place PPARγ and PGC1α at the center of a regulatory loop between circadian networks and metabolic performance of the liver and adipose tissue [128]. The expression patterns of PPARγ and PGC1α show a circadian pattern in several tissues [128]. Notably, liver oscillations of PPARγ levels are increased by excess lipid consumption, and the diurnal rhythm of blood pressure is altered in T2DM patients under treatment with RSG [128]. Gene deletion of PGC1α in mice disrupts circadian feeding behavior and energy expenditure [129]. The major circadian regulator of PPARγ is nocturnin, which reaches its peak expression level in the dark cycle in metabolic tissues [128]. Mice deficient for nocturnin exhibit impaired circadian expression of PPARγ and interestingly are protected from diet-induced obesity and have increased bone mass [128]. Recent advances show that bone is an important but still unexplored player in glucose homeostasis [130]. For instance, osteocalcin, a bone-derived mediator that increases bone mineralization, may act as a regulator of fat mass and glucose utilization [130]. Increased levels of osteocalcin are associated with β-cell hyperplasia in mice and with elevated levels of fasting glucose in T2DM patients [70, 131]. The increased osteocalcin levels and consequent hyperinsulinemia in mice is due to deficiency in the forkhead transcription factor FoxO1 [130], which is essential for adipocyte differentiation, [132]. In skeletal muscle PPARδ/β regulates FoxO1 expression, thereby affecting metabolism [96]. It is still unknown whether PPARγ targets FoxO1 in the skeleton. These novel findings on circadian PPARγ expression and the involvement of bone in glycemic control add new facets to our understanding of PPAR biology in homeostasis regulation.

2.3. PPARs and cardiovascular disease (CVD)

Since the discovery of the PPAR family, its potential as a therapeutic target in CVD has received much attention. PPARα and PPARγ have been shown to exert important functions in atherosclerosis, cardiac fibrosis, angiogenesis, cardiac ischemia-reperfusion (I/R) injury, infarct healing and cardiac hypertrophy (for reviews see [51, 133]). Although many studies point to beneficial effects of PPAR ligands in CVD, the exact molecular mechanism is still largely unsolved. Unlike the great majority of clinical trials with fibrates, which point to a reduced risk of coronary and cardiovascular events (reviewed in [16]), the effects of TZDs on human CVD are hotly debated. An update on the cardiovascular safety of PPARγ agonists is available in another article in this issue. Due to the later development of PPARδ/β-specific ligands, their potential in CVD remains controversial.

Below, we present an overview of the molecular and cellular events connected with the expression, function, and regulation of PPARs in the vascular system, and discuss the diverse biological actions of PPAR ligands on CVD processes.

2.3.1. PPARs and atherosclerosis

Atherogenesis is a combination of events in the wall of large arteries resulting in the formation of a lipid plaque. If the plaque continues to develop, it can promote the formation of a thrombus, causing ischemia in the surrounding tissues. According to Russell Ross's "response to injury" hypothesis, atherosclerosis is a response to damage, primarily to the endothelium, followed by an increase in the expression of adhesion molecules and chemokines that promotes the infiltration of atherogenic lipoprotein and the entry of monocytes and T-cells into the subendothelial space. This allows adhesion of monocytes and their differentiation into macrophages, accumulation of lipid by these cells leading to the formation of foam cells, and finally production of a lesion known as a fatty streak. At later stages, proliferation and migration of VSMCs results in expansion of the lesion, with death of both macrophages and VSMCs and further accumulation of lipid, producing the characteristic necrotic core of an advanced fibro-fatty lesion.

PPAR isotypes are expressed in VSMCs and cells of the immune system in varying amounts and these cells are therefore potential targets of PPAR agonists. Several lines of evidence indicate that PPARs exert anti-atherogenic effects by modulating the recruitment of monocytes to the arterial wall, their differentiation into macrophages, and the migration and proliferation of VSMCs. However, the principal atheroprotective effects of PPAR ligands are related to their negative influence on the two crucial atherogenic processes: lipid accumulation and inflammation in vascular wall cells.

2.3.1.1. PPARs and lipid homeostasis: link to atherogenesis

Macrophages localized in the arterial vessel wall are the most important regulators of lipid metabolism in this context in both normal and pathological conditions. They normally reverse cholesterol transport by endocytosis of LDL, cholesterol transfer to newly formed HDL, and their later elimination by the liver. If modified LDL (mLDL) accumulates in the subendothelium, macrophages become unable to perform this function, begin to accumulate lipids, and transform into foam cells. The balance between cholesterol uptake and reverse cholesterol transport determines the transformation of macrophages into foam cells in the atherosclerotic plaque.

PPARs, as systemic lipid sensors, play a crucial role in almost all these processes (reviewed in [134]). A number of studies in mice and humans have provided direct evidence for a critical role of PPARα and PPARγ in the regulation of cholesterol and fatty acid homeostasis in macrophages. Generally speaking, the effects of PPARα and PPARγ ligands on the expression of genes involved in macrophage cholesterol homeostasis are the same, the net effect being a reduction in cholesterol content. The mechanism mediating these effects implies the modulation of macrophage scavenger receptors, including scavenger receptor A (SR-A) and CD36, which mediate uptake of modified lipoproteins, especially oxidized LDL (oxLDL). The involvement of PPARγ in the regulation of lipid metabolism in macrophages was initially suggested by the discovery of CD36 as a positive PPARγ target gene in macrophages [135]. Other studies showed that SR-A, another receptor for mLDL uptake, is a negative target of PPARγ in macrophages [136]. Later studies showed that oxLDL transactivates CD36 in macrophages through a mechanism dependent on the expression of PPARγ [137] or PPARα [138]. Although these findings suggested that transcriptional activation of PPARs might promote foam-cell formation resulting from increased uptake of oxLDL by CD36, several studies involving activation or deletion of PPARs in animal models of atherogenesis provide direct evidence for antiatherogenic roles of PPARα [139-142] and PPARγ [140, 141, 143-146] (Tables 5 and 6). However, in some studies PPARα ligands either do not influence or even enhance atherosclerotic lesion area [147, 148], and in a mouse model of hyperlipidemia PPARα-deficiency reduced rather than increased the atherosclerotic area [149].

PPARs also control genes implicated in cholesterol efflux pathways, including ATP-binding cassette (ABC) transporters (ABCA-1, ABCG-1, and ABCG-4), the scavenger receptor B1 (SR-B1), and caveolin-1 (the main component of caveolae). The expression of ABCA-1 and ABCG-1 is induced by PPARα and PPARγ either directly [150], or indirectly via the liver-X-receptor (LXR), the expression of which is enhanced by PPARs [151]. In human macrophages, PPARα ligands enhance the expression of SR-B1 via an uncharacterized posttranslational mechanism [152]. ABCG-1, some apolipoproteins and caveolin-1 have also been identified as PPARα or PPARγ target genes [153-155], thus corroborating the role of PPARα and PPARγ in cholesterol removal from macrophages.

PPARs also modulate the expression of enzymes involved in lipid processing. For instance, PPARγ inhibits acyl-coenzyme A (CoA):cholesterol acyltransferase 1 (ACAT-1), thereby limiting the storage of cholesterol in lipid droplets in the form of cholesteryl esters [156]. A recent report indicates that ghrelin, an endogenous ligand of the growth hormone secretagogue receptor (GHS-R) with known cardioprotective effects, inhibits foam cell formation via simultaneous PPARγ-dependent down-regulation of ACAT-1 and up-regulation of ABCA-1 [157]. PPARα activation reduced ACAT-1 activity, and contributes to reduced cholesterol esterification by inducing the expression of carnitine palmitoyltransferase-1 (CPT1), a key enzyme in mitochondrial fatty acid catabolism [158]. Increased expression of CPT1 might result in reduced availability of fatty acids as substrates for ACAT-1, which could explain the decreased cholesterol esterification. In addition, PPARα and PPARγ activation might influence hydrolysis of cholesterol esters by increasing gene expression of neutral cholesteryl ester hydrolase (NCEH) [156, 159]. Furthermore, PPARα induces the expression of Niemann Pick type C (NPC) proteins 1 and 2 (NPC1 and NPC2), thereby stimulating post-lysosomal mobilization of stored cholesterol and leading to an enrichment of cholesterol in the plasma membrane [160].

Although available data are conflicting, a role for PPARδ/β in macrophage lipid homeostasis has been suggested. Work by *Li et al.* in 2001 indicated that agonists of PPARα and PPARγ, but not PPARδ/β, inhibit macrophage foam-cell formation *in vivo* [140]. However, in the three other mouse studies published to date, PPARδ/β ligands were found to reduce the atherosclerosis lesion area (Table 5) [123, 161, 162]. In addition, selective deletion of PPARδ/β in macrophages reduces lesion area in $LDLR^{-/-}$ mice [9] (Table 6). The mechanism mediating this anti-atherogenic effect is not likely to be regulation of cholesterol homeostasis. Indeed, *in vitro* studies indicated that

PPARδ/β might promote loading and storage of VLDL, TGs and cholesterol in macrophages via the induction of SR-A, CD36, the adipogenic gene A/FABP, and adipophilin (ADRP), which is a ubiquitous component of lipid droplets [163, 164]. In contrast, activation of PPARδ/β has been shown to reverse cholesterol transport by inducing expression of ABCA-1 [165] and Apo-E [163]. However, most studies suggest that PPARδ/β has an anti-atherogenic effect through the control of macrophage inflammation, as discussed below (section 2.3.1.2).

Apart from their direct effects in the vessel wall, PPARs also influence atherosclerosis by modulating lipid homeostasis in other tissues, such as liver, muscle, and adipose tissue. As described above, PPARα and PPARδ/β promote the clearance of TGs and LDL from the circulation, primarily by increasing tissue FAO and HDL metabolism. PPARγ achieves a similar effect by promoting the storage of lipids in adipose tissue. Because increased levels of HDL and decreased levels of TG and LDL are associated with low atherosclerosis risk, net effects of PPAR ligands on lipid metabolism may protect against atherosclerosis. Other effects of PPAR ligands in other tissues affecting lipid homeostasis have been reported. For example, activation of PPARα and PPARδ/β has been shown to reduce intestinal cholesterol absorption by inhibiting the expression of NCP1 in the proximal small intestine [166, 167].

2.3.1.2. PPARs and vascular wall inflammation

Accumulation of oxidized mLDL in the subendothelial space, induced by endothelial injury, infections or other pathogenic factors, leads to further weakening of the endothelium, accompanied by increased inflammatory potential of VSMCs and resident macrophages. In parallel, production of reactive oxygen species (ROS) by macrophages in response to inflammatory stimuli increases production of mLDL in the vascular wall, thus generating a vicious cycle of inflammation and lipid accumulation.

Several studies suggest a potential role of PPAR ligands in inflammatory processes in the vessel wall and in macrophages. For example, PPARα and PPARγ ligands have been shown to inhibit the synthesis of pro-inflammatory agents such as IL-6, IL-8, PGs, and COX-2 in the vascular wall [168]. Other studies demonstrated that the antiatherogenic effect of PPARγ ligands in $LDLR^{-/-}$ knockout mice correlates with decreased tissue expression of TNF-α [143]. Attenuation of the expression of pro-inflammatory mediators by PPAR ligands probably occurs through inhibition of the master transcription factor NF-κB in VSMCs. PPARα agonists have also been shown to abolish the IL-1β-induced expression of group IIA secretory phospholipase A2 (sPLA2-IIA), a proinflammatory mediator of atherosclerosis [168].

Apart from controlling endothelium inflammation, PPAR activation also confers other vasoprotective effects, such as vasodilation and suppression of VSMC growth. ECs regulate vascular tone by balancing the release of the vasoconstrictor endothelin-1 (ET-1, which also regulates VSMC proliferation) and the vasodilator nitric oxide (NO), generated by endothelial NO synthase (eNOS). Disturbed NO release, for example in the context of a lipid disorder, is associated with endothelial dysfunction and local lesion development. PPARα and PPARγ ligands have been shown to enhance eNOS expression and NO release, suggesting a vasoprotective effect [169-171]. Moreover, PPARα ligands inhibit the synthesis of ET-1 in ECs through the repression of AP-1 [172].Taking these effects together, PPAR activators may counterbalance endothelial dysfunction at various steps, including inhibition of inflammation and vasoconstriction.

Besides these direct effects on ECs, PPARα and PPARγ activation also interferes with the recruitment of inflammatory cells to the vascular endothelium. This effect is mediated through the regulation of chemokines and adhesion molecules needed for the recruitment of these cells to the damaged endothelium in the early steps of

atherogenesis. PPARα and PPARγ ligands have been shown to reduce expression of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), PECAM-1, E-selectin, MHC-II, and monocyte chemoattractant protein-1 (MCP-1) in response to various pro-inflammatory stimuli *in vitro* [173-176]. In addition, PPARγ, but not PPARα, inhibits INF-γ-induced expression of the chemokines IP-10, Mig, and I-TAC, with a subsequent decrease in lymphocyte chemotaxis [177]. PPARδ/β ligands have also been shown to attenuate the expression in aortic lesions *in vivo* of inflammatory genes and adhesion molecules associated with atherosclerosis, such as IFN-γ, TNF-α, MCP-1, VCAM-1 and ICAM-1 [123, 161, 178]. Deletion of PPARδ/β from foam cells by bone marrow transplantation from PPARδ/$\beta^{-/-}$ mice into $LDLR^{-/-}$ mice increases the availability of inflammatory suppressors, which in turn reduces atherosclerotic lesion area by more than 50% [9]. The authors of this study showed that ligand-activation of PPARδ/β also decreases the production of inflammatory molecules, and proposed an unconventional ligand-dependent transcriptional pathway in which PPARδ/β controls an inflammatory switch through its association with and disassociation from transcriptional repressors. In another study, using a model of angiotensin II (AngII)-accelerated atherosclerosis, which is characterized by increased vascular inflammation related to repression of the anti-inflammatory corepressor B cell lymphoma-6 (Bcl-6), the authors suggested that the effects of PPARδ/β ligands are based on the physical interaction between unliganded PPARδ/β and Bcl-6 [162].

As we have mentioned in previous sections, activation of PPARs leads to inhibition of macrophage functions related to inflammation. PPAR ligands have the potential to dampen inflammation in the vascular endothelium. Apart from direct effects, PPARs can modulate inflammation indirectly by regulating monocyte/macrophage differentiation. M1 and M2 macrophages are both found in undamaged regions of vessels and in atherosclerotic lesions, but in different ratios: M2 cells are present in undamaged vessels, while M1 cells predominate in atherosclerotic lesions. Under the influence of macrophage colony-stimulating factor (M-CSF), secreted by the endothelium and VSMCs, monocytes differentiate into macrophages with a prevalent M1 phenotype, which promotes a pro-inflammatory environment in the endothelial space; M1 macrophages secrete pro-inflammatory cytokines and growth factors, matrix proteinases, and pro-coagulants, and are active in triggering innate immune reactions in response to bacterial infection. Since activation of PPARγ is related to the differentiation of monocytes into M2-type macrophages in humans and mice [179], PPARγ might contribute to the mitigation of inflammation in this environment. Moreover, PPARγ was recently shown to be more highly expressed in circulating anti-inflammatory monocytes ($Ly6C^{low}$ monocytes) than in pro-inflammatory $Ly6C^{high}$ monocytes in mice, but not in humans [180]. Although there are no available data on the ability of PPAR ligands to alter the profile of circulating monocyte populations, it is reasonable to propose that PPAR activation would modulate the formation and fate of these subpopulations, thus ameliorating the inflammatory state in the whole organism, including the subendothelial space.

Finally, activation of PPARα and PPARγ limits the expression of Th1cell-derived proinflammatory cytokines, such as INF-γ, TNF-α and IL-2, which can activate other cells of the vessel wall during the initial stages of atherogenesis [181]. PPAR ligands can also modulate circulating levels of atherosclerosis-associated inflammatory markers such as TNFα, IL-1, IL1, and hepatic C-reactive protein (CRP) (reviewed in [182]).

2.3.1.3. PPARs and VSMC proliferation and migration

The chronic inflammatory response in the arterial wall stimulates VSMCs to migrate and proliferate, which contributes to neointima formation and plaque growth. Activated VSMCs synthesize and deposit extracellular matrix, contributing

to the formation of the fibrous cap of the atheroma. Thinning of the fibrous cap renders the plaque more vulnerable, increasing the risk of plaque rupture and subsequent thrombus formation.

PPARs have also been shown to influence proliferation, migration, extracellular matrix production, and apoptosis in VSMCs. Activation of PPARα, PPARδ/β, and PPARγ inhibits proliferation and migration of VSMCs both *in vitro* and *in vivo* (reviewed in [133]). The mechanisms responsible of these effects are related to the antiproliferative action of these NRs, via a mechanism involving control of DNA replication, cell-cycle progression, and apoptosis. Genes implicated in these processes include cyclin D1, the cyclin-dependent kinases CDK2 and CDK4, and CDK inhibitors such as p21, p16, p21, p53 and p27 [183]. PPAR activation also inhibits retinoblastoma protein (Rb) phosphorylation [184] and interferes with E2F signaling [185]. In addition, PPARα and PPARγ activation was shown to suppress telomerase activity in VSMCs [186]. Moreover, PPAR activation also interferes with endothelial expression of VEGFR2 (vascular endothelial growth factor receptor 2) and ET-1 [168, 172], both of which are involved in VSMC growth and proliferation.

PPAR activators also inhibit the release of matrix-degrading enzymes such as metalloproteinases (MMPs) and the expression of the AngII type receptor, and induce the expression of proteinase inhibitors [187]. These effects could modulate fatty streak formation and attenuate the arterial response to injury that occurs after coronary intervention. Aside from their effects on proliferation, PPAR ligands decrease the migration of VSMCs and reduce neointima formation *in vitro* and *in vivo*, possibly due to reduced MMP activity [188]. Moreover, specific PPARα ligands inhibit VSMC migration by reducing TGF-β-induced integrin expression [189]. All these PPAR actions could render the fibrous cap less vulnerable.

In conclusion, the potential involvement of PPARs in the development and progression of atherosclerotic lesion formation remains inconclusive; however, much of the existing data suggest that PPAR activation has an overall anti-atherosclerotic effect.

2.3.2. PPARs and heart disease

In addition to the well-studied role of PPARs in atherosclerosis, recent studies have demonstrated numerous pleiotropic effects of their ligands on the heart and cardiovascular system. Both the regulation of energy metabolism and the anti-inflammatory properties of PPARs are likely to play a role here. This suggests additional potential of PPAR ligands in the prevention of hypertensive heart damage, cardiac hypertrophy, and other vascular endothelial dysfunction-associated heart abnormalities such as heart failure, myocardial infarction and stroke.

2.3.2.1. PPARs and hypertensive heart disease

Persistent hypertension enhances the risk of cardiovascular abnormalities. Increased arterial blood pressure is associated with microvascular dysfunction, increased peripheral vascular resistance, and impaired post ischemic neovascularization in clinical studies and animal models of hypertension [190]. Recent research has revealed roles for PPARα and PPARγ in blood pressure regulation, expanding the possible therapeutic use of PPAR ligands (for reviews see [8, 51]). PPAR gene mutations lead to disturbances in blood pressure regulation. In humans, both the Pro12Ala polymorphism and mutations in the PPARγ gene contribute to hypertension [191]. Animal models of hypertension support these data (Table 6). Indeed, mice lacking PPARγ in VSMCs and ECs show altered vascular NO production

and hypertension [192-195], while systemic PPARα-knockout mice develop salt-sensitive hypertension [196]. In addition, transgenic mice expressing a dominant-negative PPARγ P465L mutation show a similar hypertensive phenotype to patients with an equivalent PPARγ P465L mutation [197, 198], and VSMC-selective PPARγ deletion leads to hypotension [199]. Blood-pressure-lowering effects of PPAR ligands have been demonstrated in several studies (Table 5). The PPARα ligand fenofibrate reduces blood pressure in stroke-prone spontaneously-hypertensive rats and salt-sensitive rats [200], and also in hypertensive transgenic mice expressing human renin and human angiotensinogen transgenes [201]. Importantly, several clinical studies have demonstrated the blood pressure-lowering effect of TZDs in humans [202].

The anti-hypertensive effects of PPARα and PPARγ ligands are mediated by several mechanisms. For instance, TZDs have been shown to inhibit VSMC L-type Ca^{2+}-channels [203]. In hypertensive rats, the prevention of heart damage and myocardial fibrosis by fenofibrates is mediated by reduction of NF-κB-induced myocardial inflammatory gene expression [204]. Furthermore, fenofibrate prevents cardiac fibrosis and abrogates overexpression of ET-1in the left ventricle (LV) of hypertensive rats [205]. Many of the anti-hypertensive effects of PPAR ligands are mediated by modulation of the renin-angiotensin-aldosterone system (RAAS), a major regulator of systemic blood pressure and interstitial fluid volume [8]. AngII is a pivotal molecule in RAAS, regulating blood pressure and contributing to endothelial dysfunction and atherosclerosis progression. Interestingly, activation of PPARα by fenofibrate prevents the development of hypertension, myocardial inflammation and fibrosis in AngII-infused rats by decreasing the cardiac expression of VCAM-1, PECAM, ICAM-1 and TGF-β and preventing collagen deposition [206]. Recent studies indicate that PPARα- and PPARγ-regulated gene expression can also influence the function of RAAS via the transcriptional control of renin, angiotensinogen, angiotensin converting enzyme (ACE), and AngII receptor 1 (AT-R1) (reviewed in [8]). Blockade of RAAS is an important therapeutic target in hypertension management and attenuates microvascular damage, glomerular inflammation and LV hypertrophy in hypertensive patients, and shows antidiabetic effects, thus reducing morbidity and mortality in patients with heart failure. Interestingly, telmisartan, a clinically approved RAAS inhibitor and AT-R1 blocker (ARB), is a partial agonist of PPARγ [8]. The clinical effectiveness of telmisartan has been demonstrated for the control of blood pressure and vascular risk in the elderly [207].

2.3.2.2 PPARs and cardiac hyperthophy

Cardiac hypertrophy, a dominant risk factor for the development of cardiac abnormality, is characterized by increased cardiomyocyte size and re-induction of the fetal gene program. Cardiac hypertrophy is generally considered to be an adaptive mechanism to compensate for a chronic increase in workload secondary to hypertension or regional myocardial infarction. Over the long-term, however, it becomes maladaptive: fibrosis takes place, and compensated hypertrophy can evolve into decompensated cardiac failure [208]. It has been postulated that the failing heart suffers from “energy starvation”, resulting from a diminished capacity to oxidize fatty acids, the main source of energy in the healthy heart [209]. Concurrently, activation of inflammatory signaling pathways, especially NF-κB, promotes both hypertrophy and fibrosis [210].

The role of PPARs in cardiac hypertrophy is unclear; although control of inflammation by PPARs is beneficial, the regulation of energy metabolism in the heart by PPARs has been shown to promote the progression of cardiac hypertrophy (reviews in [51, 133]). Many studies have reported the efficiency of PPAR ligands in ameliorating cardiac hypertrophy (Table 5). For example, *in vitro* studies using isolated cardiomyocytes showed that fenofibrates inhibit ET-1-induced cardiomyocyte enlargement and protein synthesis, and that antagonism of PPARγ enhances the promoter

activity of brain natriuretic peptide (BNP), a marker of transcriptional activation in hypertrophy [211]. Ligand activation of PPARδ/β inhibits hypertrophy of neonatal rat cardiomyocytes following α1-adrenergic stimulation [212]. Moreover, in an *in vivo* model of congestive heart failure, PPARδ/β normalizes cardiac substrate metabolism and reduces cardiac hypertrophy [213]. Activation of PPARα attenuates LV hypertrophy and cardiac fibrosis [172, 211], and its deletion in mice results in increased cardiac hypertyrophy and fibrosis [214-216]. PPARγ activators inhibit cardiac hypertrophy in cardiac myocytes [217], and heterozygous PPARγ mice and cardiac-specific PPARγ$^{-/-}$ mice display a more pronounced increase than wild-type mice in cardiac mass following pressure-overload [218-220]. These beneficial effects of the three PPAR isoforms have been linked to their anti-inflammatory properties, mainly to the inhibition of the essential hypertrophic growth signal NF-κB.

In spite of these positive effects, PPARα and PPARγ ligands have been shown to promote hypertrophy (Table 5). The negative effects of PPARα are linked to its role in the regulation of energy metabolism in the hypertrophied heart. During hypertrophy, PPARα, its heterodimerization partner RXR and the coactivator PGC1-α are down-regulated [221]. This leads to a decrease in FAO capacity, which can lead to energy starvation in the long-term [209]. Although the well-known function of PPARα ligands in the activation of β-oxidation should help to restore cardiac pump function, available data do not support this supposition. Indeed, treatment with PPARα ligands decreases glucose oxidation rather than increasing FAO, leading to a poor hemodynamic function of the hypertrophied heart [222]. Moreover, cardiac overexpression of PPARα in mice resulted not only in reduced myocardial glucose oxidation, but also in increased FAO, a metabolic phenotype strikingly similar to that of the diabetic heart [223-225]. In contrast, in a cardiac-specific PPARδ/β knockout mouse model, myocardial FAO production was decreased, oxidative damage increased, and the animals consequently developed cardiac hypertrophy and lipotoxic cardiomyopathy [226, 227]. This shift in substrate utilization has been linked to impaired cardiac function and the development of a cardiomyopathic phenotype. These findings suggest that stimulation of FAO in heart failure patients is not a desirable therapeutic goal. The role of PPARγ in the development of cardiac hypertrophy is highly controversial. In spite of its above-described anti-inflammatory properties, evidence acquired in recent years suggests that activation of PPARγ is pro- rather than anti-hypertrophic; indeed, cardiomyocyte expression of PPARγ leads to cardiac dysfunction in mice [228]. These negative effects have been linked to an increase in blood volume, suggesting that the observed development of hypertrophy in rodents treated with TZDs [219, 220, 229] might be due to volume overloading secondary to PPARγ-mediated effects on renal sodium reabsorption [230]. Indeed, PPARγ ligands have been reported to increase the risk of edema in cardiac patients, which is one of the main reasons why TZDs are contraindicated in patients with type II diabetes at risk of developing heart disease.

2.3.3.1 PPARs and heart failure

Heart failure is an outcome of various cardiovascular disorders including cardiac hypertrophy and hypertension, myocardial infarction and other forms of ischemic heart disease. Interruption of blood supply eventually results in loss of functional tissue through cardiomyocyte necrosis and apoptosis. The subsequent infarct healing process is characterized by distinct phases: the early infiltration of inflammatory cells, mainly neutrophils and monocytes, is followed by the replacement of necrotic tissue by granulation tissue (wound repair) and the development of a mature scar. Paralleling this, there is remodeling of the non-infarcted myocardium, characterized mainly by cardiomyocyte hypertrophy and interstitial fibrosis.

Recent studies suggest that PPAR ligands have the potential to prevent the progression of heart failure (reviewed in [51, 133, 231]) (Table 5). Apart from the described effect on the prevention of hypertension and hypertrophy, PPAR ligands have been shown to attenuate reperfusion injury after coronary artery occlusion, and to influence the fibrotic process that takes place during remodeling.

The role of PPAR in cardiac protection under transient I/R conditions has been described. Most *in vivo* studies performed with PPARα- and PPARγ-specific ligands point to a protective role for these molecules. For example, pre-treatment of rodents with PPARα- and PPARγ agonist causes a marked decrease in infarct area and improves cardiac function post I/R [232-235]. In addition, hearts from PPARα-null mice exhibit augmented susceptibility to ischemic damage [234, 235]. *In vivo* studies attribute these beneficial effects of PPARα and PPARγ ligands to their anti-inflammatory properties, mainly the attenuation of NF-κB signaling [235]. This is important since limitation of inflammatory responses during reinstallation of flow (reperfusion) is a major target for limiting I/R-induced injury. The PPAR-mediated decline in NF-κB activation has also been linked to a reduction of apoptosis in the reperfused ischemic myocardium [236], which might also contribute to the cardioprotective effects of PPAR ligands. Given the low expression of PPARγ in the heart, it is possible that the effect of its ligands on heart failure might be also attributable to their systemic insulin-sensitizing effects in adipose tissue and skeletal muscle. In fact, *ex vivo* studies with PPARγ ligands have mainly been performed in diabetic heart models [237], thus making it difficult to extrapolate the results obtained to the non-diabetic heart. Contrasting with these studies, investigations in *ex vivo*-perfused hearts showed improved post-ischemic functional recovery in PPARα-null mice, while PPARα overexpression was associated with depressed functional recovery [225]. It has been argued that this negative effect of PPARα could be mediated by the above-mentioned effects of PPARα on cardiac energy homeostasis, since the observed decline in GLUT4 expression might force the reperfused myocardium to use fatty acids instead of glucose, its preferred substrate in the early reperfusion phase [49, 223]. Consistent with this, one of the few studies addressing the role of PPARδ/β in I/R demonstrated that its overexpression in cardiomyocytes attenuates myocardial injury induced by transient artery occlusion, due to its stimulation of the uptake and metabolism of glucose rather than fatty acids [238]. This correlates with a study showing a cardioprotective effect of PPARδ/β agonists, involving the amelioration of lipotoxicity and anti-inflammation and up-regulation of pro-survival signaling [239].

Few studies have addressed the role of PPARs in permanent coronary artery occlusion (Table 5). After myocardial infarction, the loss of viable myocardium and the remodeling of the surviving myocardium eventually decrease cardiac function, predisposing to heart failure. Several studies performed in rodents suggest that PPAR ligands protect against these events only when applied in the early phase of infarct healing. For example, PPARα and PPARγ ligands preserve LV function and attenuate LV remodeling only if their administration begins within the first 24 h after coronary artery occlusion [240-242]. The need for early administration of PPAR ligands implies that PPARs are primarily involved in local inflammation or the formation of granulation tissue. These studies suggest that the interval between the onset of infarction and the start of treatment is critical.

Activation of PPARα and/or PPARγ has been shown to suppress myocardial fibrosis and cardiac dysfunction in rodent models of cardiac-pressure-overload [205, 243], rat models of hypertension [205], and in type II diabetic rats [244]. No *in vivo* studies into the effect of PPARδ/β activation on cardiac fibrosis have been performed, but *in vitro* activation of PPARδ/β has been shown to inhibit proliferation and differentiation of neonatal rat fibroblasts and myofibroblasts [245]. The suppression of myocardial fibrosis was shown to occur through attenuation of collagen synthesis. PPARs might influence the fibrotic process directly by modulating cardiac fibroblast phenotype and function or indirectly by modulating the synthesis of pro- and anti-fibrotic factors from neighboring or infiltrating cells. Indeed,

the inhibition of cardiac fibrosis by PPAR ligands in these rodent models has been ascribed to the suppression of ET-1 activity and NF-κB signaling. Regulation of ET-1 and proteins involved in cell-cycle progression might result in fibroblast proliferation. In addition, interaction of PPARs with the pro-fibrotic TGFβ-SMAD2/3 signaling pathway might inhibit the production of extracellular matrix constituents such as collagen-I and III and the myofibroblast marker smooth muscle α-actin [206].

In *in vitro* assays, both telmisartan and TZDs increase the number of human peripheral-blood derived and bone-marrow derived endothelial progenitor cells (EPCs) via a PPARγ-dependent pathway [246, 247]. The number of EPCs in peripheral blood is inversely correlated with mortality and the occurrence of cardiovascular events, since they contribute to postnatal vessel repair and neovascularization. EPC dysfunction may also contribute to the pathogenesis of hypertension [248]. Thus in a clinical setting, PPARγ ligands might be expected to improve vascular function and promote neovascularization via the proliferation of EPCs in ischemic tissue.

These studies reveal therapeutic potential for PPAR agonists in ischemic myocardial injury and cardiovascular diseases associated with endothelial dysfunction. PPAR ligands exert anti-ischemic effects through their anti-inflammatory properties. In addition, PPAR-ligand-induced improvement of NO-mediated responses and enhancement of EPC function probably enhances the antioxidant capacity of the vessel wall and its neovascularization in response to injury. The effect of PPAR ligands on infarct healing and the remodeling of the viable myocardium need further study.

2.3. PPAR ligands in acute and chronic inflammation

2.3.1. Anti-inflammatory profile of PPAR ligands

Beneficial effects of PPAR ligands in the treatment of IR and atherosclerosis involve anti-inflammatory mechanisms, as described above. Activation of PPARγ interferes with several signaling pathways regulating the expression of pro-inflammatory cytokines, chemokines and cell-adhesion molecules, thereby limiting the recruitment of inflammatory cells [4]. Modulation of PPARs, especially PPARγ and PPARδ/β, also has the potential to resolve inflammation. PPAR ligands are therefore of growing interest for the possible treatment of inflammatory diseases such as osteoarthritis, diabetic and autoimmune nephritis, chronic bowel disease, and psoriasis [7, 249-251].

2.3.2. Potential use of PPAR ligands in arthritis treatment: pros and cons

Osteoarthritis, one of the most prevalent chronic inflammatory diseases, is characterized by cartilage damage at the joints, synovitis, and remodeling of the subchondral bone in the inflamed region. Inflammatory cytokines such as IL-1β, TNF-α and IL-17, and prostaglandin E2, decrease PPARγ1 expression in chondrocytes through activation of MAPKs (p38 and JNK) and NF-κB signaling [252]. Advanced glycation end products, which can accumulate with aging or in diabetes, also reduce PPARγ expression in chondrocytes, and thus might promote osteoarthritis development [253]. In experimental models of osteoarthritis, pioglitazone reduces cartilage lesions, possibly through resolution of the prevailing inflammatory condition and by inhibiting cartilage degradation [249]. TZDs also inhibit NF-κB associated downstream COX-2 and iNOS signaling in osteoblasts, and thus might improve the inflammatory environment at ossification sites [254]. Recent findings show that extracellular matrix production by chondrocytes is controlled not only by PPARγ but also by PPARα and PPARβ/δ [255]. In an experimental model of rheumatoid arthritis,

administration of the PPARα ligand fenofibrate reduces skeletal muscle wasting, thus alleviating the external symptoms of arthritis [256]. The possible effects of PPARα and PPARβ/δ ligands on cartilage homeostasis should be determined, however. Interestingly, chondrocyte lipid metabolism is a target of PPARs, since PPARγ2 increases expression of hormone sensitive lipase during the chondrocyte differentiation program [257]. Toxic lipid derivatives contribute to cartilage and bone loss [258], thus the normalization of chondrocyte lipid handling is another possible PPAR target in osteoarthritis management.

Although PPARγ activation has chondroprotective effects *in vivo*, overall bone homeostasis is negatively affected by TZDs [259]. Activation of PPARγ reduces osteoblast differentiation and promotes adipocyte and osteoclast differentiation [260, 261]. Adipocytes and osteoblasts are derived from the same mesenchymal precursors, and PPARγ promotes adipogenic differentiation, explaining the reduced osteoblast activity in response to PPARγ ligand treatment [260]. Accordingly, mice with PPARγ haploinsufficiency develop elevated bone mineral density as a consequence of enhanced ossification [46](Table 1). Moreover, in mouse osteoblastic cell cultures the PPARγ ligand *15*-deoxy-Δ-*12,14*-prostaglandin J2 (15d-PGJ_2) causes oxidative stress, Akt inactivation, transient activation of ERK1/2, sustained activation of JNK, and mitochondrial injury with consequent apoptosis [262]. Two TZDs, troglitazone and ciglitazone, also trigger osteoblast apoptosis through free radical generation and the activation of ERK, p38 and caspase-3 [263, 264]. Ciglitazone-induced osteoblast cell death can be prevented by antioxidants, suggesting a primary role of reactive oxygen species [264]. The cytotoxicity of troglitazone and ciglitazone can be blocked by the PPARγ antagonist GW9662, confirming the active participation of PPARγ in osteoblast apoptosis [263, 264]. In addition to their pro-apoptotic effects, ciglitazone and 15d-PGJ_2 decrease mineralized bone nodules, alkaline phosphatase activity and osteocalcin transcription in cultured osteoblasts [263, 264]. In rats, oral administration of RSG decreases tibia BMD and serum ALP levels, indicating diminished osteoblast activity [254]. Clinical observations also reflect these findings, showing that chronic TZD treatment reduces bone volume and concomitantly increases fracture risk [265]. These unwanted effects of PPARγ ligands limit the use of these compounds in osteoarthritis management.

2.3.3. Inflammatory kidney disease and PPAR ligands

The kidney is another important target of anti-inflammatory PPAR ligand therapy. PPAR activators have well-characterized beneficial effects on kidney function in diabetes, mainly as a consequence of their anti-inflammatory profile [266]. Activation of PPARγ in mesangial cells and podocytes mitigates renal inflammation, reduces mesangial expansion, protects against podocyte loss, and improves overall renal function [266]. Indirect PPARγ effects, such as interaction with the renin-angiotensin-aldosterone system and attenuation of IR, also contribute to improved kidney physiology [8, 266]. Increased adiponectin levels in response to PPARγ activation also reduce renal inflammation [267]. PPARβ/δ activation has anti-apoptotic effects in the diabetic and ischemic kidney [268], possibly through activation of Akt signaling [266]. This effect might delay the progression of kidney disease associated with diabetes and atherosclerosis. The anti-inflammatory effects of PPARα activation also impair glomerulonephritis progression [269].

Recently our group and others have shown that PPARγ and PPARβ/δ ligands can alleviate autoimmune kidney disease by increasing the removal of apoptotic cell debris by macrophages [13, 270]. Deficient clearance of apoptotic cells is an important mechanism underlying self-immunity, and a causal factor of kidney disease in human lupus erythematosus [271]. PPARγ is required for proper phagocytosis in macrophages, monocytes and foam cells [13, 272-

275]. The ability of macrophages to engulf apoptotic cells is reduced by ablation of mouse macrophage PPARγ and by inhibition of PPARγ during human monocyte/macrophage differentiation [13, 275]. Similarly, non-professional macrophages engulf apoptotic cells more efficiently upon treatment with PPARγ ligands [276, 277]. Ligands of PPARγ (RSG, 15d-PGJ_2) enhance phagocytosis through the transcriptional control of cell-surface receptor molecules, complement receptors and opsonins [13, 278]. A possible natural PPARγ ligand (*trans*-10, *cis*-12-conjugated linoleic acid) also facilitates phagocytosis by porcine peripheral blood polymorphonuclear cells [279]. PPARγ-dependent apoptotic cell clearance is also required for the anti-inflammatory reprogramming of macrophages [13].

Importantly, similar effects have been shown for the PPARβ/δ agonist GW0742. Activation of PPARβ/δ enhances the phagocytosis of apoptotic cells by mouse splenic macrophages and human monocyte-derived macrophages [270]. Macrophage-specific deletion of PPARβ/δ impairs the expression of complement factors and opsonins, which reduces the binding of apoptotic cells to macrophage cell-surface receptors [270]. These findings suggest that PPAR ligands can increase the expression of macrophage cell-surface receptors and bridging molecules, which promote the proper engulfment of apoptotic debris. Ligands of PPARγ and PPARβ/δ therefore might provide promising targets for the treatment of lupus nephritis.

2.3.4. Psoriasis treatment and PPARγ

Psoriasis is a chronic inflammatory skin disease, characterized by accelerated keratinocyte proliferation, dendritic cell accumulation and activation of a Th17 subset of T cells [280]. Administration of TZDs (pioglitazone and RSG) alleviates the symptoms of psoriasis, possibly via a mechanism involving the growth-inhibiting action of TZDs on rapidly proliferating epidermal keratinoctyes [281]. Treatment of keratinocytes with TZDs suppresses epidermal growth factor receptor autophosphorylation and inhibits signaling through the ERK/MAPK pathway, leading to suppressed proliferation *in vitro* [281]. Beneficial effects of TZDs in psoriasis might also involve inhibition of TGF-β signaling in keratinocytes [282]. Psoriasis is often associated with IR, obesity or metabolic syndrome [283], and is alleviated by improved glucose and lipid homeostasis [284]. Administration of TZDs in patients with metabolic syndrome and concomitant psoriasis thus yields a dual benefit; however, further studies are needed to define the optimum therapies [285, 286].

Importantly, PPARα and PPARβ/δ are expressed in wounded skin [7], and recent studies show that PPARβ/δ mRNA levels are significantly elevated in skin lesions of psoriasis patients [287] and in a mouse model of psoriasis [280]. Key transcriptional programs activated by PPARβ/δ in psoriasis include IL-1-related signaling, cholesterol biosynthesis and phosphorylation of STAT3 [280, 288]. PPARβ/δ is also expressed in activated human T cells purified from peripheral blood as well as in T cells isolated from affected psoriasis skin lesions. PPARβ/δ enhances proliferation of primary T cells and blocks their apoptosis, and thus may contribute to the persistence of activated T cells in psoriasis skin lesions [289]. Administration of PPARγ ligands and PPARβ/δ inhibitors therefore might provide a viable strategy for psoriasis treatment. PPARs are involved in sebocyte and hair-follicle differentiation [7], and lipid metabolites of the sebaceous gland can activate PPARs. Targeting of PPARs thus has potential use in the treatment of milder skin inflammation, such as acne [290]. PPARγ-mediated signaling might also maintain normal hair-follicle cell function and reduce inflammatory skin scarring and alopecia [291].

2.3.5. Inflammatory bowel disease

Ulcerative colitis and Crohn's disease, the two main forms of chronic inflammatory bowel disease (IBD), are also possible targets of PPAR ligand therapy. The Pro12Ala PPARγ polymorphism might predispose to a subset of ulcerative colitis and Crohn's disease [292-294], and PPARγ downregulation has been detected in lesions of ulcerarive colitis [293, 295] and in intestinal epithelia [296]. Similarly, increased susceptibility to experimentally-induced colitis has been reported in mice with PPARγ haploinsufficiency [297] (Table 2). TZDs improve the impaired PPARγ activity in inflamed colonic epithelium, and have beneficial clinical effects in patients with active distal ulcerative colitis [250, 298]. The protective effects of PPARγ ligands on intestinal inflammation may be due to an increased Th2 cytokine response [297]. Similarly to PPARγ ligands, PPARα agonists reduce colonic inflammation in experimental models of IBD [299-301]. The beneficial effects of treatment with 5-aminosalicylic acid or glucocorticoids are observed only in mice expressing PPARγ or PPARα, respectively, and not in PPARγ deficient [302] or PPARα systemic knockout [303] mice. These studies indicate that both PPARα and PPARγ have anti-inflammatory effects in mouse models of chemically-induced colitis.

PPARγ also improves mucosal barrier function by maintaining constitutive epithelial expression of a subset of beta-defensins in the colon (mDefB10 in mice and DEFB1 in humans), thus improving host defense against intestinal microbiota [304]. In line with this finding, the colonic mucosa of PPARγ-deficient animals shows impaired microbial killing and compromised protection against *Candida albicans*, *Bacteroides fragilis*, *Enterococcus faecalis*, and *Escherichia coli* [304]. PPARγ activation thus has the potential to mitigate chronic bowel disease by reducing inflammation and restoring mucosal defense. Mice lacking IL-10 also develop an intestinal immunopathology resembling Crohn's disease [301]. In this animal model, administration of fenofibrate delays disease onset and reduces lesion severity and inflammation [301]. Future studies should define the mechanisms underlying PPARα activation and the subsequent reduced severity of IBD.

2.3.6. Action of PPARs in chronic airway inflammation and pancreatitis

Beneficial effects of PPARγ have also been shown in chronic airway inflammation [305], and the treatment of chronic obstructive pulmonary disease has emerged as another novel candidate target of PPARγ ligands [306]. An association has also been demonstrated between chronic obstructive pulmonary disease (COPD) and PPARγ allele polymorphisms [307], underscoring the importance of PPARγ in this pathology. Pharmacological PPARγ activation reduces oxidative stress and chemokine expression in inflamed airways, thereby mitigating COPD and associated pulmonary pathologies [305, 308, 309]. Most recently, impaired activation of PPARγ has been shown to account for the inflammation that provokes mucus retention in cystic fibrosis patients [310]. Airway mucus is retained and thickened in these patients, which leads to the obstruction and inflammation of luminal organs, such as the lungs. In a mouse model of cystic fibrosis, RSG treatment partially normalizes the altered gene expression pattern associated with cystic fibrosis, and reduces mucus retention and disease severity [310]. In cystic fibrosis patients, the compromised PPARγ activation may be a consequence of the reduced bioavailability of an endogenous PPARγ ligand (15-keto-prostaglandin E2) [310].

Acute pancreatitis can lead to the activation of lung macrophages and secondary pulmonary inflammation [311]. This pathology is also attenuated by PPARγ ligands such as RSG and pioglitazone [312, 313]. In a pancreas-specific PPARγ knockout mouse model, RSG fails to inhibit acute pancreatitis, showing that TZDs mitigate pancreatic

inflammation by targeting pancreatic cells and not immune cells [314]. But although pioglitazone has potential in the treatment of acute pancreatitis, RSG is linked to adverse adipose cell infiltration of the exocrine pancreas [315].

2.3.7. PPARs in neuroprotection and inflammatory hyperalgesia

Recent findings show that PPARs have positive effects on neuronal survival after ischemia-reperfusion injury of the brain and also mitigate neuroinflammation [316-318]. The therapeutic potential of PPARs could thus be expanded to the treatment of neurodegenerative conditions such as stroke, Alzheimer disease, Parkinson disease, multiple sclerosis, and amyotrophic lateral sclerosis [318, 319].

PPARα activation by fenofibrate reduces stroke susceptibility in mice and protects neurons from cell death in cerebral ischemia [320]. A rat model of stroke showed similar improvements in cerebral lesions and survival [316]. Neuroprotective effects of fenofibrate are absent from mice lacking PPARα, showing that PPARα activation is pivotal to mitigating stroke outcome [320]. PPARα-mediated neuroprotection is mediated through improved cerebral artery sensitivity to endothelium-dependent relaxation, upregulation of antioxidant enzyme activities, and the prevention of ischemia-induced expression of adhesion molecules in cerebral vessels [320]. These effects improve blood flow, mitigate oxidative injury, and reduce inflammatory cell evasion. PPARα might also reduce neuronal cell death in neurodegenerative conditions. For instance, oxidative stress and mitochondrial dysfunction in early Alzheimer disease is associated with reduced PPARα expression [321] and a correlation has been detected between human PPARα polymorphisms and increased risk of Alzheimer disease [322]. PPARα activation reduces the activation of inflammatory microglia and macrophages in response to amyloid deposition, and thus could slow the development of Alzheimer disease [323]. The anti-inflammatory effects of PPARα agonists also reduce disease severity in animal models of multiple sclerosis, through reductions in IL-4 and IL-5 expression [324]. Lipid lowering drugs have the potential to delay the progression of Parkinson disease; however, the positive effect of fibrates in this disease is still debated [325].

Ligands of PPARβ/δ and PPARγ have antioxidant effects and reduce neuronal cell loss in models of cerebral ischemia [318, 326, 327]. Anti-apoptotic effects of PPARγ and PPARβ/δ agonists have also been shown *in vitro*: PPARβ/δ activation reduces neuronal apoptosis, and various TZDs (troglitazone, RSG, NP00111 and NP01138) protect cultured cortical neurons from cell death induced by cell-free supernatant of activated microglia [328, 329]. In most neurodegenerative disorders, including multiple sclerosis, Parkinson disease and Alzheimer disease, neuronal cell death is induced by an uncontrolled inflammatory response of activated astrocytes and microglia [330]. PPARβ/δ and PPARγ not only protect neurons from the apoptosis-inducing effects of these inflammatory stimuli, but also inhibit inflammatory activation of cultured astrocytes and microglia and diminish their neurotoxic production of IL-6, TNF-α and NO [329, 331]. For instance, various PPARγ agonists reduce disease severity in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis [332-335]. The underlying mechanisms might include PPARγ-mediated inhibition of IL-12 production by microglia [335], blocked proliferation and activation of neuronal antigen-specific Th1 cells, and reduced differentiation of Th17 cells, the main effector cells in neuroinflammation and autoimmunity [333, 336, 337]. Similar roles have been attributed to PPARβ/δ, since PPARβ/δ-deficient mice develop prolonged EAE in association with augmented Th1 and Th17 responses [338]. Accordingly, PPARβ/δ agonists show neuroprotective potential in *in vivo* models of cerebral ischemia and Parkinson disease [327]. The anti-inflammatory effects of PPARγ agonists also reduce cell death in experimental Parkinson disease [339], and they reduce amyloid

deposition, mitigating disease progression and improving learning and memory in animal models of Alzheimer disease [318, 340]. Clinical trials with RSG have shown significant improvement in memory and cognition in Alzheimer disease patients [341]. Since PPAR ligands inhibit oxidative stress, inflammation and neuron apoptosis, they have the potential to mitigate other neurodegenerative diseases such as amyotrophic lateral sclerosis [342] and radiation-induced brain injury [317]; however, these clinical implications are still largely unexplored.

Inflammation is associated with increased pain (hyperalgesia), due at least in part to the local acidosis of the inflamed tissue. Interestingly, inflammatory hyperalgesia is reduced by the PPARγ ligand 15d-PGJ_2 [115, 343]. This effect is possibly mediated by tissue macrophages and involves endogenous opioid-signaling pathways [343]. TZDs may play a similar role in the central nervous system [115], raising the interesting possibility that anti-inflammatory PPARγ ligands could be used to combat inflammatory pain. These findings suggest future applications of PPAR activators in the management of chronic inflammatory conditions.

2.4. PPARs and cancer

2.4.1. PPARs: carcinogens or tumor suppressors?

Due to their anti-inflammatory, anti-angiogenic, anti-proliferative, pro-apoptotic and differentiation promoting activities, PPARs have been intensively studied as targets for anti-cancer therapy in preclinical models [344]. However, PPARs have been reported to act both as promoters and suppressors of neoplasia, and the clinical potential of PPAR ligands and antagonists remains controversial. In some tissues, expression or activation of these receptors correlates with a positive clinical outcome, while in others they have the opposite effect. Indeed, firm genetic evidence supporting an association between the various polymorphisms/mutations in PPAR genes and the occurrence of cancer is at present lacking. For instance, some studies have linked somatic mutations in the PPARγ gene or inhibition of its function to the frequency of colon, thyroid, or prostate tumors (reviewed in [344]); however, another study did not detect mutations in PPARγ in a large sample of clinical cancer specimens, including colon, prostate breast, and lung cancers and leukaemias [345]. Additionally, total loss of both PPARγ alleles has never been described in any tumor, which would indicate that PPARγ is not a true tumor suppressor.

These contradictory findings suggest that the action of PPARs in cancer is likely to depend on several factors. First, the outcome might be affected by the differentiation state of cells or tumors. Second, PPAR activity is influenced by numerous other factors (cofactors, mutations in target genes, etc.). Third, the differing characteristics of the animal models studied might affect the results obtained (some models are useful for the study of spontaneous development of cancer, whereas others are suitable for analyzing the behaviour of clonal cancerous cell populations). Also, given the pleiotropic activity of PPARs and their wide expression profile, the outcome might be the average of the different responses of diverse cell types present in the tumor bed. Finally, outcomes could be influenced by the bioavailability and concentration of PPAR agonists and the duration of treatment. In this regard, it is important to note that high concentrations of PPAR ligands elicit biological effects that arise from the cross-reactivity with different PPAR isotypes, or that might even be independent of PPAR activation. Also, in preclinical studies with rosiglitazone (RGZ), the concentrations used were far higher than those used in clinical trials, which are in the antidiabetic therapeutic range and consequently might not be effective for antitumor actions. Therefore the dosage of PPAR ligands in clinical trials

for cancer therapy needs to be defined thoroughly and monitored closely. Below, we highlight the latest studies on the role of PPARs in cancer.

2.4.2. PPARs and gastrointestinal neoplasia

The chronic inflammation caused by infections or autoimmune diseases has been recognized to contribute to inflamed stroma and tumor initiation, growth, and metastasis. The proteome and transcriptome of the tumor micro-environment undergo dramatic changes associated with the upregulation of inflammatory cytokines, suggesting the presence of an inflammatory response in the host tissue surrounding the tumor. Epidemiologic studies indicate that chronic inflammation is associated with increased cancer risk. For example, it has long been known that patients with persistent infection with hepatitis B or *Helicobacter pylori*, or with an immune disorder such as IBD, are at increased risk of developing liver or gastrointestinal tract cancer.

The anti-inflammatory effects associated with the activation of PPARs led several groups to explore the involvement of PPARs in colorectal cancer (CRC), which has been linked to chronic inflammatory disorders of the gastrointestinal tract. Direct demonstration of the link between inflammation and tumor progression comes from a clinical trial showing that the use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the relative risk of developing CRC by 40% to 50% [346].

PPARα and PPARγ are both expressed in epithelial cells of the mouse gastrointestinal tract [347]. PPARα expression is higher in small intestine than in colon, whereas PPARγ shows the reverse pattern. The physiological roles of PPAR proteins in the intestine are not fully defined, but are thought to involve the regulatory actions of PPARα and PPARγ on inflammation in the colon. The expression of PPARβ/δ in the gastrointestinal tract is very high compared with that in other tissues [348]. However, although PPARβ/δ deletion significantly exacerbates adverse symptoms in mouse models of experimental colitis, treatment with PPARβ/δ agonists not only does not reduce clinical symptoms of colitis [349], it enhances colitis in IL-10-deficient mice [301]. In addition to epithelial cells, expression of PPARs in immune cells might contribute to their protective role against inflammation and cancer in the gastrointestinal tract.

Studies of the role of PPARs in the intestinal tract suggest that PPARα and PPARγ agonists have great potential to alleviate the symptoms of intestinal inflammatory diseases, and could prevent the development of inflammation-associated cancer.

2.4.3. PPARs and tumor proliferation/suppression

Uncontrolled tumor cell proliferation requires the up-regulation of multiple intracellular signaling pathways, including those involved in survival, proliferation, and cell-cycle progression. Several studies suggest that PPAR activation results in growth arrest of tumor cells though the induction of cell-cycle arrest and/or apoptosis.

2.4.3.1 PPARα and PPARγ

Chronic administration of certain PPARα agonists induces hepatocarcinogenesis in rodents [350], and therefore PPARα was initially not considered as a molecular target for cancer therapy. However, epidemiologic risk evaluation studies showed that PPARα ligands (which include clinically used hypolipidemic fibrates and also industrial plasticizers, pesticides and solvents) do not trigger the same responses in human hepatocytes as they do in rodent liver,

demonstrating their safety [351]. Moreover, in the last decade several studies have revealed that PPARα is expressed in tumor cells of prostate, breast, or endometrial origin (reviewed in [344]). These findings raised great interest in the link between PPARα and cancer, because epidemiologic data suggest that dietary fat and cholesterol, by increasing circulating estrogen levels, might increase the risk of hormone-dependent cancer [352]. Importantly, several *in vitro* studies have demonstrated that activation of PPARα inhibits the proliferation of mouse and human malignant cells, including those derived from melanoma, skin, breast, glia, colon, endometrium, lung, and ovary (reviewed in [344]. In contrast to PPARα, the anticancer effects of PPARγ agonists have been extensively studied (for reviews see [344, 353]). PPARγ activation exerts anti-proliferative effects in several tumor cell lines, including liposarcoma, glial brain tumors, pituitary tumors, adrenocortical cancers, bladder cancers, and carcinomas of diverse origin including breast, prostate, colon, ovary, non-small cell lung, pancreas, and gastric. In addition, ligand-activation of PPARγ induces apoptosis of breast, prostate, brain, and non-small lung cancer cells, as well as of human monocyte leukaemia cells. Induction of PPARα has also been linked to the induction of apoptosis in malignant cells. PPARα-specific agonists trigger cell death in human glioblastomas and endometrial cancers. Also, treatment of malignant cells of different origins (particularly liver and brain) with conjugated linoleic acid induces PPARα expression, and there is a direct correlation between the highest increase in PPARα and the induction of the apoptotic program. These cytotoxic and cytostatic effects of PPARs are linked to changes in expression of genes that regulate cell growth and maturation and apoptosis. These genes include cyclin D1, the cyclin-dependent kinase inhibitors p18, p21 and p27, tumor suppressor genes such as PTEN and p53, oncogenes such as MDM-2, anti-apoptotic genes such as Bcl-2 and Akt, and molecules with pro-apoptotic activity including Bax, PARP, Caspase 3 and AP-1. In addition, PPARγ activation inhibits E2F/DP DNA binding, which is required for cell proliferation, and the phosphorylation of Rb, which also contributes to tumor-cell arrest. Recent studies suggest that PPARα activity is more related to apoptosis, while PPARγ activation is more related to the control of cell proliferation [354]. The authors show that treatment of human hepatocarcinoma HepG2 cells with a PPARα-specific ligand induces apoptosis in a time- and dose-dependent manner, whereas incubation of the same cell line with a PPARγ-specific ligand provokes a time- and concentration-dependent inhibition of cell proliferation.

In spite of these results, *in vivo* evidence for an anti-tumorigenic role of PPARγ and PPARα is controversial because of conflicting results from different mouse models of cancer (Table 7 and 8). On the one hand, PPARγ and/or PPARα activation inhibits tumor growth and progression in xenografts and chemically-induced models of colon, prostate, adrenocortical, pituitary, ovarian, skin, and breast cancer [355-360]. On the other hand, PPARα-specific knockout mice are resistant to chemically-induced carcinogenesis [361], and several studies have demonstrated that activation of PPARγ promotes the development of colon tumors in C57BL6J-APC$^{min/+}$ mice, a clinically-relevant model of familial adenomatous polyposis and sporadic colon cancer [362, 363]. However, intestinal-specific PPARγ knockdown promotes tumor growth in C57BL6J-APC$^{min/+}$ mice [364], and PPARγ knockdown has also been shown to increase the occurrence of chemically-induced ovarian and colon cancer [365, 366]. These divergent effects of PPARγ might be related to drug doses and bioavailability, and to the animal models used.

Clinical studies have not provided a conclusive answer to the question of whether PPARα or especially PPARγ activity favors or inhibits cancer formation and progression. Clinical trials of TZD for the treatment of different types of solid tumors have given controversial results. Striking results were obtained in clinical trials of PPARγ-agonist efficiency in the treatment of liposarcomas, showing that triglitazone efficiently induced differentiation and cell-cycle arrest of liposarcome in three patients [367]. A few studies found a positive therapeutic effect of TZD, particularly if combined with chemotherapeutic and angiostatic agents [368]. Importantly, a retrospective cohort study in humans

revealed that treatment of diabetic patients with TZD slightly reduced the risk of CRC and prostate cancer, and reduced the risk of lung cancer by 33% [369].

2.4.2.2. PPARβ/δ

It is unclear whether PPARβ/δ has pro- or anti-tumorigenic effects, since the evidence is conflicting. Several reports present evidence of a role for PPARβ/δ in cell proliferation in various cancer models, including colon, ovarian, breast and lung cancers. The following observations strongly suggest the existence of a crosstalk between oncogenic signaling and PPARβ/δ, and thus a tendency of PPARβ/δ to enhance cancer formation. First, PPARβ/δ expression is elevated in colon cancer cells, and its endogenous activation has been proposed to mediate the pro-tumorigenic effect of PGs in the colon [370]. Importantly, tissue expression of PPARβ/δ has been associated with poor prognosis in CRC patients [371], and its genetic disruption decreases the tumorigenicity of human colon cancer cells [372]. Moreover, repression of PPARβ/δ by NSAIDs has been shown to mediate the tumor suppressor activity of these agents in CRC [373] and ovarian cancer [374] by a mechanism that includes a decrease of COX-dependent PG production and a direct inhibition of the DNA-binding activity of PPARβ/δ. In a later report using NO-donating aspirin, the authors describe a relationship between reduced PPARβ/δ expression and the degree of chemoprevention, accompanied by a quantitatively corresponding induction of apoptosis [375]. Furthermore, expression of PPARβ/δ increases after activation of the oncogene k-Ras [376], and is repressed by the tumor suppressor APC via the β-catenin/Tcf-4 response elements in its promoter [373]. Indeed, pharmacological activation of PPARβ/δ has been related to an acceleration of intestinal adenoma growth in C57BL6J-APC$^{min/+}$ mice [377, 378], and tumorigenesis is significantly inhibited after PPARβ/δ knockdown [372, 379, 380]. However, several studies reported that PPARβ/δ is dispensable for polyp formation in the intestine and colon of C57BL6J-APC$^{min/+}$ mice [381], and several other studies point to an anti-tumorigenic activity of PPARβ/δ. For instance, activation of PPARβ/δ by the synthetic ligand GW0742 attenuates skin tumorigenesis, and its efficacy is increased when combined with COX-2 inhibitors [382]. The strongest evidence for an anti-tumor action comes from animal studies with PPARβ/δ–null mice. PPARβ/δ expression attenuates colon polyp formation and predisposition to intestinal tumorigenesis in C57BL6J-APC$^{min/+}$ mice and in mice with chemically induced cancers [383, 384]. Moreover, a recent study demonstrated that the proliferation of colon cancer cell lines is significantly accelerated after PPARβ/δ knockdown [385]. Finally, in spite of a report suggesting that PPARβ/δ is elevated in most human CDRs [370], other reports show that PPARβ/δ expression is lower in human tumors than in normal control tissues [386].

2.4.4. PPARs and angiogenesis

Cancer is not simply attributable to the loss of growth control of a single cell clone, but is rather a developmental disease that involves interactions between tumor cells and the stromal tissue. The microenvironment includes ECs, inflammatory cells, and other stromal elements. Angiogenesis and inflammation are central processes through which the tumor microenvironment influences tumor growth. The process of neovascularization requires that ECs proliferate, migrate, disrupt the matrix in order to invade, form tubes, and mature through the recruitment of surrounding pericytes. Angiogenesis is also tightly linked to tumor secretion of specific cytokines and inflammatory mediators (e.g. IL-6, IL-8, COX-2 and iNOS) [387]. PPARs have been shown to affect each stage of angiogenesis, and therefore the effects of PPAR ligands on cancer will not be mediated exclusively by tumor cells, thus extending the repertoire of potential targets of PPAR ligands beyond cell autonomous mechanisms of cancer.

2.4.1. PPARα

PPARα is expressed in tumor, endothelial and inflammatory cells [388]. Endothelial expression of PPARα inhibits proliferation and migration, and induces apoptosis *in vitro* [389]. Other *in vitro* studies have revealed an anti-metastatic activity of PPARα ligands. Activation of PPARα inhibits proliferation of mouse lung ECs [360] and VEGF- and FGF2-stimulated proliferation of human umbilical vein and bovine capillary ECs [390]. In addition to its anti-endothelial effects, fenofibrate directly suppresses VEGF production, and increases tumor-cell production of the angiogenesis inhibitors thrombospondin (TSP-1) and endostatin. In a study assessing the role of clofibric acid (CA, a specific ligand of PPARα) in human ovarian cancer, the authors showed that CA decreased PGE_2 levels in correlation with decreased VEGF expression [359] Other studies have shown that PPARα activation leads to a down-regulation of Akt phosphorylation in melanoma cells [391]. Since Akt predisposes fibrosarcoma cells to an aggressive phenotype by increasing their migration, invasion and MMP production, the inhibition of Akt signaling might be involved in the anti-metastatic activity of fenofibrate. Moreover, fenofibrate inhibits metastatic spread from melanoma tumors *in vivo* [392], reduces adventitial angiogenesis and inflammation in a porcine model [393], and inhibits corneal neovascularization induced by the angiogenic factor fibroblast growth factor 2 (FGF2) [390]. Importantly, fenofibrate has been shown to decrease VEGF levels in patients with hyperlipidaemia and atherosclerosis [394]. Reduction of tumor growth and vascularization induced by treatment with PPARα ligands has been linked to decreases in the plasma levels of pro-angiogenic epoxygenase metabolites (ETTs), hepatic EET biosynthesis, and Cyp2c epoxygenase expression [360]. Panigrahy and co-workers demonstrated that systemic therapy with PPARα ligands inhibits primary tumor growth through a mechanism dependent on PPARα expression in host stroma, but not in tumor cells. These findings together suggest that PPARα activation suppresses tumor growth through direct actions on tumor cells and indirect actions on angiogenesis.

2.4.4.2. PPARγ

PPARγ is expressed in normal ECs, and also in the tumor endothelium [395]. In fact, PPARγ is more highly expressed in ECs of lung cancer and renal cell carcinoma than in corresponding healthy tissue [396]. In *in vitro* angiogenesis assays PPARγ agonists inhibit angiogenesis at several steps. PPARγ ligands inhibit EC growth and migration as well as tube formation induced by the angiogenic factors FGF2, leptin, phorbol myristate acetate (PMA) and VEGF [395]. PPARγ agonists also induce EC apoptosis at nanomolar doses, suggesting a specific PPARγ-mediated effect [397]. When used to treat tumor cells, TZDs have been shown to reduce the invasiveness of adrenocortical cancer cell lines (H295R and SW13) through matrigel by about 85%, and to inhibit MMP2 secretion in a dose-dependent manner [398]. PPARγ ligands have also been shown to inhibit fibronectin-induced expression of α5 integrin (a promotor of angiogenesis) and the growth of non-small lung carcinoma cells [399].

Due to its multiple pleiotropic effects, PPARγ has been proposed to modulate angiogenesis *in vivo* by affecting the expression of molecules in tumor cells and also in the tumor microenvironment, including ECs, pericytes, and inflammatory cells. PPARγ ligands have been shown to directly modulate the expression of leptin [388], the anti-angiogenic molecule maspin (mammary serine protease inhibitor) [400], the pro-angiogenic molecules TNFα and iNOS [136, 401], and CD36, the receptor of the anti-angiogenic molecule TSP-1. In addition, TGZs and 15d-PGJ_2 have both been shown to suppress secretion of VEGF and/or FGF2 by human glioblastoma or lung and renal carcinoma cell lines [402]. However, in other cell types PPARγ ligands upregulate VEGF and/or FGF2 production [403, 404]. In fact, recent

studies have demonstrated that inhibition of PPARγ blocks tumor cell invasion in squamous cell and hepatocellular carcinoma [405, 406], suggesting a cell type- and dose-dependent effect of PPARγ. Evidence of *in vivo* inhibition of angiogenesis by PPARγ ligands has been obtained using two models of neovascularization: the corneal neovascularization and chorioallantroic membrane (CAM) assays [395]. The authors of this work demonstrated that the anti-angiogenic effect of PPARγ ligands include a component that is independent of inflammatory processes, but also an indirect function inhibiting macrophage activation and invasion, which are important modulators of tumor angiogenesis.

Preclinical studies with PPARγ agonists have demonstrated that they may be effective in preventing metastasis. In a xenograft model injected subcutaneously with H295R cells and treated with RGZ, tumor growth and invasiveness were significantly reduced compared with the control group, correlating with a significant reduction in the expression of angiogenic and vascular genes such as VEGF and CD31 [407]. When non-small cell lung cancer cells overexpressing PPARγ were implanted orthotopically in mice, tumor number and metastasis were significantly lower compared with controls, correlating with improved survival [408]. PPARγ ligands improve the anti-angiogenic and anti-tumor effects of TSP-1 in tumor xenofrafts through the induction of endothelial CD36 expression [409]. Troglitazone potently inhibits human papillary thyroid tumor growth and prevents distant metastasis of thyroid tumors to the liver [410]. Systemic therapy with PPARγ ligands prevents metastatic invasion after removal of primary lung carcinoma [395]. In addition, PPARγ expression levels in human tumors correlate with positive prognosis: PPARγ levels are inversely associated with tumor grade and invasive capacity, and directly associated with positive clinical outcome [411, 412].

In conclusion, conflicting data mean that it is not possible at present to define the exact role of PPARs in cancer development. However, it is clear that PPAR ligand activation has a major influence on cancer development that requires further investigation. What is certain is that, in a limited number of patients, treatment with PPAR ligands has had exciting anti-cancer effects. We have presented here findings supporting the rationale for developing PPAR agonists as anti-tumor agents. However, early diagnosis and assessment of genetic predisposition will be pivotal for the success of PPAR-targeted therapy. Therefore further research is needed before PPAR modulation can be used as an effective therapy for chemoprevention and treatment of cancer.

3. SUMMARY AND PERSPECTIVES

Today PPARα and PPARγ ligands are clinically used in the management of diseases associated with IR and dyslipidemia. However, the abundance of pleiotropic actions of PPARs in mammalian physiology and human pathologies implies an enormous therapeutic potential for PPAR agonists that goes far beyond their use as lipid-lowering and insulin-sensitizing drugs. Recent advances in the field have begun to expand the potential medical applications of PPAR ligands, and today we should consider the possible use of PPAR agonists in various forms of chronic inflammatory disorders and cancer. Since concomitant activation of PPARs in distinct target cells often leads to undesirable side effects, the development of cell-specific PPAR agonists and improvements to current PPAR-based therapies are of great interest. The achievement of cell-specific PPAR activation or overexpression is the new challenge in basic research into PPARs, while trials of dual agonists and SPPARMs are the new directions in clinical research aimed at improving PPAR applications in medicine.

Acknowledgments

The work performed in the authors' laboratory was funded by awards from the Spanish Ministry of Science and Innovation (SAF2009 07466) and the Fundación Genoma España, Marató TV3 to M. Ricote, and a "People" Marie Curie Intra European Fellowship within the 7th European Community Framework Programme to T. Rőszer. The CNIC is supported by the Spanish Ministry of Health and Consumer Affairs and the Pro-CNIC Foundation. Simon Bartlett (CNIC) provided English-language editing. We apologize to our many colleagues for not being able to cite all relevant references because of space limitations.

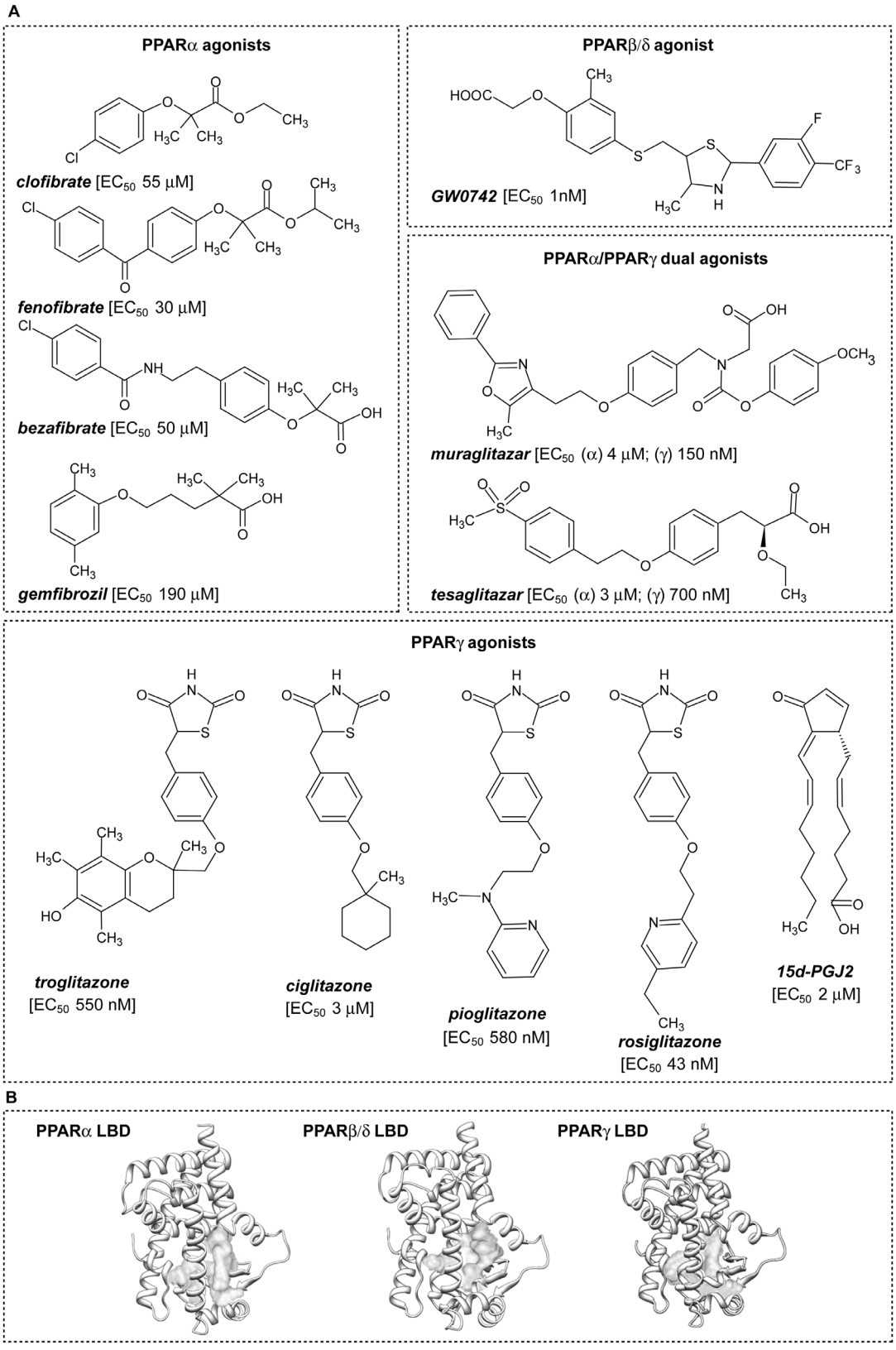


Figure 1. Chemical structure of medically-relevant PPAR ligands

(**A**) Fibrates, agonists of PPARα, are used in clinical practice, while tests of the PPARβ/δ activator GW0742 are in the preclinical phase. PPARα-PPARγ dual agonists have also been tested clinically. Troglitazone and ciglitazone are the prototypic thiazolidinedione (TZD)-type PPARγ agonists. Troglitazone has been withdrawn from the market due to its liver toxicity, and ciglitazone was never used in clinical practice. Today the clinically available TZDs are pioglitazone and rosiglitazone. 15d-PGJ2 is a non-TZD type natural PPARγ ligand. (**B**) Secondary structure prediction of PPAR

ligand binding domains (LBDs). *Left:* Human PPARα LBD in a complex with a synthetic agonist (PDB: 2ZNN_A, [413]). *Middle:* LBD of PPARβ/δ complexed with a partial agonist (PDB: 2Q5G_B, [414]). *Right:* Human PPARγ LBD complexed with a potent and selective agonist (PDB: 3GBK_B, Lin [415]). The solvent-accessible ligand-binding pocket is shown as a dotted gray surface. Three-dimensional molecule models were reconstructed with Chimera 1.5 software using secondary structure prediction generated with the local meta threading server (LOMETS) of the University of Michigan, USA.

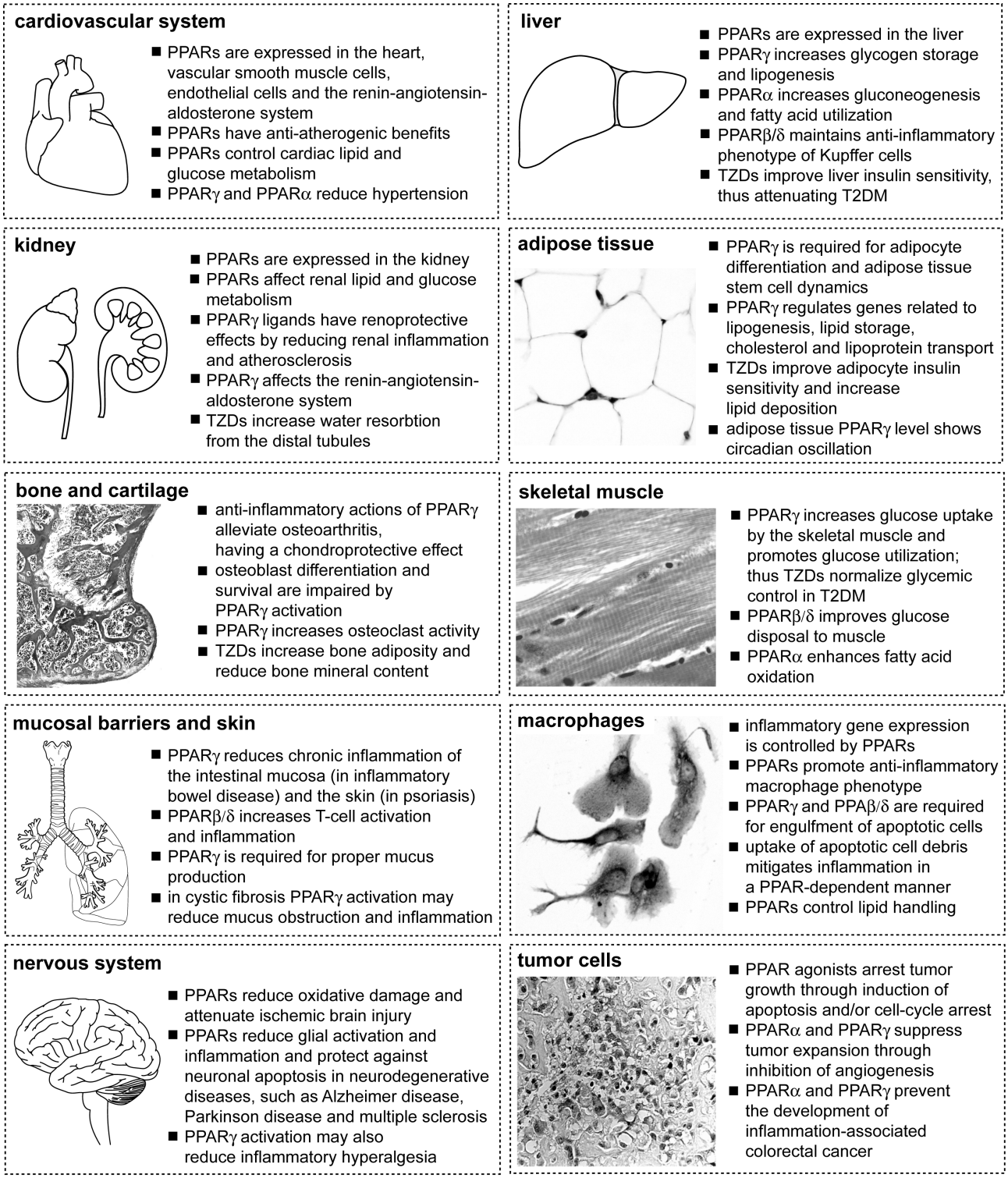


Figure 2. Biology and pharmacological effects of PPARs in different organ systems

PPARs are present in several organ systems, and are involved in their development, differentiation and metabolism by regulating a plethora of cellular pathways. The main pharmacological PPAR-targets are the cardiovascular system and the insulin-responsive metabolic organs (liver, adipose tissue and skeletal muscle). PPARs also affect inflammatory responses in various cell types (e.g. macrophages, microglia) in tissues including kidney, skin, mucosal barriers and brain.

Table 1. Effect of PPAR ligands in animal models of metabolic disorders			
Isoform	**Ligand**	**Effect**	**Reference**
PPARα	WY 14,643	Improved insulin sensitivity; reduced liver and muscle lipid accumulation	[416, 417]
	Fenofibrate	Increased hepatic glucose production in fasting state and IR	[85]
PPARβ/δ	GW501516	Improved glycemic control; increased FAO	[54]
	GW610742	Inhibited skeletal muscle carbohydrate oxidation; normalized cardiac muscle carbohydrate utilization	[94]
	GW0742	Increased glucose disposal to skeletal muscle	[19]
	NNC61-5920	Reduced metabolic abnormalities in mice; exacerbated IR in rats	[54]
PPARγ	RSG	Improved glucose disposal and insulin signaling; increased glycogen synthesis, FAO and lipogenesis	[24, 54]
	Troglitazone		
	Pioglitazone		
	Ciglitazone		
	$15dPGJ_2$	Increased adipocyte differentiation	[65]

Table 2. Characteristic metabolic effects of PPAR gene ablations in mouse

Gene deletion	Phenotype	References
PPARα deletion	May protect from IR, although it has no effect on high fat diet-induced IR development and β-cell function; disturbs the normal circadian regulation of certain SREBP-sensitive genes in the liver	[23, 87, 88]
PPARβ/δ deletion	Glucose intolerance, increased hepatic gluconeogenesis; inflammatory Kupffer-cell phenotype;	[25, 26]
PPARγ systemic deletion	Lethal developmental deficits; mice that survive embryonic lethality show IR and lipodistrophy; TZDs may increase β-cell and adipose tissue growth	[39, 40, 42, 418]
PPARγ2 systemic deletion	Decreased fat mass, severe IR, β-cell failure, and dyslipidaemia in leptin-deficient mice	[419]
PPARγ haploinsufficiency	Leptin overexpression, decreased fat mass, protection from IR; increased bone mass and reduced leptin levels	[43, 46, 418]
PPARγ deletion in adipose tissue	Adipocyte hypocellularity and hypertrophy, dyslipidemia, increased hepatic glucose production, IR	[34]
PPARγ deletion in muscle	Glucose intolerance and progressive IR development	[33]
PPARγ deletion in liver	Reduced liver steatosis and increased plasma lipids in leptin-deficient mice	[420, 421]
PPARγ deletion in the endothelium	Decreased adiposity and increased insulin sensitivity; increased serum FFA and triglyceride levels; impaired response to RSG	[37]
PPARγ deletion in macrophages	Altered cholesterol efflux and lipid metabolism; increased inflammatory macrophage polarization; augmented diet-induced IR	[36, 121, 153]
PPARγ deletion in neurons	Reduced food intake and increased energy expenditure, resulting in reduced weight gain; lack of RSG-induced hyperphagia and weight gain and lack of RSG effect on hepatic IR; silencing brain PPARγ provokes similar effects	[38, 119]

Table 3. Effects of PPAR ligands on inflammation in animal models			
Isoform	**Ligand**	**Effect**	**Reference**
PPARα	Wy 14,464	Reduced inflammatory activation of astrocytes and myeloid cells	[323, 331]
	WY14643	Reduced inflammatory gene expression in hepatocytes	[422]
	Fenofibrate	Reduced inflammatory response of myeloid cells, glial cells and T cells; beneficial effects in neuroinflammation and fibrosis	[206, 301, 331, 423]
	Bezafibrate	Reduced inflammation in colitis	[357]
	Gemfibrozil	Mitigated inflammatory activation of astrocytes, microglia and vascular cells	[331, 423, 424]
PPARβ/δ	L-165041	Anti-inflammatory effects in renal disease; protection against neuroinflammation	[327, 425]
	GW501516	Inhibited inflammatory signaling in liver and heart; protection from neuronal cell death, mitigated neuroinflammation	[122, 125, 327]
	GW0742	Reduced lung inflammation and inflammatory signaling in cardiomyocytes	[124, 426]
PPARγ	RSG	Mitigated colitis, reduced pancreatitis and lung inflammation, diminished kidney diseases; neuroprotection; mitigated renal manifestation of systemic lupus erythematosus	[266, 267, 297, 315, 316, 339]
	Troglitazone	Reduced colitis and autoimmune encephalomyelitis	[357, 427]
	Pioglitazone	Mitigated colitis, arthritis and autoimmune encephalomyelitis; neuroprotection	[297, 328 , 357, 428, 429]
	Ciglitazone	Inhibited inflammatory cell activation; reduced neuroinflammation	[174, 277]
	$15dPGJ_2$	inflammatory pain reduction	[115, 343]
	15-keto-PG E2	Required for proper mucus production; may reduce mucus obstruction in cystic fibrosis	[310]

Table 4. Effects of PPAR gene ablations on the immune system in mouse		
Gene deletion	**Phenotype**	**References**
PPARα deletion	Increased susceptibility to glomerular damage; lack of effect of anti-inflammatory agents on intestinal inflammation	[269, 303]
PPARδ/β deletion	Phagocytosis deficits; altered T-cell functions and development of autoimmune diseases; impaired anti-inflammatory macrophage polarization	[270] [338]
PPARγ haploinsufficiency	Increased susceptibility to intestinal inflammation; protection from high fat-induced kidney inflammation; exacerbated experimental allergic encephalomyelitis	[297, 302, 430, 431]
PPARγ deletion in macrophage	Impaired phagocytosis, autoimmune disorder; impaired anti-inflammatory macrophage polarization; altered lipid handling and cholesterol efflux	[13, 36, 121, 153]
PPARγ deletion in T-cells	Loss of negative effect on Th17 cell differentiation; predisposes to autoimmune diseases	[337]
PPARγ deletion in pancreas	Abolishes TZD effect on pancreatitis	[314]

Table 5. Effect of PPAR ligands in preclinical models of CVDs			
Isoform	**Ligand**	**Effect**	**Reference**
PPARα	WY 14,643	Protection against I/R injury in mice Protective effect in heart hypertrophy in rodents	[233] [211]
		Induction of cardiac lipotoxicity in I/R mice models Depression of cardiac power in hypertrophied hearts	[432] [222]
	GW7647	Reduced atherosclerotic lesion in hyperlipidemic mice Protection against I/R injury in mice	[140] [235]
	Fenofibrate	Reduced atherosclerotic lesion in hyperlipidemic mice Protection against I/R injury in mice Protective effect in heart hypertrophy in rodents Protection against hypertension Attenuation of cardiac fibrosis in mice and rats	[139] [234] [172, 211] [200, 201, 206] [204-206]
		No protection against I/R injury in pigs No protection against infarct healing in rodents (late treatment)	[433] [242]
	Cipofibrate	Increased atherosclerotic lesion in hyperlipidemic mice	[147]
	Gemfibrozil	Reduced atherosclerotic lesion in hyperlipidemic mice	[141]
	Clofibrate	Protection against I/R injury in mice	[233]
PPARβ/δ	L-165041	Protective effect in heart hypertrophy in rodents	[212]
	GW501516	Reduced atherosclerotic lesion in hyperlipidemic mice	[123]
	GW0742	Reduced atherosclerotic lesion in hyperlipidemic mice Protection against I/R injury in rats Protective effect in heart hypertrophy in rodents	[161, 162] [239] [213]
		No effect on atherosclerotic lesion in hyperlipidemic mice	[140]
PPARγ	RGZ	Reduced atherosclerotic lesion in hyperlipidemic mice Protection against I/R injury in mice and rats Attenuation of cardiac fibrosis in mice and rats	[140, 141] [205, 233]
		No effect on atherosclerotic lesion in hyperlipidemic mice Induction of heart hypertrophy in mice and rats	[148] [219]
	Troglitazone	Reduced atherosclerotic lesion in hyperlipidemic mice Protection against I/R injury in rats Protective effect in heart hypertrophy *in vitro*	[144, 145] [232] [217]
		No protection against I/R injury in pigs	[434]
	Pioglitazone	Reduced atherosclerotic lesions in hyperlipidemic mice Protective effect in myocardial infarction in mice (early treatment) Protection against I/R injury in mice Attenuation of cardiac fibrosis in rodents	[146] [241] [220, 233]
		No effect on atherosclerotic lesions in hyperlipidemic mice No protection in myocardial infarction in rodents (late treatment) Induction of heart hypertrophy in mice	[148] [220]
	Ciglitazone	Protection against I/R injury in mice Attenuation of cardiac fibrosis in mice and rats	[233] [243]
	$15dPGJ_2$	Protection against I/R injury in mice Protective effect in heart hypertrophy *in vitro*	[217]
	T-174	Induction of heart hypertrophy in rats	[229]

Table 6. Effects of PPAR gene ablations on CVD in mouse		
Gene deletion	**Phenotype**	**References**
PPARα$^{-/-}$	Increased cardiac hypertrophy and fibrosis	[214-216]
	Salt-sensitive hypertension	[196]
	Susceptibility to I/R damages	[234]
	Loss of ligand-mediated protection against I/R injury	[235]
PPARα$^{-/-}$ in *ex vivo* hearts	Decreased myocardial FAO/Increased glucose uptake Normal recovery after I/R	[225]
PPARα$^{-/-}$ in heart	Alteration in myocardial carbohydrate metabolism Increased FAO/Normal glucose uptake	[49]
PPARα$^{-/-}$/ApoE$^{-/-}$	Reduced atherosclerosis and blood pressure under HFD	[149]
PPARα$^{-/-}$/LDLR$^{-/-}$ BMT	Increased atherosclerosis under HFD	[142]
PPARδ/β$^{-/-}$ in heart	Decreased myocardial FAO	[226]
	Induction of lipotoxic cardiomyopathy Increased oxidative damaged/Cardiac hypertrophy	[227]
PPARδ/β$^{-/-}$/LDLR$^{-/-}$ BMT	Reduced atherosclerotic lesion area under HFD	[9]
PPARγ$^{+/-}$	Tendency to hypertrophy	[218]
PPARγ$^{-/-}$ in heart	Increased cardiac hypertrophy	[219, 220]
PPARγ$^{-/-}$ in VSMC	Altered arterial vasoconstriction	[195]
	Impaired vasoactivity and hypotension	[199]
PPARγ$^{-/-}$ in ECs	Reduced vascular NO production/hypertension	[193, 194]
	Hypertension in response to HFD	[192]
PPARγ$^{P465L/+}$	Hypertension	[197]
PPARα$^{-/-}$/LDLR$^{-/-}$ BMT	Enhanced atherosclerosis under HFD	[151]
Gene overexpression	**Phenotype**	**References**
PPARα in heart	Increased myocardial FAO/Decreased glucose uptake	[223, 225]
	Decreased glucose uptake/Diabetic cardiac myopathy	[224]
	Detrimental to recovery after reperfusion	[225]
PPARδ/β in heart	Increased glucose uptake Attenuation of myocardial injury after I/R	[238]
PPARγ1 in heart	Increased myocardial FAO/Cardiac hypertrophy	[228]
PPARγ1 in ApoE$^{-/-}$ mice	Reduced atherosclerosis	[435]

SMC: smooth muscle cells; **BMT**: bone marrow transplant; **ECs**: endothelial cells;

VSMC: vascular smooth muscle cells; **HFD:** high-fat diet

Table 7. *In vivo* effects of PPAR ligands in cancer			
Isoform	**Ligand**	**Effect**	**Reference**
PPARα	Wy 14,464	Reduced tumorigenesis in mice	[360]
	Fenofibrate	Reduced tumorigenesis in mice Suppression of angiogenesis	[390] [392]
	Bezafibrate	Reduced tumorigenesis in mice	[357]
	Clofibric acid	Reduced tumorigenesis in mice Increased survival	[359]
	Nafenopin	Induction of hepatocarcinoma in mice	[350]
PPARβ/δ	PGE_2	Induction of tumorigenesis in $APC^{min/+}$ mice	[377]
	GW501516	Induction of tumorigenesis in $APC^{min/+}$ mice	[378]
	GW0742	Reduced chemically-induced tumorigenesis in mice	[382]
PPARγ	RGZ	Reduced tumorigenesis in mice Suppression of angiogenesis	[355] [395]
		No objective response in humans Promotion of carcinogenesis in $APC^{min/+}$ mice	[436] [362]
	Troglitazone	Reduced tumorigenesis in mice Suppression of angiogenesis	[358] [407]
		Promotion of carcinogenesis in $APC^{min/+}$ mice	[362]
	Pioglitazone	Reduced tumorigenesis in normal and $APC^{min/+}$ mice Reduced metastasis in humans	[358, 368]
		Promotion of carcinogenesis in $APC^{min/+}$ mice	[363]
	GW7845	Reduced tumorigenesis in rats	[356]

Table 8. Effects of PPAR gene ablations on cancer in mouse		
Gene deletion	**Phenotype**	**References**
$PPAR\alpha^{+/-}$	Resistance to chemically-induced carcinogenesis	[361]
$PPAR\delta/\beta^{-/-}$	Increased colon polyp formation in $APC^{min/+}$ mice Increased chemically-induced polyp formation Reduced intestinal polyp formation in $APC^{min/+}$ mice	[384] [383] [379]
$PPAR\delta/\beta^{-/-}$ in colon	Inhibition of chemically-induced carcinogenesis	[380]
$PPAR\delta/\beta^{-/-}$ xenograft tumors	Decreased tumorigenesis	[372]
$PPAR\gamma^{(-/-) \text{ or } (+/-)}$	Increased chemically-induced skin, ovarian and breast cancer Increased metastasis and decreased survival	[366]
$PPAR\gamma^{(-/-) \text{ or } (+/-)}$/ in intestine	Promotion of intestinal tumor growth	[364]
$PPAR\gamma^{+/-}$	Increased chemically-induced colon cancer	[365]

REFERENCES

[1] Tontonoz, P.; Spiegelman, B.M. Fat and beyond: the diverse biology of PPARgamma. *Annu Rev Biochem*, **2008**, *77*, 289-312.

[2] Pascual, G.; Sullivan, A.L.; Ogawa, S.; Gamliel, A.; Perissi, V.; Rosenfeld, M.G.; Glass, C.K. Anti-inflammatory and antidiabetic roles of PPARgamma. *Novartis Found Symp*, **2007**, *286*, 183-196; discussion 196-203.

[3] Billin, A.N. PPAR-beta/delta agonists for Type 2 diabetes and dyslipidemia: an adopted orphan still looking for a home. *Expert Opin Investig Drugs*, **2008**, *17(10)*, 1465-1471.

[4] Fuentes, L.; Roszer, T.; Ricote, M. Inflammatory mediators and insulin resistance in obesity: role of nuclear receptor signaling in macrophages. *Mediators Inflamm*, **2010**, *2010*, 219583.

[5] Willson, T.; Brown, P.; Sternbach, D.; Henke, B. The PPARs: From Orphan receptors to Drug Discovery. *J. Med. Chem.*, **2000**, *43(4)*, 527-550.

[6] Mandard, S.; Muller, M.; Kersten, S. Peroxisome proliferator-activated receptor alpha target genes. *Cell Mol Life Sci*, **2004**, *61(4)*, 393-416.

[7] Michalik, L.; Wahli, W. Peroxisome proliferator-activated receptors (PPARs) in skin health, repair and disease. *Biochim Biophys Acta*, **2007**, *1771(8)*, 991-998.

[8] Roszer, T.; Ricote, M. PPARs in the Renal Regulation of Systemic Blood Pressure. *PPAR Res*, **2010**, *2010*, 698730.

[9] Lee, C.H.; Chawla, A.; Urbiztondo, N.; Liao, D.; Boisvert, W.A.; Evans, R.M. Transcriptional repression of atherogenic inflammation: modulation by PPARdelta. *Science*, **2003**, *302(5644)*, 453-457.

[10] Michalik, L.; Desvergne, B.; Wahli, W. Peroxisome proliferator-activated receptors beta/delta: emerging roles for a previously neglected third family member. *Curr Opin Lipidol*, **2003**, *14(2)*, 129-135.

[11] Fajas, L.; Auboeuff, D.; Raspé, E.; Schoonjans, K.; Lefebvre, A.-M.; Saladin, R.; Najib, J.; Laville, M.; Fruchart, J.-C.; Deeb, S.; Vidal-Puig, A.; Flier, J.; Briggs, M.R.; Staels, B.; Vidal, H.; Auwerx, J. The organization, promoter analysis, and expression of the human PPARγ gene. *J. Biol. Chem.*, **1997**, *272(30)*, 18779-18789.

[12] Ricote, M.; Huang, J.T.; Welch, J.S.; Glass, C.K. The peroxisome proliferator-activated receptor(PPARgamma) as a regulator of monocyte/macrophage function. *J Leukoc Biol*, **1999**, *66(5)*, 733-739.

[13] Roszer, T.; Menendez-Gutierrez, M.P.; Lefterova, M.I.; Alameda, D.; Nunez, V.; Lazar, M.A.; Fischer, T.; Ricote, M. Autoimmune kidney disease and impaired engulfment of apoptotic cells in mice with macrophage peroxisome proliferator-activated receptor gamma or retinoid X receptor alpha deficiency. *J Immunol*, **2011**, *186(1)*, 621-631.

[14] Kersten, S.; Wahli, W. Peroxisome proliferator activated receptor agonists. *EXS*, **2000**, *89*, 141-151.

[15] Ricote, M.; Glass, C.K. PPARs and molecular mechanisms of transrepression. *Biochim Biophys Acta*, **2007**, *1771(8)*, 926-935.

[16] Remick, J.; Weintraub, H.; Setton, R.; Offenbacher, J.; Fisher, E.; Schwartzbard, A. Fibrate therapy: an update. *Cardiol Rev*, **2008**, *16(3)*, 129-141.

[17] Tang, W.; Zeve, D.; Seo, J.; Jo, A.Y.; Graff, J.M. Thiazolidinediones regulate adipose lineage dynamics. *Cell Metab*, **2011**, *14(1)*, 116-122.

[18] Rubenstrunk, A.; Hanf, R.; Hum, D.W.; Fruchart, J.C.; Staels, B. Safety issues and prospects for future generations of PPAR modulators. *Biochim Biophys Acta*, **2007**, *1771(8)*, 1065-1081.

[19] Kramer, D.K.; Al-Khalili, L.; Perrini, S.; Skogsberg, J.; Wretenberg, P.; Kannisto, K.; Wallberg-Henriksson, H.; Ehrenborg, E.; Zierath, J.R.; Krook, A. Direct activation of glucose transport in primary human myotubes after activation of peroxisome proliferator-activated receptor delta. *Diabetes*, **2005**, *54(4)*, 1157-1163.

[20] Lee, C.H.; Olson, P.; Evans, R.M. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. *Endocrinology*, **2003**, *144(6)*, 2201-2207.

[21] Hiukka, A.; Maranghi, M.; Matikainen, N.; Taskinen, M.R. PPARalpha: an emerging therapeutic target in diabetic microvascular damage. *Nat Rev Endocrinol*, **2010**, *6(8)*, 454-463.

[22] Caton, P.W.; Holness, M.J.; Bishop-Bailey, D.; Sugden, M.C. PPARalpha-LXR as a novel metabolostatic signaling axis in skeletal muscle which acts to optimize substrate selection in response to nutrient status. *Biochem J*, **2011**.

[23] Patel, D.D.; Knight, B.L.; Wiggins, D.; Humphreys, S.M.; Gibbons, G.F. Disturbances in the normal regulation of SREBP-sensitive genes in PPAR alpha-deficient mice. *J Lipid Res*, **2001**, *42(3)*, 328-337.

[24] Ehrenborg, E.; Krook, A. Regulation of skeletal muscle physiology and metabolism by peroxisome proliferator-activated receptor delta. *Pharmacol Rev*, **2009**, *61(3)*, 373-393.

[25] Lee, C.H.; Olson, P.; Hevener, A.; Mehl, I.; Chong, L.W.; Olefsky, J.M.; Gonzalez, F.J.; Ham, J.; Kang, H.; Peters, J.M.; Evans, R.M. PPARdelta regulates glucose metabolism and insulin sensitivity. *Proc Natl Acad Sci U S A*, **2006**, *103(9)*, 3444-3449.

[26] Odegaard, J.I.; Ricardo-Gonzalez, R.R.; Red Eagle, A.; Vats, D.; Morel, C.R.; Goforth, M.H.; Subramanian, V.; Mukundan, L.; Ferrante, A.W.; Chawla, A. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. *Cell Metab*, **2008**, *7(6)*, 496-507.

[27] Mukherjee, R.; Hoener, P.A.; Jow, L.; Bilakovics, J.; Klausing, K.; Mais, D.E.; Faulkner, A.; Croston, G.E.; Paterniti, J.R., Jr. A selective peroxisome proliferator-activated receptor-gamma (PPARgamma) modulator blocks adipocyte differentiation but stimulates glucose uptake in 3T3-L1 adipocytes. *Mol Endocrinol*, **2000**, *14(9)*, 1425-1433.

[28] Gastaldelli, A.; Miyazaki, Y.; Pettiti, M.; Santini, E.; Ciociaro, D.; Defronzo, R.A.; Ferrannini, E. The effect of rosiglitazone on the liver: decreased gluconeogenesis in patients with type 2 diabetes. *J Clin Endocrinol Metab*, **2006**, *91(3)*, 806-812.

[29] Gastaldelli, A.; Ferrannini, E.; Miyazaki, Y.; Matsuda, M.; Mari, A.; DeFronzo, R.A. Thiazolidinediones improve beta-cell function in type 2 diabetic patients. *Am J Physiol Endocrinol Metab*, **2007**, *292(3)*, E871-883.

[30] Hotamisligil, G.S. Inflammation and metabolic disorders. *Nature*, **2006**, *444(7121)*, 860-867.

[31] Perelas, A.; Tsoulkani, A.; Perrea, D. Effects of lipid-lowering drugs on adiponectin. *Curr Vasc Pharmacol*, **2010**, *8(6)*, 836-848.

[32] Heald, M.; Cawthorne, M.A. Dual acting and pan-PPAR activators as potential anti-diabetic therapies. *Handb Exp Pharmacol*, **2011***(203)*, 35-51.

[33] Hevener, A.L.; He, W.; Barak, Y.; Le, J.; Bandyopadhyay, G.; Olson, P.; Wilkes, J.; Evans, R.M.; Olefsky, J. Muscle-specific Pparg deletion causes insulin resistance. *Nat. Med.*, **2003**, *9(12)*, 1491-1497.

[34] He, W.; Barak, Y.; Hevener, A.; Olson, P.; Liao, D.; Le, J.; Nelson, M.; Ong, E.; Olefsky, J.M.; Evans, R.M. Adipose-specific peroxisome proliferator-activated receptor γ knockout causes insulin resistance in fat and liver but not in muscle. *Proc. Natl. Acad. Sci. USA*, **2003**, *100(26)*, 15712-15717.

[35] Sugii, S.; Olson, P.; Sears, D.D.; Saberi, M.; Atkins, A.R.; Barish, G.D.; Hong, S.H.; Castro, G.L.; Yin, Y.Q.; Nelson, M.C.; Hsiao, G.; Greaves, D.R.; Downes, M.; Yu, R.T.; Olefsky, J.M.; Evans, R.M. PPARgamma activation in adipocytes is sufficient for systemic insulin sensitization. *Proc Natl Acad Sci U S A*, **2009**, *106(52)*, 22504-22509.

[36] Hevener, A.L.; Olefsky, J.M.; Reichart, D.; Nguyen, M.T.; Bandyopadyhay, G.; Leung, H.Y.; Watt, M.J.; Benner, C.; Febbraio, M.A.; Nguyen, A.K.; Folian, B.; Subramaniam, S.; Gonzalez, F.J.; Glass, C.K.; Ricote, M.

Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. *J Clin Invest*, **2007**, *117(6)*, 1658-1669.

[37] Kanda, T.; Brown, J.D.; Orasanu, G.; Vogel, S.; Gonzalez, F.J.; Sartoretto, J.; Michel, T.; Plutzky, J. PPARgamma in the endothelium regulates metabolic responses to high-fat diet in mice. *J Clin Invest*, **2009**, *119(1)*, 110-124.

[38] Lu, M.; Sarruf, D.A.; Talukdar, S.; Sharma, S.; Li, P.; Bandyopadhyay, G.; Nalbandian, S.; Fan, W.; Gayen, J.R.; Mahata, S.K.; Webster, N.J.; Schwartz, M.W.; Olefsky, J.M. Brain PPAR-gamma promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. *Nat Med*, **2011**, *17(5)*, 618-622.

[39] Duan, S.Z.; Ivashchenko, C.Y.; Whitesall, S.E.; D'Alecy, L.G.; Duquaine, D.C.; Brosius, F.C., 3rd; Gonzalez, F.J.; Vinson, C.; Pierre, M.A.; Milstone, D.S.; Mortensen, R.M. Hypotension, lipodystrophy, and insulin resistance in generalized PPARgamma-deficient mice rescued from embryonic lethality. *J Clin Invest*, **2007**, *117(3)*, 812-822.

[40] Gupta, D.; Jetton, T.L.; Mortensen, R.M.; Duan, S.Z.; Peshavaria, M.; Leahy, J.L. In vivo and in vitro studies of a functional peroxisome proliferator-activated receptor gamma response element in the mouse pdx-1 promoter. *J Biol Chem*, **2008**, *283(47)*, 32462-32470.

[41] Vernochet, C.; Milstone, D.S.; Iehle, C.; Belmonte, N.; Phillips, B.; Wdziekonski, B.; Villageois, P.; Amri, E.Z.; O'Donnell, P.E.; Mortensen, R.M.; Ailhaud, G.; Dani, C. PPARgamma-dependent and PPARgamma-independent effects on the development of adipose cells from embryonic stem cells. *FEBS Lett*, **2002**, *510(1-2)*, 94-98.

[42] Duan, S.Z.; Usher, M.G.; Foley, E.L.t.; Milstone, D.S.; Brosius, F.C., 3rd; Mortensen, R.M. Sex dimorphic actions of rosiglitazone in generalised peroxisome proliferator-activated receptor-gamma (PPAR-gamma)-deficient mice. *Diabetologia*, *53(7)*, 1493-1505.

[43] Yamauchi, T.; Waki, H.; Kamon, J.; Murakami, K.; Motojima, K.; Komeda, K.; Miki, H.; Kubota, N.; Terauchi, Y.; Tsuchida, A.; Tsuboyama-Kasaoka, N.; Yamauchi, N.; Ide, T.; Hori, W.; Kato, S.; Fukayama, M.; Akanuma, Y.; Ezaki, O.; Itai, A.; Nagai, R.; Kimura, S.; Tobe, K.; Kagechika, H.; Shudo, K.; Kadowaki, T. Inhibition of RXR and PPARgamma ameliorates diet-induced obesity and type 2 diabetes. *J Clin Invest*, **2001**, *108(7)*, 1001-1013.

[44] Yamauchi, T.; Kamon, J.; Waki, H.; Murakami, K.; Motojima, K.; Komeda, K.; Ide, T.; Kubota, N.; Terauchi, Y.; Tobe, K.; Miki, H.; Tsuchida, A.; Akanuma, Y.; Nagai, R.; Kimura, S.; Kadowaki, T. The mechanisms by which both heterozygous peroxisome proliferator-activated receptor gamma (PPARgamma) deficiency and PPARgamma agonist improve insulin resistance. *J Biol Chem*, **2001**, *276(44)*, 41245-41254.

[45] Altshuler, D.; Hirschhorn, J.N.; Klannemark, M.; Lindgren, C.M.; Vohl, M.C.; Nemesh, J.; Lane, C.R.; Schaffner, S.F.; Bolk, S.; Brewer, C.; Tuomi, T.; Gaudet, D.; Hudson, T.J.; Daly, M.; Groop, L.; Lander, E.S. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet*, **2000**, *26(1)*, 76-80.

[46] Akune, T.; Ohba, S.; Kamekura, S.; Yamaguchi, M.; Chung, U.I.; Kubota, N.; Terauchi, Y.; Harada, Y.; Azuma, Y.; Nakamura, K.; Kadowaki, T.; Kawaguchi, H. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J Clin Invest*, **2004**, *113(6)*, 846-855.

[47] Li, W.D.; Lee, J.H.; Price, R.A. The peroxisome proliferator-activated receptor gamma 2 Pro12Ala mutation is associated with early onset extreme obesity and reduced fasting glucose. *Mol Genet Metab*, **2000**, *70(2)*, 159-161.

[48] Zisman, A.; Peroni, O.D.; Abel, E.D.; Michael, M.D.; Mauvais-Jarvis, F.; Lowell, B.B.; Wojtaszewski, J.F.; Hirshman, M.F.; Virkamaki, A.; Goodyear, L.J.; Kahn, C.R.; Kahn, B.B. Targeted disruption of the glucose transporter 4 selectively in muscle causes insulin resistance and glucose intolerance. *Nat Med*, **2000**, *6(8)*, 924-928.

[49] Panagia, M.; Gibbons, G.F.; Radda, G.K.; Clarke, K. PPAR-alpha activation required for decreased glucose uptake and increased susceptibility to injury during ischemia. *Am J Physiol Heart Circ Physiol*, **2005**, *288(6)*, H2677-2683.

[50] Yan, J.; Young, M.E.; Cui, L.; Lopaschuk, G.D.; Liao, R.; Tian, R. Increased glucose uptake and oxidation in mouse hearts prevent high fatty acid oxidation but cause cardiac dysfunction in diet-induced obesity. *Circulation*, **2009**, *119(21)*, 2818-2828.

[51] Balakumar, P.; Rohilla, A.; Mahadevan, N. Pleiotropic actions of fenofibrate on the heart. *Pharmacol Res*, **2011**, *63(1)*, 8-12.

[52] Luptak, I.; Balschi, J.A.; Xing, Y.; Leone, T.C.; Kelly, D.P.; Tian, R. Decreased contractile and metabolic reserve in peroxisome proliferator-activated receptor-alpha-null hearts can be rescued by increasing glucose transport and utilization. *Circulation*, **2005**, *112(15)*, 2339-2346.

[53] Terada, S.; Wicke, S.; Holloszy, J.O.; Han, D.H. PPARdelta activator GW-501516 has no acute effect on glucose transport in skeletal muscle. *Am J Physiol Endocrinol Metab*, **2006**, *290(4)*, E607-611.

[54] Ye, J.M.; Tid-Ang, J.; Turner, N.; Zeng, X.Y.; Li, H.Y.; Cooney, G.J.; Wulff, E.M.; Sauerberg, P.; Kraegen, E.W. PPARdelta agonists have opposing effects on insulin resistance in high fat-fed rats and mice due to different metabolic responses in muscle. *Br J Pharmacol*, **2011**, *163(3)*, 556-566.

[55] Kramer, D.K.; Al-Khalili, L.; Guigas, B.; Leng, Y.; Garcia-Roves, P.M.; Krook, A. Role of AMP kinase and PPARdelta in the regulation of lipid and glucose metabolism in human skeletal muscle. *J Biol Chem*, **2007**, *282(27)*, 19313-19320.

[56] Sugita, S.; Kamei, Y.; Akaike, F.; Suganami, T.; Kanai, S.; Hattori, M.; Manabe, Y.; Fujii, N.; Takai-Igarashi, T.; Tadaishi, M.; Oka, J.; Aburatani, H.; Yamada, T.; Katagiri, H.; Kakehi, S.; Tamura, Y.; Kubo, H.; Nishida, K.; Miura, S.; Ezaki, O.; Ogawa, Y. Increased Systemic Glucose Tolerance with Increased Muscle Glucose Uptake in Transgenic Mice Overexpressing RXRgamma in Skeletal Muscle. *PLoS One*, **2011**, *6(5)*, e20467.

[57] Armoni, M.; Kritz, N.; Harel, C.; Bar-Yoseph, F.; Chen, H.; Quon, M.J.; Karnieli, E. Peroxisome proliferator-activated receptor-gamma represses GLUT4 promoter activity in primary adipocytes, and rosiglitazone alleviates this effect. *J Biol Chem*, **2003**, *278(33)*, 30614-30623.

[58] Al-Khalili, L.; Forsgren, M.; Kannisto, K.; Zierath, J.R.; Lonnqvist, F.; Krook, A. Enhanced insulin-stimulated glycogen synthesis in response to insulin, metformin or rosiglitazone is associated with increased mRNA expression of GLUT4 and peroxisomal proliferator activator receptor gamma co-activator 1. *Diabetologia*, **2005**, *48(6)*, 1173-1179.

[59] Liao, W.; Nguyen, M.T.; Yoshizaki, T.; Favelyukis, S.; Patsouris, D.; Imamura, T.; Verma, I.M.; Olefsky, J.M. Suppression of PPAR-gamma attenuates insulin-stimulated glucose uptake by affecting both GLUT1 and GLUT4 in 3T3-L1 adipocytes. *Am J Physiol Endocrinol Metab*, **2007**, *293(1)*, E219-227.

[60] Golfman, L.S.; Wilson, C.R.; Sharma, S.; Burgmaier, M.; Young, M.E.; Guthrie, P.H.; Van Arsdall, M.; Adrogue, J.V.; Brown, K.K.; Taegtmeyer, H. Activation of PPARgamma enhances myocardial glucose oxidation and improves contractile function in isolated working hearts of ZDF rats. *Am J Physiol Endocrinol Metab*, **2005**, *289(2)*, E328-336.

[61] Ding, S.Y.; Shen, Z.F.; Chen, Y.T.; Sun, S.J.; Liu, Q.; Xie, M.Z. Pioglitazone can ameliorate insulin resistance in low-dose streptozotocin and high sucrose-fat diet induced obese rats. *Acta Pharmacol Sin*, **2005**, *26(5)*, 575-580.

[62] Armoni, M.; Harel, C.; Bar-Yoseph, F.; Milo, S.; Karnieli, E. Free fatty acids repress the GLUT4 gene expression in cardiac muscle via novel response elements. *J Biol Chem*, **2005**, *280(41)*, 34786-34795.

[63] Gross, D.N.; Farmer, S.R.; Pilch, P.F. Glut4 storage vesicles without Glut4: transcriptional regulation of insulin-dependent vesicular traffic. *Mol Cell Biol*, **2004**, *24(16)*, 7151-7162.

[64] Nugent, C.; Prins, J.B.; Whitehead, J.P.; Wentworth, J.M.; Chatterjee, V.K.; O'Rahilly, S. Arachidonic acid stimulates glucose uptake in 3T3-L1 adipocytes by increasing GLUT1 and GLUT4 levels at the plasma membrane. Evidence for involvement of lipoxygenase metabolites and peroxisome proliferator-activated receptor gamma. *J Biol Chem*, **2001**, *276(12)*, 9149-9157.

[65] Sinha, D.; Addya, S.; Murer, E.; Boden, G. 15-Deoxy-delta(12,14) prostaglandin J2: a putative endogenous promoter of adipogenesis suppresses the ob gene. *Metabolism*, **1999**, *48(6)*, 786-791.

[66] Fu, Y.; Luo, N.; Klein, R.L.; Garvey, W.T. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. *J Lipid Res*, **2005**, *46(7)*, 1369-1379.

[67] Sharabi, Y.; Oron-Herman, M.; Kamari, Y.; Avni, I.; Peleg, E.; Shabtay, Z.; Grossman, E.; Shamiss, A. Effect of PPAR-gamma agonist on adiponectin levels in the metabolic syndrome: lessons from the high fructose fed rat model. *Am J Hypertens*, **2007**, *20(2)*, 206-210.

[68] Maeda, N.; Takahashi, M.; Funahashi, T.; Kihara, S.; Nishizawa, H.; Kishida, K.; Nagaretani, H.; Matsuda, M.; Komuro, R.; Ouchi, N.; Kuriyama, H.; Hotta, K.; Nakamura, T.; Shimomura, I.; Matsuzawa, Y. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes*, **2001**, *50(9)*, 2094-2099.

[69] Lennon, R.; Welsh, G.I.; Singh, A.; Satchell, S.C.; Coward, R.J.; Tavare, J.M.; Mathieson, P.W.; Saleem, M.A. Rosiglitazone enhances glucose uptake in glomerular podocytes using the glucose transporter GLUT1. *Diabetologia*, **2009**, *52(9)*, 1944-1952.

[70] Coward, R.J.; Welsh, G.I.; Koziell, A.; Hussain, S.; Lennon, R.; Ni, L.; Tavare, J.M.; Mathieson, P.W.; Saleem, M.A. Nephrin is critical for the action of insulin on human glomerular podocytes. *Diabetes*, **2007**, *56(4)*, 1127-1135.

[71] Zhang, H.; Schin, M.; Saha, J.; Burke, K.; Holzman, L.B.; Filipiak, W.; Saunders, T.; Xiang, M.; Heilig, C.W.; Brosius, F.C., 3rd. Podocyte-specific overexpression of GLUT1 surprisingly reduces mesangial matrix expansion in diabetic nephropathy in mice. *Am J Physiol Renal Physiol*, **2010**, *299(1)*, F91-98.

[72] Douard, V.; Ferraris, R.P. Regulation of the fructose transporter GLUT5 in health and disease. *Am J Physiol Endocrinol Metab*, **2008**, *295(2)*, E227-237.

[73] Samuel, V.T. Fructose induced lipogenesis: from sugar to fat to insulin resistance. *Trends Endocrinol Metab*, **2011**, *22(2)*, 60-65.

[74] Stuart, C.A.; Howell, M.E.; Yin, D. Overexpression of GLUT5 in diabetic muscle is reversed by pioglitazone. *Diabetes Care*, **2007**, *30(4)*, 925-931.

[75] Kim, H.S.; Noh, J.H.; Hong, S.H.; Hwang, Y.C.; Yang, T.Y.; Lee, M.S.; Kim, K.W.; Lee, M.K. Rosiglitazone stimulates the release and synthesis of insulin by enhancing GLUT-2, glucokinase and BETA2/NeuroD expression. *Biochem Biophys Res Commun*, **2008**, *367(3)*, 623-629.

[76] Gilde, A.J.; van der Lee, K.A.; Willemsen, P.H.; Chinetti, G.; van der Leij, F.R.; van der Vusse, G.J.; Staels, B.; van Bilsen, M. Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. *Circ Res*, **2003**, *92(5)*, 518-524.

[77] Dressel, U.; Allen, T.L.; Pippal, J.B.; Rohde, P.R.; Lau, P.; Muscat, G.E. The peroxisome proliferator-activated receptor beta/delta agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. *Mol Endocrinol*, **2003**, *17(12)*, 2477-2493.

[78] Shah, A.; Rader, D.J.; Millar, J.S. The effect of PPAR-alpha agonism on apolipoprotein metabolism in humans. *Atherosclerosis*, **2010**, *210(1)*, 35-40.

[79] Muhlhausler, B.S.; Morrison, J.L.; McMillen, I.C. Rosiglitazone increases the expression of peroxisome proliferator-activated receptor-gamma target genes in adipose tissue, liver, and skeletal muscle in the sheep fetus in late gestation. *Endocrinology*, **2009**, *150(9)*, 4287-4294.

[80] Buse, J.B.; Rubin, C.J.; Frederich, R.; Viraswami-Appanna, K.; Lin, K.C.; Montoro, R.; Shockey, G.; Davidson, J.A. Muraglitazar, a dual (alpha/gamma) PPAR activator: a randomized, double-blind, placebo-controlled, 24-week monotherapy trial in adult patients with type 2 diabetes. *Clin Ther*, **2005**, *27(8)*, 1181-1195.

[81] Henry, R.R.; Lincoff, A.M.; Mudaliar, S.; Rabbia, M.; Chognot, C.; Herz, M. Effect of the dual peroxisome proliferator-activated receptor-alpha/gamma agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study. *Lancet*, **2009**, *374(9684)*, 126-135.

[82] Balakumar, P.; Rose, M.; Ganti, S.S.; Krishan, P.; Singh, M. PPAR dual agonists: are they opening Pandora's Box? *Pharmacol Res*, **2007**, *56(2)*, 91-98.

[83] Lecka-Czernik, B. Aleglitazar, a dual PPARalpha and PPARgamma agonist for the potential oral treatment of type 2 diabetes mellitus. *IDrugs*, **2010**, *13(11)*, 793-801.

[84] Cassuto, H.; Aran, A.; Cohen, H.; Eisenberger, C.L.; Reshef, L. Repression and activation of transcription of phosphoenolpyruvate carboxykinase gene during liver development. *FEBS Lett*, **1999**, *457(3)*, 441-444.

[85] Im, S.S.; Kim, M.Y.; Kwon, S.K.; Kim, T.H.; Bae, J.S.; Kim, H.; Kim, K.S.; Oh, G.T.; Ahn, Y.H. Peroxisome proliferator-activated receptor {alpha} is responsible for the up-regulation of hepatic glucose-6-phosphatase gene expression in fasting and db/db Mice. *J Biol Chem*, **2011**, *286(2)*, 1157-1164.

[86] Shankar, K.; Vaidya, V.S.; Corton, J.C.; Bucci, T.J.; Liu, J.; Waalkes, M.P.; Mehendale, H.M. Activation of PPAR-alpha in streptozotocin-induced diabetes is essential for resistance against acetaminophen toxicity. *FASEB J*, **2003**, *17(12)*, 1748-1750.

[87] Guerre-Millo, M.; Rouault, C.; Poulain, P.; Andre, J.; Poitout, V.; Peters, J.M.; Gonzalez, F.J.; Fruchart, J.C.; Reach, G.; Staels, B. PPAR-alpha-null mice are protected from high-fat diet-induced insulin resistance. *Diabetes*, **2001**, *50(12)*, 2809-2814.

[88] Haluzik, M.; Gavrilova, O.; LeRoith, D. Peroxisome proliferator-activated receptor-alpha deficiency does not alter insulin sensitivity in mice maintained on regular or high-fat diet: hyperinsulinemic-euglycemic clamp studies. *Endocrinology*, **2004**, *145(4)*, 1662-1667.

[89] Zhang, L.; Keung, W.; Samokhvalov, V.; Wang, W.; Lopaschuk, G.D. Role of fatty acid uptake and fatty acid beta-oxidation in mediating insulin resistance in heart and skeletal muscle. *Biochim Biophys Acta*, **2010**, *1801(1)*, 1-22.

[90] Wolf, G. Retinoic acid activation of peroxisome proliferation-activated receptor delta represses obesity and insulin resistance. *Nutr Rev*, **2010**, *68(1)*, 67-70.

[91] Degenhardt, T.; Saramaki, A.; Malinen, M.; Rieck, M.; Vaisanen, S.; Huotari, A.; Herzig, K.H.; Muller, R.; Carlberg, C. Three members of the human pyruvate dehydrogenase kinase gene family are direct targets of the peroxisome proliferator-activated receptor beta/delta. *J Mol Biol*, **2007**, *372(2)*, 341-355.

[92] Holness, M.J.; Kraus, A.; Harris, R.A.; Sugden, M.C. Targeted upregulation of pyruvate dehydrogenase kinase (PDK)-4 in slow-twitch skeletal muscle underlies the stable modification of the regulatory characteristics of PDK induced by high-fat feeding. *Diabetes*, **2000**, *49(5)*, 775-781.

[93] Constantin, D.; Constantin-Teodosiu, D.; Layfield, R.; Tsintzas, K.; Bennett, A.J.; Greenhaff, P.L. PPARdelta agonism induces a change in fuel metabolism and activation of an atrophy programme, but does not impair mitochondrial function in rat skeletal muscle. *J Physiol*, **2007**, *583(Pt 1)*, 381-390.

[94] Constantin-Teodosiu, D.; Baker, D.J.; Constantin, D.; Greenhaff, P.L. PPARdelta agonism inhibits skeletal muscle PDC activity, mitochondrial ATP production and force generation during prolonged contraction. *J Physiol*, **2009**, *587(Pt 1)*, 231-239.

[95] Muoio, D.M.; MacLean, P.S.; Lang, D.B.; Li, S.; Houmard, J.A.; Way, J.M.; Winegar, D.A.; Corton, J.C.; Dohm, G.L.; Kraus, W.E. Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) alpha knock-out mice. Evidence for compensatory regulation by PPAR delta. *J Biol Chem*, **2002**, *277(29)*, 26089-26097.

[96] Nahle, Z.; Hsieh, M.; Pietka, T.; Coburn, C.T.; Grimaldi, P.A.; Zhang, M.Q.; Das, D.; Abumrad, N.A. CD36-dependent regulation of muscle FoxO1 and PDK4 in the PPAR delta/beta-mediated adaptation to metabolic stress. *J Biol Chem*, **2008**, *283(21)*, 14317-14326.

[97] Jiang, G.; Zhang, B.B. Modulation of insulin signalling by insulin sensitizers. *Biochem Soc Trans*, **2005**, *33(Pt 2)*, 358-361.

[98] Rieusset, J.; Auwerx, J.; Vidal, H. Regulation of gene expression by activation of the peroxisome proliferator-activated receptor gamma with rosiglitazone (BRL 49653) in human adipocytes. *Biochem Biophys Res Commun*, **1999**, *265(1)*, 265-271.

[99] Iwata, M.; Haruta, T.; Usui, I.; Takata, Y.; Takano, A.; Uno, T.; Kawahara, J.; Ueno, E.; Sasaoka, T.; Ishibashi, O.; Kobayashi, M. Pioglitazone ameliorates tumor necrosis factor-alpha-induced insulin resistance by a mechanism independent of adipogenic activity of peroxisome proliferator--activated receptor-gamma. *Diabetes*, **2001**, *50(5)*, 1083-1092.

[100] Suzuki, A.; Yasuno, T.; Kojo, H.; Hirosumi, J.; Mutoh, S.; Notsu, Y. Alteration in expression profiles of a series of diabetes-related genes in db/db mice following treatment with thiazolidinediones. *Jpn J Pharmacol*, **2000**, *84(2)*, 113-123.

[101] Wang, Z.J.; Liu, Q.; Li, P.P.; Zou, C.H.; Shen, Z.F. Effect of GCP-02, a PPARalpha/gamma dual activator, on glucose and lipid metabolism in insulin-resistant mice. *Eur J Pharmacol*, **2008**, *580(1-2)*, 277-283.

[102] Zhang, B.; Berger, J.; Zhou, G.; Elbrecht, A.; Biswas, S.; White-Carrington, S.; Szalkowski, D.; Moller, D.E. Insulin- and mitogen-activated protein kinase-mediated phosphorylation and activation of peroxisome proliferator-activated receptor gamma. *J Biol Chem*, **1996**, *271(50)*, 31771-31774.

[103] Chen, F.; Wang, M.; O'Connor, J.P.; He, M.; Tripathi, T.; Harrison, L.E. Phosphorylation of PPARgamma via active ERK1/2 leads to its physical association with p65 and inhibition of NF-kappabeta. *J Cell Biochem*, **2003**, *90(4)*, 732-744.

[104] Derlacz, R.A.; Hyc, K.; Usarek, M.; Jagielski, A.K.; Drozak, J.; Jarzyna, R. PPAR-gamma-independent inhibitory effect of rosiglitazone on glucose synthesis in primary cultured rabbit kidney-cortex tubules. *Biochem Cell Biol*, **2008**, *86(5)*, 396-404.

[105] Jucker, B.M.; Schaeffer, T.R.; Haimbach, R.E.; McIntosh, T.S.; Chun, D.; Mayer, M.; Ohlstein, D.H.; Davis, H.M.; Smith, S.A.; Cobitz, A.R.; Sarkar, S.K. Normalization of skeletal muscle glycogen synthesis and glycolysis in rosiglitazone-treated Zucker fatty rats: an in vivo nuclear magnetic resonance study. *Diabetes*, **2002**, *51(7)*, 2066-2073.

[106] Davies, G.F.; Khandelwal, R.L.; Wu, L.; Juurlink, B.H.; Roesler, W.J. Inhibition of phosphoenolpyruvate carboxykinase (PEPCK) gene expression by troglitazone: a peroxisome proliferator-activated receptor-gamma (PPARgamma)-independent, antioxidant-related mechanism. *Biochem Pharmacol*, **2001**, *62(8)*, 1071-1079.

[107] Stafford, J.M.; Elasy, T. Treatment update: thiazolidinediones in combination with metformin for the treatment of type 2 diabetes. *Vasc Health Risk Manag*, **2007**, *3(4)*, 503-510.

[108] Tontonoz, P.; Hu, E.; Devine, J.; Beale, E.G.; Spiegelman, B.M. PPAR gamma 2 regulates adipose expression of the phosphoenolpyruvate carboxykinase gene. *Mol Cell Biol*, **1995**, *15(1)*, 351-357.

[109] Berger, J.; Tanen, M.; Elbrecht, A.; Hermanowski-Vosatka, A.; Moller, D.E.; Wright, S.D.; Thieringer, R. Peroxisome proliferator-activated receptor-gamma ligands inhibit adipocyte 11beta -hydroxysteroid dehydrogenase type 1 expression and activity. *J Biol Chem*, **2001**, *276(16)*, 12629-12635.

[110] Eubank, D.W.; Duplus, E.; Williams, S.C.; Forest, C.; Beale, E.G. Peroxisome proliferator-activated receptor gamma and chicken ovalbumin upstream promoter transcription factor II negatively regulate the phosphoenolpyruvate carboxykinase promoter via a common element. *J Biol Chem*, **2001**, *276(32)*, 30561-30569.

[111] Guo, X.; Xu, K.; Zhang, J.; Li, H.; Zhang, W.; Wang, H.; Lange, A.J.; Chen, Y.E.; Huo, Y.; Wu, C. Involvement of inducible 6-phosphofructo-2-kinase in the anti-diabetic effect of peroxisome proliferator-activated receptor gamma activation in mice. *J Biol Chem*, **2010**, *285(31)*, 23711-23720.

[112] Huo, Y.; Guo, X.; Li, H.; Wang, H.; Zhang, W.; Wang, Y.; Zhou, H.; Gao, Z.; Telang, S.; Chesney, J.; Chen, Y.E.; Ye, J.; Chapkin, R.S.; Wu, C. Disruption of inducible 6-phosphofructo-2-kinase ameliorates diet-induced adiposity but exacerbates systemic insulin resistance and adipose tissue inflammatory response. *J Biol Chem*, **2010**, *285(6)*, 3713-3721.

[113] Atsumi, T.; Nishio, T.; Niwa, H.; Takeuchi, J.; Bando, H.; Shimizu, C.; Yoshioka, N.; Bucala, R.; Koike, T. Expression of inducible 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase/PFKFB3 isoforms in adipocytes and their potential role in glycolytic regulation. *Diabetes*, **2005**, *54(12)*, 3349-3357.

[114] Chesney, J.; Telang, S.; Yalcin, A.; Clem, A.; Wallis, N.; Bucala, R. Targeted disruption of inducible 6-phosphofructo-2-kinase results in embryonic lethality. *Biochem Biophys Res Commun*, **2005**, *331(1)*, 139-146.

[115] Morgenweck, J.; Abdel-Aleem, O.S.; McNamara, K.C.; Donahue, R.R.; Badr, M.Z.; Taylor, B.K. Activation of peroxisome proliferator-activated receptor gamma in brain inhibits inflammatory pain, dorsal horn expression of Fos, and local edema. *Neuropharmacology*, **2010**, *58(2)*, 337-345.

[116] Uemura, E.; Greenlee, H.W. Insulin regulates neuronal glucose uptake by promoting translocation of glucose transporter GLUT3. *Experimental Neurology*, **2006**, *198(1)*, 48-53.

[117] Wang, R.; Liu, X.; Hentges, S.T.; Dunn-Meynell, A.A.; Levin, B.E.; Wang, W.; Routh, V.H. The regulation of glucose-excited neurons in the hypothalamic arcuate nucleus by glucose and feeding-relevant peptides. *Diabetes*, **2004**, *53(8)*, 1959-1965.

[118] Izawa, Y.; Takahashi, S.; Suzuki, N. Pioglitazone enhances pyruvate and lactate oxidation in cultured neurons but not in cultured astroglia. *Brain Res*, **2009**, *1305*, 64-73.

[119] Ryan, K.K.; Li, B.; Grayson, B.E.; Matter, E.K.; Woods, S.C.; Seeley, R.J. A role for central nervous system PPAR-gamma in the regulation of energy balance. *Nat Med*, *17(5)*, 623-626.

[120] Prieur, X.; Mok, C.Y.; Velagapudi, V.R.; Nunez, V.; Fuentes, L.; Montaner, D.; Ishikawa, K.; Camacho, A.; Barbarroja, N.; O'Rahilly, S.; Sethi, J.K.; Dopazo, J.; Oresic, M.; Ricote, M.; Vidal-Puig, A. Differential lipid partitioning between adipocytes and tissue macrophages modulates macrophage lipotoxicity and M2/M1 polarization in obese mice. *Diabetes*, *60(3)*, 797-809.

[121] Odegaard, J.I.; Ricardo-Gonzalez, R.R.; Goforth, M.H.; Morel, C.R.; Subramanian, V.; Mukundan, L.; Red Eagle, A.; Vats, D.; Brombacher, F.; Ferrante, A.W.; Chawla, A. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. *Nature*, **2007**, *447(7148)*, 1116-1120.

[122] Serrano-Marco, L.; Rodriguez-Calvo, R.; El Kochairi, I.; Palomer, X.; Michalik, L.; Wahli, W.; Vazquez-Carrera, M. Activation of Peroxisome Proliferator-Activated Receptor-{beta}/-{delta} (PPAR-{beta}/-{delta}) Ameliorates Insulin Signaling and Reduces SOCS3 Levels by Inhibiting STAT3 in Interleukin-6-Stimulated Adipocytes. *Diabetes*, **2011**, *60(7)*, 1990-1999.

[123] Barish, G.D.; Atkins, A.R.; Downes, M.; Olson, P.; Chong, L.W.; Nelson, M.; Zou, Y.; Hwang, H.; Kang, H.; Curtiss, L.; Evans, R.M.; Lee, C.H. PPARdelta regulates multiple proinflammatory pathways to suppress atherosclerosis. *Proc Natl Acad Sci U S A*, **2008**, *105(11)*, 4271-4276.

[124] Galuppo, M.; Di Paola, R.; Mazzon, E.; Esposito, E.; Paterniti, I.; Kapoor, A.; Thiemermann, C.; Cuzzocrea, S. GW0742, a high affinity PPAR-beta/delta agonist reduces lung inflammation induced by bleomycin instillation in mice. *Int J Immunopathol Pharmacol*, **2010**, *23(4)*, 1033-1046.

[125] Alvarez-Guardia, D.; Palomer, X.; Coll, T.; Serrano, L.; Rodriguez-Calvo, R.; Davidson, M.M.; Merlos, M.; El Kochairi, I.; Michalik, L.; Wahli, W.; Vazquez-Carrera, M. PPARbeta/delta activation blocks lipid-induced inflammatory pathways in mouse heart and human cardiac cells. *Biochim Biophys Acta*, **2011**, *1811(2)*, 59-67.

[126] Palee, S.; Chattipakorn, S.; Phrommintikul, A.; Chattipakorn, N. PPARgamma activator, rosiglitazone: Is it beneficial or harmful to the cardiovascular system? *World J Cardiol*, **2011**, *3(5)*, 144-152.

[127] Tolman, K.G. The safety of thiazolidinediones. *Expert Opin Drug Saf*, **2011**, *10(3)*, 419-428.

[128] Kawai, M.; Rosen, C.J. PPARgamma: a circadian transcription factor in adipogenesis and osteogenesis. *Nat Rev Endocrinol*, **2010**, *6(11)*, 629-636.

[129] Liu, C.; Li, S.; Liu, T.; Borjigin, J.; Lin, J.D. Transcriptional coactivator PGC-1alpha integrates the mammalian clock and energy metabolism. *Nature*, **2007**, *447(7143)*, 477-481.

[130] Rached, M.T.; Kode, A.; Silva, B.C.; Jung, D.Y.; Gray, S.; Ong, H.; Paik, J.H.; DePinho, R.A.; Kim, J.K.; Karsenty, G.; Kousteni, S. FoxO1 expression in osteoblasts regulates glucose homeostasis through regulation of osteocalcin in mice. *J Clin Invest*, **2010**, *120(1)*, 357-368.

[131] Kanazawa, I.; Yamaguchi, T.; Yamamoto, M.; Yamauchi, M.; Kurioka, S.; Yano, S.; Sugimoto, T. Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. *J Clin Endocrinol Metab*, **2009**, *94(1)*, 45-49.

[132] Costa Cdos, S.; Rohden, F.; Hammes, T.O.; Margis, R.; Bortolotto, J.W.; Padoin, A.V.; Mottin, C.C.; Guaragna, R.M. Resveratrol upregulated SIRT1, FOXO1, and adiponectin and downregulated PPARgamma1-3 mRNA expression in human visceral adipocytes. *Obes Surg*, **2011**, *21(3)*, 356-361.

[133] van Bilsen, M.; van Nieuwenhoven, F.A. PPARs as therapeutic targets in cardiovascular disease. *Expert Opin Ther Targets*, **2010**, *14(10)*, 1029-1045.

[134] Smirnov, A.N. Lipid signaling in the atherogenesis context. *Biochemistry (Mosc)*, **2010**, *75(7)*, 793-810.

[135] Tontonoz, P.; Nagy, L.; Alvarez, J.G.A.; Thomazy, V.A.; Evans, R.M. PPARγ promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell*, **1998**, *93*, 241-252.

[136] Ricote, M.; Li, A.C.; Willson, T.M.; Kelly, C.J.; Glass, C.K. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. *Nature*, **1998**, *391(6662)*, 79-82.

[137] Feng, J.; Han, J.; Pearce, S.F.; Silverstein, R.L.; Gotto, A.M., Jr.; Hajjar, D.P.; Nicholson, A.C. Induction of CD36 expression by oxidized LDL and IL-4 by a common signaling pathway dependent on protein kinase C and PPAR-gamma. *J Lipid Res*, **2000**, *41(5)*, 688-696.

[138] Jedidi, I.; Couturier, M.; Therond, P.; Gardes-Albert, M.; Legrand, A.; Barouki, R.; Bonnefont-Rousselot, D.; Aggerbeck, M. Cholesteryl ester hydroperoxides increase macrophage CD36 gene expression via PPARalpha. *Biochem Biophys Res Commun*, **2006**, *351(3)*, 733-738.

[139] Duez, H.; Chao, Y.S.; Hernandez, M.; Torpier, G.; Poulain, P.; Mundt, S.; Mallat, Z.; Teissier, E.; Burton, C.A.; Tedgui, A.; Fruchart, J.C.; Fievet, C.; Wright, S.D.; Staels, B. Reduction of atherosclerosis by the peroxisome proliferator-activated receptor alpha agonist fenofibrate in mice. *J. Biol. Chem.*, **2002**, *277(50)*, 48051-48057.

[140] Li, A.C., Binder, C.J., Gutierrez, A., Brown, K.K., Plotkin, C.R., Pattison, J.W., Valledor, A., Davis, R.A., Willson, T.M., Witztum, J.L., Palinski, W., Glass, C.K. Differential inhibition of macrophage foam cell formation and atherosclerosis in mice by PPAR α, β/δ, and γ. *J Clin Invest*, **2004**, *114(11)*, 1564-1576.

[141] Calkin, A.C.; Allen, T.J.; Lassila, M.; Tikellis, C.; Jandeleit-Dahm, K.A.; Thomas, M.C. Increased atherosclerosis following treatment with a dual PPAR agonist in the ApoE knockout mouse. *Atherosclerosis*, **2007**, *195(1)*, 17-22.

[142] Babaev, V.R.; Ishiguro, H.; Ding, L.; Yancey, P.G.; Dove, D.E.; Kovacs, W.J.; Semenkovich, C.F.; Fazio, S.; Linton, M.F. Macrophage expression of peroxisome proliferator-activated receptor-alpha reduces atherosclerosis in low-density lipoprotein receptor-deficient mice. *Circulation*, **2007**, *116(12)*, 1404-1412.

[143] Li, A.; Brown, K.; Silvestre, M.; Willson, T.; Palinski, W.; Glass, C. Peroxisome proliferator-activated receptor γ ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. *J. CIin. Invest.*, **2000**, *106(4)*, 523-531.

[144] Collins, A.R.; Meehan, W.P.; Kintscher, U.; Jackson, S.; Wakino, S.; Noh, G.; Palinski, W.; Hsueh, W.A.; Law, R.E. Troglitazone inhibits formation of early atherosclerotic lesions in diabetic and nondiabetic low density lipoprotein receptor-deficient mice. *Arterioscler. Thromb. Vasc. Biol.*, **2001**, *21(3)*, 365-371.

[145] Chen, Z.; Ishibashi, S.; Perrey, S.; Osuga, J.; Gotoda, T.; Kitamine, T.; Tamura, Y.; Okazaki, H.; Yahagi, N.; Iizuka, Y.; Shionoiri, F.; Ohashi, K.; Harada, K.; Shimano, H.; Nagai, R.; Yamada, N. Troglitazone inhibits atherosclerosis in apolipoprotein E-knockout mice: pleiotropic effects on CD36 expression and HDL. *Arterioscler. Thromb. Vasc. Biol.*, **2001**, *21(3)*, 372-377.

[146] Nakaya, H.; Summers, B.D.; Nicholson, A.C.; Gotto, A.M., Jr.; Hajjar, D.P.; Han, J. Atherosclerosis in LDLR-knockout mice is inhibited, but not reversed, by the PPARgamma ligand pioglitazone. *Am J Pathol*, **2009**, *174(6)*, 2007-2014.

[147] Fu, T.; Mukhopadhyay, D.; Davidson, N.O.; Borensztajn, J. The peroxisome proliferator-activated receptor alpha (PPARalpha) agonist ciprofibrate inhibits apolipoprotein B mRNA editing in low density lipoprotein receptor-deficient mice: effects on plasma lipoproteins and the development of atherosclerotic lesions. *J Biol Chem*, **2004**, *279(27)*, 28662-28669.

[148] Hennuyer, N.; Tailleux, A.; Torpier, G.; Mezdour, H.; Fruchart, J.C.; Staels, B.; Fievet, C. PPARalpha, but not PPARgamma, activators decrease macrophage-laden atherosclerotic lesions in a nondiabetic mouse model of mixed dyslipidemia. *Arterioscler Thromb Vasc Biol*, **2005**, *25(9)*, 1897-1902.

[149] Tordjman, K.; Bernal-Mizrachi, C.; Zemany, L.; Weng, S.; Feng, C.; Zhang, F.; Leone, T.C.; Coleman, T.; Kelly, D.P.; Semenkovich, C.F. PPARalpha deficiency reduces insulin resistance and atherosclerosis in apoE-null mice. *J. Clin. Invest.*, **2001**, *107(8)*, 1025-1034.

[150] Chinetti, G.; Lestavel, S.; Bocher, V.; Remaley, A.T.; Neve, B.; Torra, I.P.; Teissier, E.; Minnich, A.; Jaye, M.; Duverger, N.; Brewer, H.B.; Fruchart, J.C.; Clavey, V.; Staels, B. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. *Nat Med*, **2001**, *7(1)*, 53-58.

[151] Chawla, A.; Boisvert, W.A.; Lee, C.H.; Laffitte, B.A.; Barak, Y.; Joseph, S.B.; Liao, D.; Nagy, L.; Edwards, P.A.; Curtiss, L.K.; Evans, R.M.; Tontonoz, P. A PPAR γ-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. *Mol. Cell*, **2001**, *7(1)*, 161-171.

[152] Chinetti, G.; Gbaguidi, F.G.; Griglio, S.; Mallat, Z.; Antonucci, M.; Poulain, P.; Chapman, J.; Fruchart, J.C.; Tedgui, A.; Najib-Fruchart, J.; Staels, B. CLA-1/SR-BI is expressed in atherosclerotic lesion macrophages and regulated by activators of peroxisome proliferator-activated receptors. *Circulation*, **2000**, *101(20)*, 2411-2417.

[153] Akiyama, T.E.; Sakai, S.; Lambert, G.; Nicol, C.J.; Matsusue, K.; Pimprale, S.; Lee, Y.H.; Ricote, M.; Glass, C.K.; Brewer, H.B., Jr.; Gonzalez, F.J. Conditional disruption of the peroxisome proliferator-activated receptor gamma gene in mice results in lowered expression of ABCA1, ABCG1, and apoE in macrophages and reduced cholesterol efflux. *Mol Cell Biol*, **2002**, *22(8)*, 2607-2619.

[154] Haraguchi, G.; Kobayashi, Y.; Brown, M.L.; Tanaka, A.; Isobe, M.; Gianturco, S.H.; Bradley, W.A. PPAR(alpha) and PPAR(gamma) activators suppress the monocyte-macrophage apoB-48 receptor. *J Lipid Res*, **2003**, *44(6)*, 1224-1231.

[155] Llaverias, G.; Vazquez-Carrera, M.; Sanchez, R.M.; Noe, V.; Ciudad, C.J.; Laguna, J.C.; Alegret, M. Rosiglitazone upregulates caveolin-1 expression in THP-1 cells through a PPAR-dependent mechanism. *J Lipid Res*, **2004**, *45(11)*, 2015-2024.

[156] Hirakata, M.; Tozawa, R.; Imura, Y.; Sugiyama, Y. Comparison of the effects of pioglitazone and rosiglitazone on macrophage foam cell formation. *Biochem Biophys Res Commun*, **2004**, *323(3)*, 782-788.

[157] Cheng, B.; Wan, J.; Wang, Y.; Mei, C.; Liu, W.; Ke, L.; He, P. Ghrelin inhibits foam cell formation via simultaneously down-regulating the expression of acyl-coenzyme A:cholesterol acyltransferase 1 and up-regulating adenosine triphosphate-binding cassette transporter A1. *Cardiovasc Pathol*, **2010**, *19(5)*, e159-166.

[158] Chinetti, G.; Lestavel, S.; Fruchart, J.C.; Clavey, V.; Staels, B. Peroxisome proliferator-activated receptor alpha reduces cholesterol esterification in macrophages. *Circ Res*, **2003**, *92(2)*, 212-217.

[159] Ghosh, S.; Natarajan, R. Cloning of the human cholesteryl ester hydrolase promoter: identification of functional peroxisomal proliferator-activated receptor responsive elements. *Biochem Biophys Res Commun*, **2001**, *284(4)*, 1065-1070.

[160] Chinetti-Gbaguidi, G.; Rigamonti, E.; Helin, L.; Mutka, A.L.; Lepore, M.; Fruchart, J.C.; Clavey, V.; Ikonen, E.; Lestavel, S.; Staels, B. Peroxisome proliferator-activated receptor alpha controls cellular cholesterol trafficking in macrophages. *J Lipid Res*, **2005**, *46(12)*, 2717-2725.

[161] Graham, T.L.; Mookherjee, C.; Suckling, K.E.; Palmer, C.N.; Patel, L. The PPARdelta agonist GW0742X reduces atherosclerosis in LDLR(-/-) mice. *Atherosclerosis*, **2005**, *181(1)*, 29-37.

[162] Takata, Y.; Liu, J.; Yin, F.; Collins, A.R.; Lyon, C.J.; Lee, C.H.; Atkins, A.R.; Downes, M.; Barish, G.D.; Evans, R.M.; Hsueh, W.A.; Tangirala, R.K. PPARdelta-mediated antiinflammatory mechanisms inhibit angiotensin II-accelerated atherosclerosis. *Proc Natl Acad Sci U S A*, **2008**, *105(11)*, 4277-4282.

[163] Vosper, H.; Patel, L.; Graham, T.L.; Khoudoli, G.A.; Hill, A.; Macphee, C.H.; Pinto, I.; Smith, S.A.; Suckling, K.E.; Wolf, C.R.; Palmer, C.N. The peroxisome proliferator-activated receptor delta promotes lipid accumulation in human macrophages. *J Biol Chem*, **2001**, *276(47)*, 44258-44265.

[164] Chawla, A.; Lee, C.H.; Barak, Y.; He, W.; Rosenfeld, J.; Liao, D.; Han, J.; Kang, H.; Evans, R.M. PPARdelta is a very low-density lipoprotein sensor in macrophages. *Proc Natl Acad Sci U S A*, **2003**, *100(3)*, 1268-1273.

[165] Oliver, W.R., Jr.; Shenk, J.L.; Snaith, M.R.; Russell, C.S.; Plunket, K.D.; Bodkin, N.L.; Lewis, M.C.; Winegar, D.A.; Sznaidman, M.L.; Lambert, M.H.; Xu, H.E.; Sternbach, D.D.; Kliewer, S.A.; Hansen, B.C.; Willson, T.M. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc. Natl. Acad. Sci. U.S.A.*, **2001**, *98(9)*, 5306-5311.

[166] Valasek, M.A.; Clarke, S.L.; Repa, J.J. Fenofibrate reduces intestinal cholesterol absorption via PPARalpha-dependent modulation of NPC1L1 expression in mouse. *J Lipid Res*, **2007**, *48(12)*, 2725-2735.

[167] Mathur, S.N.; Watt, K.R.; Field, F.J. Regulation of intestinal NPC1L1 expression by dietary fish oil and docosahexaenoic acid. *J Lipid Res*, **2007**, *48(2)*, 395-404.

[168] Robinson, E.; Grieve, D.J. Significance of peroxisome proliferator-activated receptors in the cardiovascular system in health and disease. *Pharmacol Ther*, **2009**, *122(3)*, 246-263.

[169] Ricote, M.; Huang, J.; Fajas, L.; Li, A.; Welch, J.; Najib, J.; Witztum, J.L.; Auwerx, J.; Palinski, W.; Glass, C.K. Expression of the peroxisome proliferator-activated receptor γ (PPARγ) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. *Proc. Natl. Acad. Sci. USA.*, **1998**, *95*, 7614-7619.

[170] Goya, K.; Sumitani, S.; Xu, X.; Kitamura, T.; Yamamoto, H.; Kurebayashi, S.; Saito, H.; Kouhara, H.; Kasayama, S.; Kawase, I. Peroxisome proliferator-activated receptor alpha agonists increase nitric oxide synthase expression in vascular endothelial cells. *Arterioscler Thromb Vasc Biol*, **2004**, *24(4)*, 658-663.

[171] Polikandriotis, J.A.; Mazzella, L.J.; Rupnow, H.L.; Hart, C.M. Peroxisome proliferator-activated receptor gamma ligands stimulate endothelial nitric oxide production through distinct peroxisome proliferator-activated receptor gamma-dependent mechanisms. *Arterioscler Thromb Vasc Biol*, **2005**, *25(9)*, 1810-1816.

[172] Irukayama-Tomobe, Y.; Miyauchi, T.; Sakai, S.; Kasuya, Y.; Ogata, T.; Takanashi, M.; Iemitsu, M.; Sudo, T.; Goto, K.; Yamaguchi, I. Endothelin-1-induced cardiac hypertrophy is inhibited by activation of peroxisome proliferator-activated receptor-alpha partly via blockade of c-Jun NH2-terminal kinase pathway. *Circulation*, **2004**, *109(7)*, 904-910.

[173] Marx, N.; Sukhova, G.K.; Collins, T.; Libby, P.; Plutzky, J. PPARalpha activators inhibit cytokine-induced vascular cell adhesion molecule-1 expression in human endothelial cells. *Circulation*, **1999**, *99(24)*, 3125-3131.

[174] Jackson, S.M.; Parhami, F.; Xi, X.P.; Berliner, J.A.; Hsueh, W.A.; Law, R.E.; Demer, L.L. Peroxisome proliferator-activated receptor activators target human endothelial cells to inhibit leukocyte-endothelial cell interaction. *Arterioscler. Thromb. Vasc. Biol.*, **1999**, *19(9)*, 2094-2104.

[175] Pasceri, V.; Cheng, J.S.; Willerson, J.T.; Yeh, E.T. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. *Circulation*, **2001**, *103(21)*, 2531-2534.

[176] Wang, N.; Verna, L.; Chen, N.G.; Chen, J.; Li, H.; Forman, B.M.; Stemerman, M.B. Constitutive activation of peroxisome proliferator-activated receptor-gamma suppresses pro-inflammatory adhesion molecules in human vascular endothelial cells. *J Biol Chem*, **2002**, *277(37)*, 34176-34181.

[177] Marx, N.; Mach, F.; Sauty, A.; Leung, J.H.; Sarafi, M.N.; Ransohoff, R.M.; Libby, P.; Plutzky, J.; Luster, A.D. Peroxisome proliferator-activated receptor-gamma activators inhibit IFN- gamma-induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells. *J. Immunol.*, **2000**, *164(12)*, 6503-6508.

[178] Rival, Y.; Beneteau, N.; Taillandier, T.; Pezet, M.; Dupont-Passelaigue, E.; Patoiseau, J.F.; Junquero, D.; Colpaert, F.C.; Delhon, A. PPARalpha and PPARdelta activators inhibit cytokine-induced nuclear translocation of NF-kappaB and expression of VCAM-1 in EAhy926 endothelial cells. *Eur J Pharmacol*, **2002**, *435(2-3)*, 143-151.

[179] Bouhlel, M.A.; Derudas, B.; Rigamonti, E.; Dievart, R.; Brozek, J.; Haulon, S.; Zawadzki, C.; Jude, B.; Torpier, G.; Marx, N.; Staels, B.; Chinetti-Gbaguidi, G. PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. *Cell Metab*, **2007**, *6(2)*, 137-143.

[180] Ingersoll, M.A.; Spanbroek, R.; Lottaz, C.; Gautier, E.L.; Frankenberger, M.; Hoffmann, R.; Lang, R.; Haniffa, M.; Collin, M.; Tacke, F.; Habenicht, A.J.; Ziegler-Heitbrock, L.; Randolph, G.J. Comparison of gene expression profiles between human and mouse monocyte subsets. *Blood*, **2010**, *115(3)*, e10-19.

[181] Marx, N.; Kehrle, B.; Kohlhammer, K.; Grub, M.; Koenig, W.; Hombach, V.; Libby, P.; Plutzky, J. PPAR activators as antiinflammatory mediators in human T lymphocytes: implications for atherosclerosis and transplantation-associated arteriosclerosis. *Circ Res*, **2002**, *90(6)*, 703-710.

[182] Zambon, A.; Gervois, P.; Pauletto, P.; Fruchart, J.C.; Staels, B. Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-alpha activators: clinical and experimental evidence. *Arterioscler Thromb Vasc Biol*, **2006**, *26(5)*, 977-986.

[183] Gizard, F.; Bruemmer, D. Transcriptional Control of Vascular Smooth Muscle Cell Proliferation by Peroxisome Proliferator-Activated Receptor-gamma: Therapeutic Implications for Cardiovascular Diseases. *PPAR Res*, **2008**, *2008*, 429123.

[184] Wakino, S.; Kintscher, U.; Kim, S.; Yin, F.; Hsueh, W.A.; Law, R.E. Peroxisome proliferator-activated receptor gamma ligands inhibit retinoblastoma phosphorylation and G1--> S transition in vascular smooth muscle cells. *J Biol Chem*, **2000**, *275(29)*, 22435-22441.

[185] Bruemmer, D.; Berger, J.P.; Liu, J.; Kintscher, U.; Wakino, S.; Fleck, E.; Moller, D.E.; Law, R.E. A non-thiazolidinedione partial peroxisome proliferator-activated receptor gamma ligand inhibits vascular smooth muscle cell growth. *Eur J Pharmacol*, **2003**, *466(3)*, 225-234.

[186] Ogawa, D.; Nomiyama, T.; Nakamachi, T.; Heywood, E.B.; Stone, J.F.; Berger, J.P.; Law, R.E.; Bruemmer, D. Activation of peroxisome proliferator-activated receptor gamma suppresses telomerase activity in vascular smooth muscle cells. *Circ Res*, **2006**, *98(7)*, e50-59.

[187] Kudo, M., Sugawara A, Saito A, Urono A, Ito S. Effects of pioglitazone, belaprost, and fluvastatin on gene expression in vascular endothelial cells revealed by DNA microarray analyses. *J Hypertens*, **2006**, *24(6)*, 238-238.

[188] Zahradka, P.; Wright, B.; Fuerst, M.; Yurkova, N.; Molnar, K.; Taylor, C.G. Peroxisome proliferator-activated receptor alpha and gamma ligands differentially affect smooth muscle cell proliferation and migration. *J Pharmacol Exp Ther*, **2006**, *317(2)*, 651-659.

[189] Kintscher, U.; Lyon, C.; Wakino, S.; Bruemmer, D.; Feng, X.; Goetze, S.; Graf, K.; Moustakas, A.; Staels, B.; Fleck, E.; Hsueh, W.A.; Law, R.E. PPARalpha inhibits TGF-beta-induced beta5 integrin transcription in vascular smooth muscle cells by interacting with Smad4. *Circ Res*, **2002**, *91(11)*, e35-44.

[190] Feihl, F.; Liaudet, L.; Waeber, B.; Levy, B.I. Hypertension: a disease of the microcirculation? *Hypertension*, **2006**, *48(6)*, 1012-1017.

[191] Horiki, M.; Ikegami, H.; Fujisawa, T.; Kawabata, Y.; Ono, M.; Nishino, M.; Shimamoto, K.; Ogihara, T. Association of Pro12Ala polymorphism of PPARgamma gene with insulin resistance and related diseases. *Diabetes Res Clin Pract*, **2004**, *66 Suppl 1*, S63-67.

[192] Nicol, C.J.; Adachi, M.; Akiyama, T.E.; Gonzalez, F.J. PPARgamma in endothelial cells influences high fat diet-induced hypertension. *Am J Hypertens*, **2005**, *18(4 Pt 1)*, 549-556.

[193] Halabi, C.M.; Beyer, A.M.; de Lange, W.J.; Keen, H.L.; Baumbach, G.L.; Faraci, F.M.; Sigmund, C.D. Interference with PPAR gamma function in smooth muscle causes vascular dysfunction and hypertension. *Cell Metab*, **2008**, *7(3)*, 215-226.

[194] Kleinhenz, J.M.; Kleinhenz, D.J.; You, S.; Ritzenthaler, J.D.; Hansen, J.M.; Archer, D.R.; Sutliff, R.L.; Hart, C.M. Disruption of endothelial peroxisome proliferator-activated receptor-gamma reduces vascular nitric oxide production. *Am J Physiol Heart Circ Physiol*, **2009**, *297(5)*, H1647-1654.

[195] Wang, N.; Symons, J.D.; Zhang, H.; Jia, Z.; Gonzalez, F.J.; Yang, T. Distinct functions of vascular endothelial and smooth muscle PPARgamma in regulation of blood pressure and vascular tone. *Toxicol Pathol*, **2009**, *37(1)*, 21-27.

[196] Obih, P.; Oyekan, A.O. Regulation of blood pressure, natriuresis and renal thiazide/amiloride sensitivity in PPARalpha null mice. *Blood Press*, **2008**, *17(1)*, 55-63.

[197] Tsai, Y.S.; Kim, H.J.; Takahashi, N.; Kim, H.S.; Hagaman, J.R.; Kim, J.K.; Maeda, N. Hypertension and abnormal fat distribution but not insulin resistance in mice with P465L PPARgamma. *J Clin Invest*, **2004**, *114(2)*, 240-249.

[198] Barroso, I.; Gurnell, M.; Crowley, V.E.F.; Agostini, M.; Schwabe, J.W.; Soos, M.A.; Maslen, G.L.; Williams, T.D.M.; Lewis, H.; Schafer, A.J.; Chatterjee, V.K.K.; O'Rahilly, S. Dominant negative mutations in human PPPARy associated with severe insulin resisitance, diabetes mellitus and hpertension. *Nature*, **1999**, *402(23/30)*, 880-883.

[199] Chang, L.; Villacorta, L.; Zhang, J.; Garcia-Barrio, M.T.; Yang, K.; Hamblin, M.; Whitesall, S.E.; D'Alecy, L.G.; Chen, Y.E. Vascular smooth muscle cell-selective peroxisome proliferator-activated receptor-gamma deletion leads to hypotension. *Circulation*, **2009**, *119(16)*, 2161-2169.

[200] Iglarz, M.; Touyz, R.M.; Amiri, F.; Lavoie, M.F.; Diep, Q.N.; Schiffrin, E.L. Effect of peroxisome proliferator-activated receptor-alpha and -gamma activators on vascular remodeling in endothelin-dependent hypertension. *Arterioscler Thromb Vasc Biol*, **2003**, *23(1)*, 45-51.

[201] Ryan, M.J.; Didion, S.P.; Mathur, S.; Faraci, F.M.; Sigmund, C.D. PPAR(gamma) agonist rosiglitazone improves vascular function and lowers blood pressure in hypertensive transgenic mice. *Hypertension*, **2004**, *43(3)*, 661-666.

[202] Sarafidis, P.A.; Lasaridis, A.N. Actions of peroxisome proliferator-activated receptors-gamma agonists explaining a possible blood pressure-lowering effect. *Am J Hypertens*, **2006**, *19(6)*, 646-653.

[203] Komers, R.; Vrana, A. Thiazolidinediones--tools for the research of metabolic syndrome X. *Physiol Res*, **1998**, *47(4)*, 215-225.

[204] Ogata, T.; Miyauchi, T.; Sakai, S.; Takanashi, M.; Irukayama-Tomobe, Y.; Yamaguchi, I. Myocardial fibrosis and diastolic dysfunction in deoxycorticosterone acetate-salt hypertensive rats is ameliorated by the peroxisome proliferator-activated receptor-alpha activator fenofibrate, partly by suppressing inflammatory responses associated with the nuclear factor-kappa-B pathway. *J Am Coll Cardiol*, **2004**, *43(8)*, 1481-1488.

[205] Iglarz, M.; Touyz, R.M.; Viel, E.C.; Paradis, P.; Amiri, F.; Diep, Q.N.; Schiffrin, E.L. Peroxisome proliferator-activated receptor-alpha and receptor-gamma activators prevent cardiac fibrosis in mineralocorticoid-dependent hypertension. *Hypertension*, **2003**, *42(4)*, 737-743.

[206] Diep, Q.N.; Benkirane, K.; Amiri, F.; Cohn, J.S.; Endemann, D.; Schiffrin, E.L. PPAR alpha activator fenofibrate inhibits myocardial inflammation and fibrosis in angiotensin II-infused rats. *J Mol Cell Cardiol*, **2004**, *36(2)*, 295-304.

[207] Jugdutt, B.I. Clinical effectiveness of telmisartan alone or in combination therapy for controlling blood pressure and vascular risk in the elderly. *Clin Interv Aging*, **2011**, *5*, 403-416.

[208] Hunter, J.J.; Chien, K.R. Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med*, **1999**, *341(17)*, 1276-1283.

[209] van Bilsen, M.; Smeets, P.J.; Gilde, A.J.; van der Vusse, G.J. Metabolic remodelling of the failing heart: the cardiac burn-out syndrome? *Cardiovasc Res*, **2004**, *61(2)*, 218-226.

[210] Li, Y.; Ha, T.; Gao, X.; Kelley, J.; Williams, D.L.; Browder, I.W.; Kao, R.L.; Li, C. NF-kappaB activation is required for the development of cardiac hypertrophy in vivo. *Am J Physiol Heart Circ Physiol*, **2004**, *287(4)*, H1712-1720.

[211] Liang, F.; Wang, F.; Zhang, S.; Gardner, D.G. Peroxisome proliferator activated receptor (PPAR)alpha agonists inhibit hypertrophy of neonatal rat cardiac myocytes. *Endocrinology*, **2003**, *144(9)*, 4187-4194.

[212] Planavila, A.; Rodriguez-Calvo, R.; Jove, M.; Michalik, L.; Wahli, W.; Laguna, J.C.; Vazquez-Carrera, M. Peroxisome proliferator-activated receptor beta/delta activation inhibits hypertrophy in neonatal rat cardiomyocytes. *Cardiovasc Res*, **2005**, *65(4)*, 832-841.

[213] Jucker, B.M.; Doe, C.P.; Schnackenberg, C.G.; Olzinski, A.R.; Maniscalco, K.; Williams, C.; Hu, T.C.; Lenhard, S.C.; Costell, M.; Bernard, R.; Sarov-Blat, L.; Steplewski, K.; Willette, R.N. PPARdelta activation normalizes cardiac substrate metabolism and reduces right ventricular hypertrophy in congestive heart failure. *J Cardiovasc Pharmacol*, **2007**, *50(1)*, 25-34.

[214] Loichot, C.; Jesel, L.; Tesse, A.; Tabernero, A.; Schoonjans, K.; Roul, G.; Carpusca, I.; Auwerx, J.; Andriantsitohaina, R. Deletion of peroxisome proliferator-activated receptor-alpha induces an alteration of cardiac functions. *Am J Physiol Heart Circ Physiol*, **2006**, *291(1)*, H161-166.

[215] Duhaney, T.A.; Cui, L.; Rude, M.K.; Lebrasseur, N.K.; Ngoy, S.; De Silva, D.S.; Siwik, D.A.; Liao, R.; Sam, F. Peroxisome proliferator-activated receptor alpha-independent actions of fenofibrate exacerbates left ventricular dilation and fibrosis in chronic pressure overload. *Hypertension*, **2007**, *49(5)*, 1084-1094.

[216] Smeets, P.J.; Teunissen, B.E.; Willemsen, P.H.; van Nieuwenhoven, F.A.; Brouns, A.E.; Janssen, B.J.; Cleutjens, J.P.; Staels, B.; van der Vusse, G.J.; van Bilsen, M. Cardiac hypertrophy is enhanced in PPAR alpha-/- mice in response to chronic pressure overload. *Cardiovasc Res*, **2008**, *78(1)*, 79-89.

[217] Yamamoto, K.; Ohki, R.; Lee, R.T.; Ikeda, U.; Shimada, K. Peroxisome proliferator-activated receptor gamma activators inhibit cardiac hypertrophy in cardiac myocytes. *Circulation*, **2001**, *104(14)*, 1670-1675.

[218] Asakawa, M.; Takano, H.; Nagai, T.; Uozumi, H.; Hasegawa, H.; Kubota, N.; Saito, T.; Masuda, Y.; Kadowaki, T.; Komuro, I. Peroxisome proliferator-activated receptor gamma plays a critical role in inhibition of cardiac hypertrophy in vitro and in vivo. *Circulation*, **2002**, *105(10)*, 1240-1246.

[219] Duan, S.Z.; Ivashchenko, C.Y.; Russell, M.W.; Milstone, D.S.; Mortensen, R.M. Cardiomyocyte-specific knockout and agonist of peroxisome proliferator-activated receptor-gamma both induce cardiac hypertrophy in mice. *Circ Res*, **2005**, *97(4)*, 372-379.

[220] Caglayan, E.; Stauber, B.; Collins, A.R.; Lyon, C.J.; Yin, F.; Liu, J.; Rosenkranz, S.; Erdmann, E.; Peterson, L.E.; Ross, R.S.; Tangirala, R.K.; Hsueh, W.A. Differential roles of cardiomyocyte and macrophage peroxisome proliferator-activated receptor gamma in cardiac fibrosis. *Diabetes*, **2008**, *57(9)*, 2470-2479.

[221] Kanda, H.; Nohara, R.; Hasegawa, K.; Kishimoto, C.; Sasayama, S. A nuclear complex containing PPARalpha/RXRalpha is markedly downregulated in the hypertrophied rat left ventricular myocardium with normal systolic function. *Heart Vessels*, **2000**, *15(4)*, 191-196.

[222] Young, M.E.; Laws, F.A.; Goodwin, G.W.; Taegtmeyer, H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. *J Biol Chem*, **2001**, *276(48)*, 44390-44395.

[223] Finck, B.N.; Lehman, J.J.; Leone, T.C.; Welch, M.J.; Bennett, M.J.; Kovacs, A.; Han, X.; Gross, R.W.; Kozak, R.; Lopaschuk, G.D.; Kelly, D.P. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest*, **2002**, *109(1)*, 121-130.

[224] Park, S.Y.; Cho, Y.R.; Finck, B.N.; Kim, H.J.; Higashimori, T.; Hong, E.G.; Lee, M.K.; Danton, C.; Deshmukh, S.; Cline, G.W.; Wu, J.J.; Bennett, A.M.; Rothermel, B.; Kalinowski, A.; Russell, K.S.; Kim, Y.B.; Kelly, D.P.; Kim, J.K. Cardiac-specific overexpression of peroxisome proliferator-activated receptor-alpha causes insulin resistance in heart and liver. *Diabetes*, **2005**, *54(9)*, 2514-2524.

[225] Sambandam, N.; Morabito, D.; Wagg, C.; Finck, B.N.; Kelly, D.P.; Lopaschuk, G.D. Chronic activation of PPARalpha is detrimental to cardiac recovery after ischemia. *Am J Physiol Heart Circ Physiol*, **2006**, *290(1)*, H87-95.

[226] Cheng, L.; Ding, G.; Qin, Q.; Huang, Y.; Lewis, W.; He, N.; Evans, R.M.; Schneider, M.D.; Brako, F.A.; Xiao, Y.; Chen, Y.E.; Yang, Q. Cardiomyocyte-restricted peroxisome proliferator-activated receptor-delta deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. *Nat Med*, **2004**, *10(11)*, 1245-1250.

[227] Wang, P.; Liu, J.; Li, Y.; Wu, S.; Luo, J.; Yang, H.; Subbiah, R.; Chatham, J.; Zhelyabovska, O.; Yang, Q. Peroxisome proliferator-activated receptor {delta} is an essential transcriptional regulator for mitochondrial protection and biogenesis in adult heart. *Circ Res*, **2010**, *106(5)*, 911-919.

[228] Son, N.H.; Park, T.S.; Yamashita, H.; Yokoyama, M.; Huggins, L.A.; Okajima, K.; Homma, S.; Szabolcs, M.J.; Huang, L.S.; Goldberg, I.J. Cardiomyocyte expression of PPARgamma leads to cardiac dysfunction in mice. *J Clin Invest*, **2007**, *117(10)*, 2791-2801.

[229] Arakawa, K.; Ishihara, T.; Aoto, M.; Inamasu, M.; Kitamura, K.; Saito, A. An antidiabetic thiazolidinedione induces eccentric cardiac hypertrophy by cardiac volume overload in rats. *Clin Exp Pharmacol Physiol*, **2004**, *31(1-2)*, 8-13.

[230] Zhang, H.; Zhang, A.; Kohan, D.E.; Nelson, R.D.; Gonzalez, F.J.; Yang, T. Collecting duct-specific deletion of peroxisome proliferator-activated receptor gamma blocks thiazolidinedione-induced fluid retention. *Proc Natl Acad Sci U S A*, **2005**, *102(26)*, 9406-9411.

[231] Smeets, P.J.; Planavila, A.; van der Vusse, G.J.; van Bilsen, M. Peroxisome proliferator-activated receptors and inflammation: take it to heart. *Acta Physiol (Oxf)*, **2007**, *191(3)*, 171-188.

[232] Shimabukuro, M.; Higa, S.; Shinzato, T.; Nagamine, F.; Komiya, I.; Takasu, N. Cardioprotective effects of troglitazone in streptozotocin-induced diabetic rats. *Metabolism*, **1996**, *45(9)*, 1168-1173.

[233] Wayman, N.S.; Hattori, Y.; McDonald, M.C.; Mota-Filipe, H.; Cuzzocrea, S.; Pisano, B.; Chatterjee, P.K.; Thiemermann, C. Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size. *FASEB J*, **2002**, *16(9)*, 1027-1040.

[234] Tabernero, A.; Schoonjans, K.; Jesel, L.; Carpusca, I.; Auwerx, J.; Andriantsitohaina, R. Activation of the peroxisome proliferator-activated receptor alpha protects against myocardial ischaemic injury and improves endothelial vasodilatation. *BMC Pharmacol*, **2002**, *2*, 10.

[235] Yue, T.L.; Bao, W.; Jucker, B.M.; Gu, J.L.; Romanic, A.M.; Brown, P.J.; Cui, J.; Thudium, D.T.; Boyce, R.; Burns-Kurtis, C.L.; Mirabile, R.C.; Aravindhan, K.; Ohlstein, E.H. Activation of peroxisome proliferator-activated receptor-alpha protects the heart from ischemia/reperfusion injury. *Circulation*, **2003**, *108(19)*, 2393-2399.

[236] Yeh, C.H.; Chen, T.P.; Lee, C.H.; Wu, Y.C.; Lin, Y.M.; Lin, P.J. Cardiomyocytic apoptosis following global cardiac ischemia and reperfusion can be attenuated by peroxisome proliferator-activated receptor alpha but not gamma activators. *Shock*, **2006**, *26(3)*, 262-270.

[237] Khandoudi, N.; Delerive, P.; Berrebi-Bertrand, I.; Buckingham, R.E.; Staels, B.; Bril, A. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma, inhibits the Jun NH(2)-terminal kinase/activating protein 1 pathway and protects the heart from ischemia/reperfusion injury. *Diabetes*, **2002**, *51(5)*, 1507-1514.

[238] Burkart, E.M.; Sambandam, N.; Han, X.; Gross, R.W.; Courtois, M.; Gierasch, C.M.; Shoghi, K.; Welch, M.J.; Kelly, D.P. Nuclear receptors PPARbeta/delta and PPARalpha direct distinct metabolic regulatory programs in the mouse heart. *J Clin Invest*, **2007**, *117(12)*, 3930-3939.

[239] Yue, T.L.; Nerurkar, S.S.; Bao, W.; Jucker, B.M.; Sarov-Blat, L.; Steplewski, K.; Ohlstein, E.H.; Willette, R.N. In vivo activation of peroxisome proliferator-activated receptor-delta protects the heart from ischemia/reperfusion injury in Zucker fatty rats. *J Pharmacol Exp Ther*, **2008**, *325(2)*, 466-474.

[240] Frantz, S.; Hu, K.; Widder, J.; Bayer, B.; Witzel, C.C.; Schmidt, I.; Galuppo, P.; Strotmann, J.; Ertl, G.; Bauersachs, J. Peroxisome proliferator activated-receptor agonism and left ventricular remodeling in mice with chronic myocardial infarction. *Br J Pharmacol*, **2004**, *141(1)*, 9-14.

[241] Geng, D.F.; Wu, W.; Jin, D.M.; Wang, J.F.; Wu, Y.M. Effect of peroxisome proliferator-activated receptor gamma ligand. Rosiglitazone on left ventricular remodeling in rats with myocardial infarction. *Int J Cardiol*, **2006**, *113(1)*, 86-91.

[242] Morgan, E.E.; Rennison, J.H.; Young, M.E.; McElfresh, T.A.; Kung, T.A.; Tserng, K.Y.; Hoit, B.D.; Stanley, W.C.; Chandler, M.P. Effects of chronic activation of peroxisome proliferator-activated receptor-alpha or high-fat feeding in a rat infarct model of heart failure. *Am J Physiol Heart Circ Physiol*, **2006**, *290(5)*, H1899-1904.

[243] Henderson, B.C.; Sen, U.; Reynolds, C.; Moshal, K.S.; Ovechkin, A.; Tyagi, N.; Kartha, G.K.; Rodriguez, W.E.; Tyagi, S.C. Reversal of systemic hypertension-associated cardiac remodeling in chronic pressure overload myocardium by ciglitazone. *Int J Biol Sci*, **2007**, *3(6)*, 385-392.

[244] Ihm, S.H.; Chang, K.; Kim, H.Y.; Baek, S.H.; Youn, H.J.; Seung, K.B.; Kim, J.H. Peroxisome proliferator-activated receptor-gamma activation attenuates cardiac fibrosis in type 2 diabetic rats: the effect of rosiglitazone on myocardial expression of receptor for advanced glycation end products and of connective tissue growth factor. *Basic Res Cardiol*, **2010**, *105(3)*, 399-407.

[245] Teunissen, B.E.; Smeets, P.J.; Willemsen, P.H.; De Windt, L.J.; Van der Vusse, G.J.; Van Bilsen, M. Activation of PPARdelta inhibits cardiac fibroblast proliferation and the transdifferentiation into myofibroblasts. *Cardiovasc Res*, **2007**, *75(3)*, 519-529.

[246] Pistrosch, F.; Herbrig, K.; Oelschlaegel, U.; Richter, S.; Passauer, J.; Fischer, S.; Gross, P. PPARgamma-agonist rosiglitazone increases number and migratory activity of cultured endothelial progenitor cells. *Atherosclerosis*, **2005**, *183(1)*, 163-167.

[247] Honda, A.; Matsuura, K.; Fukushima, N.; Tsurumi, Y.; Kasanuki, H.; Hagiwara, N. Telmisartan induces proliferation of human endothelial progenitor cells via PPARgamma-dependent PI3K/Akt pathway. *Atherosclerosis*, **2009**, *205(2)*, 376-384.

[248] Matsuura, K.; Hagiwara, N. The pleiotropic effects of ARB in vascular endothelial progenitor cells. *Curr Vasc Pharmacol*, **2011**, *9(2)*, 153-157.

[249] Fahmi, H.; Martel-Pelletier, J.; Pelletier, J.P.; Kapoor, M. Peroxisome proliferator-activated receptor gamma in osteoarthritis. *Mod Rheumatol*, **2011**, *21(1)*, 1-9.

[250] Pedersen, G.; Brynskov, J. Topical rosiglitazone treatment improves ulcerative colitis by restoring peroxisome proliferator-activated receptor-gamma activity. *Am J Gastroenterol*, **2010**, *105(7)*, 1595-1603.

[251] Sugawara, A.; Uruno, A.; Kudo, M.; Matsuda, K.; Yang, C.W.; Ito, S. Effects of PPARgamma on hypertension, atherosclerosis, and chronic kidney disease. *Endocr J*, **2010**, *57(10)*, 847-852.

[252] Afif, H.; Benderdour, M.; Mfuna-Endam, L.; Martel-Pelletier, J.; Pelletier, J.P.; Duval, N.; Fahmi, H. Peroxisome proliferator-activated receptor gamma1 expression is diminished in human osteoarthritic cartilage and is downregulated by interleukin-1beta in articular chondrocytes. *Arthritis Res Ther*, **2007**, *9(2)*, R31.

[253] Yang, Q.; Chen, C.; Wu, S.; Zhang, Y.; Mao, X.; Wang, W. Advanced glycation end products downregulates peroxisome proliferator-activated receptor gamma expression in cultured rabbit chondrocyte through MAPK pathway. *Eur J Pharmacol*, **2010**, *649(1-3)*, 108-114.

[254] Lin, T.H.; Yang, R.S.; Tang, C.H.; Lin, C.P.; Fu, W.M. PPARgamma inhibits osteogenesis via the down-regulation of the expression of COX-2 and iNOS in rats. *Bone*, **2007**, *41(4)*, 562-574.

[255] Poleni, P.E.; Etienne, S.; Velot, E.; Netter, P.; Bianchi, A. Activation of PPARs alpha, beta/delta, and gamma Impairs TGF-beta1-Induced Collagens' Production and Modulates the TIMP-1/MMPs Balance in Three-Dimensional Cultured Chondrocytes. *PPAR Res*, **2010**, *2010*, 635912.

[256] Castillero, E.; Nieto-Bona, M.P.; Fernandez-Galaz, C.; Martin, A.I.; Lopez-Menduina, M.; Granado, M.; Villanua, M.A.; Lopez-Calderon, A. Fenofibrate, a PPAR{alpha} agonist, decreases atrogenes and myostatin expression and improves arthritis-induced skeletal muscle atrophy. *Am J Physiol Endocrinol Metab*, *300(5)*, E790-799.

[257] Stanton, L.A.; Li, J.R.; Beier, F. PPARgamma2 expression in growth plate chondrocytes is regulated by p38 and GSK-3. *J Cell Mol Med*, **2010**, *14(1-2)*, 242-256.

[258] Ng, A.; Duque, G. Osteoporosis as a Lipotoxic Disease. *IBMS BoneKEy.* , **2010**, *7(3)*, 5.

[259] Habib, Z.A.; Havstad, S.L.; Wells, K.; Divine, G.; Pladevall, M.; Williams, L.K. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*, **2010**, *95(2)*, 592-600.

[260] Viccica, G.; Francucci, C.M.; Marcocci, C. The role of PPARgamma for the osteoblastic differentiation. *J Endocrinol Invest*, **2010**, *33(7 Suppl)*, 9-12.

[261] Wan, Y.; Chong, L.W.; Evans, R.M. PPAR-gamma regulates osteoclastogenesis in mice. *Nat Med*, **2007**, *13(12)*, 1496-1503.

[262] Shin, S.W.; Seo, C.Y.; Han, H.; Han, J.Y.; Jeong, J.S.; Kwak, J.Y.; Park, J.I. 15d-PGJ2 induces apoptosis by reactive oxygen species-mediated inactivation of Akt in leukemia and colorectal cancer cells and shows in vivo antitumor activity. *Clin Cancer Res*, **2009**, *15(17)*, 5414-5425.

[263] Jung, J.Y.; Yoo, C.I.; Kim, H.T.; Kwon, C.H.; Park, J.Y.; Kim, Y.K. Role of mitogen-activated protein kinase (MAPK) in troglitazone-induced osteoblastic cell death. *Toxicology*, **2007**, *234(1-2)*, 73-82.

[264] Kim, S.H.; Yoo, C.I.; Kim, H.T.; Park, J.Y.; Kwon, C.H.; Kim, Y.K. Activation of peroxisome proliferator-activated receptor-gamma (PPARgamma) induces cell death through MAPK-dependent mechanism in osteoblastic cells. *Toxicol Appl Pharmacol*, **2006**, *215(2)*, 198-207.

[265] Shah, P.; Mudaliar, S. Pioglitazone: side effect and safety profile. *Expert Opin Drug Saf*, **2010**, *9(2)*, 347-354.

[266] Kiss-Toth, E.; Roszer, T. PPARgamma in Kidney Physiology and Pathophysiology. *PPAR Res*, **2008**, *2008*, 183108.

[267] Aprahamian, T.; Bonegio, R.G.; Richez, C.; Yasuda, K.; Chiang, L.K.; Sato, K.; Walsh, K.; Rifkin, I.R. The peroxisome proliferator-activated receptor gamma agonist rosiglitazone ameliorates murine lupus by induction of adiponectin. *J Immunol*, **2009**, *182(1)*, 340-346.

[268] Liang, Y.J.; Jian, J.H.; Liu, Y.C.; Juang, S.J.; Shyu, K.G.; Lai, L.P.; Wang, B.W.; Leu, J.G. Advanced glycation end products-induced apoptosis attenuated by PPARdelta activation and epigallocatechin gallate through NF-kappaB pathway in human embryonic kidney cells and human mesangial cells. *Diabetes Metab Res Rev*, **2010**, *26(5)*, 406-416.

[269] Kamijo, Y.; Hora, K.; Nakajima, T.; Kono, K.; Takahashi, K.; Ito, Y.; Higuchi, M.; Kiyosawa, K.; Shigematsu, H.; Gonzalez, F.J.; Aoyama, T. Peroxisome proliferator-activated receptor alpha protects against glomerulonephritis induced by long-term exposure to the plasticizer di-(2-ethylhexyl)phthalate. *J Am Soc Nephrol*, **2007**, *18(1)*, 176-188.

[270] Mukundan, L.; Odegaard, J.I.; Morel, C.R.; Heredia, J.E.; Mwangi, J.W.; Ricardo-Gonzalez, R.R.; Goh, Y.P.; Eagle, A.R.; Dunn, S.E.; Awakuni, J.U.; Nguyen, K.D.; Steinman, L.; Michie, S.A.; Chawla, A. PPAR-delta senses and orchestrates clearance of apoptotic cells to promote tolerance. *Nat Med*, **2009**, *15(11)*, 1266-1272.

[271] Shao, W.H.; Cohen, P.L. Disturbances of apoptotic cell clearance in systemic lupus erythematosus. *Arthritis Res Ther*, **2011**, *13(1)*, 202.

[272] Aronoff, D.M.; Serezani, C.H.; Carstens, J.K.; Marshall, T.; Gangireddy, S.R.; Peters-Golden, M.; Reddy, R.C. Stimulatory Effects of Peroxisome Proliferator-Activated Receptor-gamma on Fcgamma Receptor-Mediated Phagocytosis by Alveolar Macrophages. *PPAR Res*, **2007**, *2007*, 52546.

[273] Berry, A.; Balard, P.; Coste, A.; Olagnier, D.; Lagane, C.; Authier, H.; Benoit-Vical, F.; Lepert, J.C.; Seguela, J.P.; Magnaval, J.F.; Chambon, P.; Metzger, D.; Desvergne, B.; Wahli, W.; Auwerx, J.; Pipy, B. IL-13 induces expression of CD36 in human monocytes through PPARgamma activation. *Eur J Immunol*, **2007**, *37(6)*, 1642-1652.

[274] Reddy, R.C. Immunomodulatory role of PPAR-gamma in alveolar macrophages. *J Investig Med*, **2008**, *56(2)*, 522-527.

[275] Majai, G.; Sarang, Z.; Csomos, K.; Zahuczky, G.; Fesus, L. PPARgamma-dependent regulation of human macrophages in phagocytosis of apoptotic cells. *Eur J Immunol*, **2007**, *37(5)*, 1343-1354.

[276] Shimizu, K.; Kobayashi, M.; Tahara, J.; Shiratori, K. Cytokines and peroxisome proliferator-activated receptor gamma ligand regulate phagocytosis by pancreatic stellate cells. *Gastroenterology*, **2005**, *128(7)*, 2105-2118.

[277] Kielian, T.; Syed, M.M.; Liu, S.; Phulwani, N.K.; Phillips, N.; Wagoner, G.; Drew, P.D.; Esen, N. The synthetic peroxisome proliferator-activated receptor-gamma agonist ciglitazone attenuates neuroinflammation and accelerates encapsulation in bacterial brain abscesses. *J Immunol*, **2008**, *180(7)*, 5004-5016.

[278] Patel, S.N.; Serghides, L.; Smith, T.G.; Febbraio, M.; Silverstein, R.L.; Kurtz, T.W.; Pravenec, M.; Kain, K.C. CD36 mediates the phagocytosis of Plasmodium falciparum-infected erythrocytes by rodent macrophages. *J Infect Dis*, **2004**, *189(2)*, 204-213.

[279] Kang, J.H.; Lee, G.S.; Jeung, E.B.; Yang, M.P. Trans-10, cis-12-conjugated linoleic acid increases phagocytosis of porcine peripheral blood polymorphonuclear cells in vitro. *Br J Nutr*, **2007**, *97(1)*, 117-125.

[280] Romanowska, M.; Reilly, L.; Palmer, C.N.; Gustafsson, M.C.; Foerster, J. Activation of PPARbeta/delta causes a psoriasis-like skin disease in vivo. *PLoS One*, **2010**, *5(3)*, e9701.

[281] Bhagavathula, N.; Nerusu, K.C.; Lal, A.; Ellis, C.N.; Chittiboyina, A.; Avery, M.A.; Ho, C.I.; Benson, S.C.; Pershadsingh, H.A.; Kurtz, T.W.; Varani, J. Rosiglitazone inhibits proliferation, motility, and matrix metalloproteinase production in keratinocytes. *J Invest Dermatol*, **2004**, *122(1)*, 130-139.

[282] Han, G.; Williams, C.A.; Salter, K.; Garl, P.J.; Li, A.G.; Wang, X.J. A role for TGFbeta signaling in the pathogenesis of psoriasis. *J Invest Dermatol*, **2010**, *130(2)*, 371-377.

[283] Krentz, A.J.; Friedmann, P.S. Type 2 diabetes, psoriasis and thiazolidinediones. *Int J Clin Pract*, **2006**, *60(3)*, 362-363.

[284] Saraceno, R.; Ruzzetti, M.; De Martino, M.U.; Di Renzo, L.; Cianci, R.; De Lorenzo, A.; Chimenti, S. Does metabolic syndrome influence psoriasis? *Eur Rev Med Pharmacol Sci*, **2008**, *12(5)*, 339-341.

[285] Varani, J.; Bhagavathula, N.; Ellis, C.N.; Pershadsingh, H.A. Thiazolidinediones: potential as therapeutics for psoriasis and perhaps other hyperproliferative skin disease. *Expert Opin Investig Drugs*, **2006**, *15(11)*, 1453-1468.

[286] Boyd, A.S. Thiazolidinediones in dermatology. *Int J Dermatol*, **2007**, *46(6)*, 557-563.

[287] El Eishi, N.; Hegazy, R.; Abou Zeid, O.; Shaker, O. Peroxisome Proliferator Receptor (PPAR) beta/delta in psoriatic patients before and after two conventional therapeutic modalities: methotrexate and PUVA. *Eur J Dermatol*, **2011**.

[288] Romanowska, M.; al Yacoub, N.; Seidel, H.; Donandt, S.; Gerken, H.; Phillip, S.; Haritonova, N.; Artuc, M.; Schweiger, S.; Sterry, W.; Foerster, J. PPARdelta enhances keratinocyte proliferation in psoriasis and induces heparin-binding EGF-like growth factor. *J Invest Dermatol*, **2008**, *128(1)*, 110-124.

[289] al Yacoub, N.; Romanowska, M.; Krauss, S.; Schweiger, S.; Foerster, J. PPARdelta is a type 1 IFN target gene and inhibits apoptosis in T cells. *J Invest Dermatol*, **2008**, *128(8)*, 1940-1949.

[290] Ottaviani, M.; Camera, E.; Picardo, M. Lipid Mediators in Acne. *Mediators of Inflammation Volume 2010*, **2010**.

[291] Harries, M.J.; Paus, R. The Pathogenesis of Primary Cicatricial Alopecias. *The American Journal of Pathology, Vol. 177, No. 5, November 2010*, **2010**, *177(5)*, 10.

[292] Atug, O.; Tahan, V.; Eren, F.; Tiftikci, A.; Imeryuz, N.; Hamzaoglu, H.O.; Tozun, N. Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-gamma (PPARgamma) gene in inflammatory bowel disease. *J Gastrointestin Liver Dis*, **2008**, *17(4)*, 433-437.

[293] Aoyagi, Y.; Nagata, S.; Kudo, T.; Fujii, T.; Wada, M.; Chiba, Y.; Ohtsuka, Y.; Yamashiro, Y.; Shimizu, T.; Ohkusa, T. Peroxisome proliferator-activated receptor gamma 2 mutation may cause a subset of ulcerative colitis. *Pediatr Int*, **2010**, *52(5)*, 729-734.

[294] Andersen, V.; Christensen, J.; Ernst, A.; Jacobsen, B.A.; Tjonneland, A.; Krarup, H.B.; Vogel, U. Polymorphisms in NF-kappaB, PXR, LXR, PPARgamma and risk of inflammatory bowel disease. *World J Gastroenterol*, **2011**, *17(2)*, 197-206.

[295] Yamamoto-Furusho, J.K.; Penaloza-Coronel, A.; Sanchez-Munoz, F.; Barreto-Zuniga, R.; Dominguez-Lopez, A. Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) expression is downregulated in patients with active ulcerative colitis. *Inflamm Bowel Dis*, **2011**, *17(2)*, 680-681.

[296] Dubuquoy, L.; Jansson, E.A.; Deeb, S.; Rakotobe, S.; Karoui, M.; Colombel, J.F.; Auwerx, J.; Pettersson, S.; Desreumaux, P. Impaired expression of peroxisome proliferator-activated receptor gamma in ulcerative colitis. *Gastroenterology*, **2003**, *124(5)*, 1265-1276.

[297] Saubermann, L.J.; Nakajima, A.; Wada, K.; Zhao, S.; Terauchi, Y.; Kadowaki, T.; Aburatani, H.; Matsuhashi, N.; Nagai, R.; Blumberg, R.S. Peroxisome proliferator-activated receptor gamma agonist ligands stimulate a Th2 cytokine response and prevent acute colitis. *Inflamm Bowel Dis*, **2002**, *8(5)*, 330-339.

[298] Dubuquoy, L.; Rousseaux, C.; Thuru, X.; Peyrin-Biroulet, L.; Romano, O.; Chavatte, P.; Chamaillard, M.; Desreumaux, P. PPARgamma as a new therapeutic target in inflammatory bowel diseases. *Gut*, **2006**, *55(9)*, 1341-1349.

[299] Su, C.G.; Wen, X.; Bailey, S.T.; Jiang, W.; Rangwala, S.M.; Keilbaugh, S.A.; Flanigan, A.; Murthy, S.; Lazar, M.A.; Wu, G.D. A novel therapy for colitis utilizing PPAR-γ ligands to inhibit the epithelial inflammatory response. *J. Clin. Invest.*, **1999**, *104(4)*, 383-389.

[300] Cuzzocrea, S.; Di Paola, R.; Mazzon, E.; Genovese, T.; Muia, C.; Centorrino, T.; Caputi, A.P. Role of endogenous and exogenous ligands for the peroxisome proliferators activated receptors alpha (PPAR-alpha) in the development of inflammatory bowel disease in mice. *Lab Invest*, **2004**, *84(12)*, 1643-1654.

[301] Lee, J.W.; Bajwa, P.J.; Carson, M.J.; Jeske, D.R.; Cong, Y.; Elson, C.O.; Lytle, C.; Straus, D.S. Fenofibrate represses interleukin-17 and interferon-gamma expression and improves colitis in interleukin-10-deficient mice. *Gastroenterology*, **2007**, *133(1)*, 108-123.

[302] Rousseaux, C.; Lefebvre, B.; Dubuquoy, L.; Lefebvre, P.; Romano, O.; Auwerx, J.; Metzger, D.; Wahli, W.; Desvergne, B.; Naccari, G.C.; Chavatte, P.; Farce, A.; Bulois, P.; Cortot, A.; Colombel, J.F.; Desreumaux, P. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. *J Exp Med*, **2005**, *201(8)*, 1205-1215.

[303] Riccardi, L.; Mazzon, E.; Bruscoli, S.; Esposito, E.; Crisafulli, C.; Di Paola, R.; Caminiti, R.; Riccardi, C.; Cuzzocrea, S. Peroxisome proliferator-activated receptor-alpha modulates the anti-inflammatory effect of glucocorticoids in a model of inflammatory bowel disease in mice. *Shock*, **2009**, *31(3)*, 308-316.

[304] Peyrin-Biroulet, L.; Beisner, J.; Wang, G.; Nuding, S.; Oommen, S.T.; Kelly, D.; Parmentier-Decrucq, E.; Dessein, R.; Merour, E.; Chavatte, P.; Grandjean, T.; Bressenot, A.; Desreumaux, P.; Colombel, J.F.; Desvergne, B.; Stange, E.F.; Wehkamp, J.; Chamaillard, M. Peroxisome proliferator-activated receptor gamma activation is required for maintenance of innate antimicrobial immunity in the colon. *Proc Natl Acad Sci U S A*, **2010**, *107(19)*, 8772-8777.

[305] Belvisi, M.G.; Hele, D.J.; Birrell, M.A. Peroxisome proliferator-activated receptor gamma agonists as therapy for chronic airway inflammation. *Eur J Pharmacol*, **2006**, *533(1-3)*, 101-109.

[306] Li, J.; Dai, A.; Hu, R.; Zhu, L.; Tan, S. Positive correlation between PPARgamma/PGC-1alpha and gamma-GCS in lungs of rats and patients with chronic obstructive pulmonary disease. *Acta Biochim Biophys Sin (Shanghai)*, **2010**, *42(9)*, 603-614.

[307] Penyige, A.; Poliska, S.; Csanky, E.; Scholtz, B.; Dezso, B.; Schmelczer, I.; Kilty, I.; Takacs, L.; Nagy, L. Analyses of association between PPAR gamma and EPHX1 polymorphisms and susceptibility to COPD in a Hungarian cohort, a case-control study. *BMC Med Genet*, **2010**, *11*, 152.

[308] Wang, X.; Wang, Y.; Zhao, X.; Andersson, R.; Song, Z.; Yang, D. Potential effects of peroxisome proliferator-activated receptor activator on LPS-induced lung injury in rats. *Pulm Pharmacol Ther*, **2009**, *22(4)*, 318-325.

[309] Bauer, C.M.; Zavitz, C.C.; Botelho, F.M.; Lambert, K.N.; Brown, E.G.; Mossman, K.L.; Taylor, J.D.; Stampfli, M.R. Treating viral exacerbations of chronic obstructive pulmonary disease: insights from a mouse model of cigarette smoke and H1N1 influenza infection. *PLoS One*, **2010**, *5(10)*, e13251.

[310] Harmon, G.S.; Dumlao, D.S.; Ng, D.T.; Barrett, K.E.; Dennis, E.A.; Dong, H.; Glass, C.K. Pharmacological correction of a defect in PPAR-gamma signaling ameliorates disease severity in Cftr-deficient mice. *Nat Med*, **2010**, *16(3)*, 313-318.

[311] Gea-Sorli, S.; Guillamat, R.; Serrano-Mollar, A.; Closa, D. Activation of lung macrophage subpopulations in experimental acute pancreatitis. *J Pathol*, *223(3)*, 417-424.

[312] Xu, P.; Xu, K.; Wang, J.; Jiang, J.P.; Chen, L.Q. Pioglitazone: a promising therapeutic tool in sodium taurocholate-induced severe acute pancreatitis. *Dig Dis Sci*, *56(4)*, 1082-1089.

[313] Sidhu, S.; Pandhi, P.; Malhotra, S.; Vaiphei, K.; Khanduja, K.L. Rosiglitazone promotes pancreatic regeneration in experimental model of acute pancreatitis. *Fundam Clin Pharmacol*, *25(2)*, 237-247.

[314] Ivashchenko, C.Y.; Duan, S.Z.; Usher, M.G.; Mortensen, R.M. PPAR-gamma knockout in pancreatic epithelial cells abolishes the inhibitory effect of rosiglitazone on caerulein-induced acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol*, **2007**, *293(1)*, G319-326.

[315] Chen, C.; Xu, S.; Wang, W.X.; Ding, Y.M.; Yu, K.H.; Wang, B.; Chen, X.Y. Rosiglitazone attenuates the severity of sodium taurocholate-induced acute pancreatitis and pancreatitis-associated lung injury. *Arch Med Res*, **2009**, *40(2)*, 79-88.

[316] Gelosa, P.; Banfi, C.; Gianella, A.; Brioschi, M.; Pignieri, A.; Nobili, E.; Castiglioni, L.; Cimino, M.; Tremoli, E.; Sironi, L. Peroxisome proliferator-activated receptor {alpha} agonism prevents renal damage and the oxidative stress and inflammatory processes affecting the brains of stroke-prone rats. *J Pharmacol Exp Ther*, **2010**, *335(2)*, 324-331.

[317] Ramanan, S.; Zhao, W.; Riddle, D.R.; Robbins, M.E. Role of PPARs in Radiation-Induced Brain Injury. *PPAR Res*, **2010**, *2010*, 234975.

[318] Kaundal, R.K.; Sharma, S.S. Peroxisome proliferator-activated receptor gamma agonists as neuroprotective agents. *Drug News Perspect*, **2010**, *23(4)*, 241-256.

[319] Carta, A.R.; Pisanu, A.; Carboni, E. Do PPAR-Gamma Agonists Have a Future in Parkinson's Disease Therapy? *Parkinsons Dis*, **2011**, *2011*, 689181.

[320] Deplanque, D.; Gele, P.; Petrault, O.; Six, I.; Furman, C.; Bouly, M.; Nion, S.; Dupuis, B.; Leys, D.; Fruchart, J.C.; Cecchelli, R.; Staels, B.; Duriez, P.; Bordet, R. Peroxisome proliferator-activated receptor-alpha activation as a mechanism of preventive neuroprotection induced by chronic fenofibrate treatment. *J Neurosci*, **2003**, *23(15)*, 6264-6271.

[321] de la Monte, S.M.; Wands, J.R. Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. *J Alzheimers Dis*, **2006**, *9(2)*, 167-181.

[322] Brune, S.; Kolsch, H.; Ptok, U.; Majores, M.; Schulz, A.; Schlosser, R.; Rao, M.L.; Maier, W.; Heun, R. Polymorphism in the peroxisome proliferator-activated receptor alpha gene influences the risk for Alzheimer's disease. *J Neural Transm*, **2003**, *110(9)*, 1041-1050.

[323] Combs, C.K.; Bates, P.; Karlo, J.C.; Landreth, G.E. Regulation of beta-amyloid stimulated proinflammatory responses by peroxisome proliferator-activated receptor alpha. *Neurochem Int*, **2001**, *39(5-6)*, 449-457.

[324] Gocke, A.R.; Hussain, R.Z.; Yang, Y.; Peng, H.; Weiner, J.; Ben, L.H.; Drew, P.D.; Stuve, O.; Lovett-Racke, A.E.; Racke, M.K. Transcriptional modulation of the immune response by peroxisome proliferator-activated receptor-{alpha} agonists in autoimmune disease. *J Immunol*, **2009**, *182(7)*, 4479-4487.

[325] Mutez, E.; Duhamel, A.; Defebvre, L.; Bordet, R.; Destee, A.; Kreisler, A. Lipid-lowering drugs are associated with delayed onset and slower course of Parkinson's disease. *Pharmacol Res*, **2009**, *60(1)*, 41-45.

[326] Pereira, M.P.; Hurtado, O.; Cardenas, A.; Bosca, L.; Castillo, J.; Davalos, A.; Vivancos, J.; Serena, J.; Lorenzo, P.; Lizasoain, I.; Moro, M.A. Rosiglitazone and 15-deoxy-Delta12,14-prostaglandin J2 cause potent neuroprotection after experimental stroke through noncompletely overlapping mechanisms. *J Cereb Blood Flow Metab*, **2006**, *26(2)*, 218-229.

[327] Iwashita, A.; Muramatsu, Y.; Yamazaki, T.; Muramoto, M.; Kita, Y.; Yamazaki, S.; Mihara, K.; Moriguchi, A.; Matsuoka, N. Neuroprotective efficacy of the peroxisome proliferator-activated receptor delta-selective agonists in vitro and in vivo. *J Pharmacol Exp Ther*, **2007**, *320(3)*, 1087-1096.

[328] Nishijima, C.; Kimoto, K.; Arakawa, Y. Survival activity of troglitazone in rat motoneurones. *J Neurochem*, **2001**, *76(2)*, 383-390.

[329] Luna-Medina, R.; Cortes-Canteli, M.; Alonso, M.; Santos, A.; Martinez, A.; Perez-Castillo, A. Regulation of inflammatory response in neural cells in vitro by thiadiazolidinones derivatives through peroxisome proliferator-activated receptor gamma activation. *J Biol Chem*, **2005**, *280(22)*, 21453-21462.

[330] Hirsch, E.C.; Breidert, T.; Rousselet, E.; Hunot, S.; Hartmann, A.; Michel, P.P. The role of glial reaction and inflammation in Parkinson's disease. *Ann N Y Acad Sci*, **2003**, *991*, 214-228.

[331] Xu, J.; Chavis, J.A.; Racke, M.K.; Drew, P.D. Peroxisome proliferator-activated receptor-alpha and retinoid X receptor agonists inhibit inflammatory responses of astrocytes. *J Neuroimmunol*, **2006**, *176(1-2)*, 95-105.

[332] Diab, A.; Deng, C.; Smith, J.D.; Hussain, R.Z.; Phanavanh, B.; Lovett-Racke, A.E.; Drew, P.D.; Racke, M.K. Peroxisome proliferator-activated receptor-gamma agonist 15-deoxy- Delta(12,14)-prostaglandin J(2) ameliorates experimental autoimmune encephalomyelitis. *J Immunol*, **2002**, *168(5)*, 2508-2515.

[333] Natarajan, C.; Bright, J.J. Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production, IL-12 signaling and Th1 differentiation. *Genes Immun*, **2002**, *3(2)*, 59-70.

[334] Raikwar, H.P.; Muthian, G.; Rajasingh, J.; Johnson, C.N.; Bright, J.J. PPARgamma antagonists reverse the inhibition of neural antigen-specific Th1 response and experimental allergic encephalomyelitis by Ciglitazone and 15-deoxy-Delta12,14-prostaglandin J2. *J Neuroimmunol*, **2006**, *178(1-2)*, 76-86.

[335] Xu, J.; Drew, P.D. Peroxisome proliferator-activated receptor-gamma agonists suppress the production of IL-12 family cytokines by activated glia. *J Immunol*, **2007**, *178(3)*, 1904-1913.

[336] Cunard, R.; Eto, Y.; Muljadi, J.T.; Glass, C.K.; Kelly, C.J.; Ricote, M. Repression of IFN-gamma expression by peroxisome proliferator-activated receptor gamma. *J Immunol*, **2004**, *172(12)*, 7530-7536.

[337] Klotz, L.; Burgdorf, S.; Dani, I.; Saijo, K.; Flossdorf, J.; Hucke, S.; Alferink, J.; Nowak, N.; Beyer, M.; Mayer, G.; Langhans, B.; Klockgether, T.; Waisman, A.; Eberl, G.; Schultze, J.; Famulok, M.; Kolanus, W.; Glass, C.; Kurts, C.; Knolle, P.A. The nuclear receptor PPAR gamma selectively inhibits Th17 differentiation in a T cell-intrinsic fashion and suppresses CNS autoimmunity. *J Exp Med*, **2009**, *206(10)*, 2079-2089.

[338] Kanakasabai, S.; Walline, C.C.; Chakraborty, S.; Bright, J.J. PPARdelta deficient mice develop elevated Th1/Th17 responses and prolonged experimental autoimmune encephalomyelitis. *Brain Res*, **2011**, *1376*, 101-112.

[339] Schintu, N.; Frau, L.; Ibba, M.; Caboni, P.; Garau, A.; Carboni, E.; Carta, A.R. PPAR-gamma-mediated neuroprotection in a chronic mouse model of Parkinson's disease. *Eur J Neurosci*, **2009**, *29(5)*, 954-963.

[340] Nicolakakis, N.; Aboulkassim, T.; Ongali, B.; Lecrux, C.; Fernandes, P.; Rosa-Neto, P.; Tong, X.K.; Hamel, E. Complete rescue of cerebrovascular function in aged Alzheimer's disease transgenic mice by antioxidants and pioglitazone, a peroxisome proliferator-activated receptor gamma agonist. *J Neurosci*, **2008**, *28(37)*, 9287-9296.

[341] Landreth, G.; Jiang, Q.; Mandrekar, S.; Heneka, M. PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. *Neurotherapeutics*, **2008**, *5(3)*, 481-489.

[342] Kiaei, M. Peroxisome Proliferator-Activated Receptor-gamma in Amyotrophic Lateral Sclerosis and Huntington's Disease. *PPAR Res*, **2008**, *2008*, 418765.

[343] Napimoga, M.H.; Souza, G.R.; Cunha, T.M.; Ferrari, L.F.; Clemente-Napimoga, J.T.; Parada, C.A.; Verri, W.A., Jr.; Cunha, F.Q.; Ferreira, S.H. 15d-prostaglandin J2 inhibits inflammatory hypernociception: involvement of peripheral opioid receptor. *J Pharmacol Exp Ther*, **2008**, *324(1)*, 313-321.

[344] Michalik, L.; Desvergne, B.; Wahli, W. Peroxisome-proliferator-activated receptors and cancers: complex stories. *Nat Rev Cancer*, **2004**, *4(1)*, 61-70.

[345] Ikezoe, T.; Miller, C.W.; Kawano, S.; Heaney, A.; Williamson, E.A.; Hisatake, J.; Green, E.; Hofmann, W.; Taguchi, H.; Koeffler, H.P. Mutational analysis of the peroxisome proliferator-activated receptor gamma gene in human malignancies. *Cancer Res*, **2001**, *61(13)*, 5307-5310.

[346] Smalley, W.E.; DuBois, R.N. Colorectal cancer and nonsteroidal anti-inflammatory drugs. *Adv Pharmacol*, **1997**, *39*, 1-20.

[347] Mansen, A.; Guardiola-Biaz, H.; Rafter, J.; Branting, C.; Gustafsson, J.-A. Expression of the peroxisome proliferator-activated receptor (PPAR) in the mouse colonic mucosa. *Bicohem. Biophys. Res. Comm.*, **1996**, *222*, 844-851.

[348] Higashiyama, H.; Billin, A.N.; Okamoto, Y.; Kinoshita, M.; Asano, S. Expression profiling of peroxisome proliferator-activated receptor-delta (PPAR-delta) in mouse tissues using tissue microarray. *Histochem Cell Biol*, **2007**, *127(5)*, 485-494.

[349] Hollingshead, H.E.; Morimura, K.; Adachi, M.; Kennett, M.J.; Billin, A.N.; Willson, T.M.; Gonzalez, F.J.; Peters, J.M. PPARbeta/delta protects against experimental colitis through a ligand-independent mechanism. *Dig Dis Sci*, **2007**, *52(11)*, 2912-2919.

[350] Reddy, J.K.; Rao, S.; Moody, D.E. Hepatocellular carcinomas in acatalasemic mice treated with nafenopin, a hypolipidemic peroxisome proliferator. *Cancer Res*, **1976**, *36(4)*, 1211-1217.

[351] Cattley, R.C.; DeLuca, J.; Elcombe, C.; Fenner-Crisp, P.; Lake, B.G.; Marsman, D.S.; Pastoor, T.A.; Popp, J.A.; Robinson, D.E.; Schwetz, B.; Tugwood, J.; Wahli, W. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol*, **1998**, *27(1 Pt 1)*, 47-60.

[352] Larsson, S.C.; Orsini, N.; Wolk, A. Milk, milk products and lactose intake and ovarian cancer risk: a meta-analysis of epidemiological studies. *Int J Cancer*, **2006**, *118(2)*, 431-441.

[353] Panigrahy, D.; Huang, S.; Kieran, M.W.; Kaipainen, A. PPARgamma as a therapeutic target for tumor angiogenesis and metastasis. *Cancer Biol Ther*, **2005**, *4(7)*, 687-693.

[354] Maggiora, M.; Oraldi, M.; Muzio, G.; Canuto, R.A. Involvement of PPARalpha and PPARgamma in apoptosis and proliferation of human hepatocarcinoma HepG2 cells. *Cell Biochem Funct*, **2010**, *28(7)*, 571-577.

[355] Elstner, E.; Muller, C.; Koshizuka, K.; Williamson, E.A.; Park, D.; Asou, H.; Shintaku, P.; Said, J.W.; Heber, D.; Koeffler, P. Ligands for peroxisome proliferator-activated receptor γ and retinoic acid receptor inhibit growth and induce apoptosis of human brest cancer cells in vitro and in BNX mice. *Proc. Natl. Acad. Sci.*, **1998**, *95*, 8806-8811.

[356] Suh, N.; Wang, Y.; Williams, C.R.; Risingsong, R.; Gilmer, T.; Willson, T.M.; Sporn, M.B. A new ligand for the peroxisome proliferator-activated receptor-gamma (PPAR-gamma), GW7845, inhibits rat mammary carcinogenesis. *Cancer Res*, **1999**, *59(22)*, 5671-5673.

[357] Tanaka, T.; Kohno, H.; Yoshitani, S.; Takashima, S.; Okumura, A.; Murakami, A.; Hosokawa, M. Ligands for peroxisome proliferator-activated receptors alpha and gamma inhibit chemically induced colitis and formation of aberrant crypt foci in rats. *Cancer Res*, **2001**, *61(6)*, 2424-2428.

[358] Osawa, E.; Nakajima, A.; Wada, K.; Ishimine, S.; Fujisawa, N.; Kawamori, T.; Matsuhashi, N.; Kadowaki, T.; Ochiai, M.; Sekihara, H.; Nakagama, H. Peroxisome proliferator-activated receptor gamma ligands suppress colon carcinogenesis induced by azoxymethane in mice. *Gastroenterology*, **2003**, *124(2)*, 361-367.

[359] Yokoyama, Y.; Xin, B.; Shigeto, T.; Umemoto, M.; Kasai-Sakamoto, A.; Futagami, M.; Tsuchida, S.; Al-Mulla, F.; Mizunuma, H. Clofibric acid, a peroxisome proliferator-activated receptor alpha ligand, inhibits growth of human ovarian cancer. *Mol Cancer Ther*, **2007**, *6(4)*, 1379-1386.

[360] Pozzi, A.; Ibanez, M.R.; Gatica, A.E.; Yang, S.; Wei, S.; Mei, S.; Falck, J.R.; Capdevila, J.H. Peroxisomal proliferator-activated receptor-alpha-dependent inhibition of endothelial cell proliferation and tumorigenesis. *J Biol Chem*, **2007**, *282(24)*, 17685-17695.

[361] Gonzalez, F.J.; Peters, J.M.; Cattley, R.C. Mechanism of action of the nongenotoxic peroxisome proliferators: role of the peroxisome proliferator-activator receptor alpha. *J Natl Cancer Inst*, **1998**, *90(22)*, 1702-1709.

[362] Lefebvre, A.-M.; Chen, I.; Desreumaux, P.; Najib, J.; Fruchart, J.-C.; Geboes, K.; Briggs, M.; Heyman, R.; Auwerx, J. Activation of the peroxisome proliferator-activated receptor γ promotes the development of colon tumors in C57BL/6J-APC^{Min}/+mice. *Nature Medicine*, **1998**, *4(9)*, 1053-1057.

[363] Pino, M.V.; Kelley, M.F.; Jayyosi, Z. Promotion of colon tumors in C57BL/6J-APC(min)/+ mice by thiazolidinedione PPARgamma agonists and a structurally unrelated PPARgamma agonist. *Toxicol Pathol*, **2004**, *32(1)*, 58-63.

[364] McAlpine, C.A.; Barak, Y.; Matise, I.; Cormier, R.T. Intestinal-specific PPARgamma deficiency enhances tumorigenesis in ApcMin/+ mice. *Int J Cancer*, **2006**, *119(10)*, 2339-2346.

[365] Girnun, G.D.; Smith, W.M.; Drori, S.; Sarraf, P.; Mueller, E.; Eng, C.; Nambiar, P.; Rosenberg, D.W.; Bronson, R.T.; Edelmann, W.; Kucherlapati, R.; Gonzalez, F.J.; Spiegelman, B.M. APC-dependent suppression of colon carcinogenesis by PPARgamma. *Proc Natl Acad Sci U S A*, **2002**, *99(21)*, 13771-13776.

[366] Nicol, C.J.; Yoon, M.; Ward, J.M.; Yamashita, M.; Fukamachi, K.; Peters, J.M.; Gonzalez, F.J. PPARgamma influences susceptibility to DMBA-induced mammary, ovarian and skin carcinogenesis. *Carcinogenesis*, **2004**, *25(9)*, 1747-1755.

[367] Tontonoz, P.; Singer, S.; Forman, B.M.; Sarraf, P.; Fletcher, J.A.; Fletcher, C.D.M.; Brun, R.P.; Mueller, E.; Altiok, S.; Oppenheim, H.; Evans, R.M.; Spiegelman, B.M. Terminal differentiation of human liposarcoma cells induced by ligands for peroxisome proliferator-activated receptor γ and the retinoid X receptor. *Proc. Natl. Acad. Sci. U.S.A.*, **1997**, *94*, 237-241.

[368] Reichle, A.; Bross, K.; Vogt, T.; Bataille, F.; Wild, P.; Berand, A.; Krause, S.W.; Andreesen, R. Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer*, **2004**, *101(10)*, 2247-2256.

[369] Govindarajan, R.; Ratnasinghe, L.; Simmons, D.L.; Siegel, E.R.; Midathada, M.V.; Kim, L.; Kim, P.J.; Owens, R.J.; Lang, N.P. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J Clin Oncol*, **2007**, *25(12)*, 1476-1481.

[370] Gupta, R.A.; Tan, J.; Krause, W.F.; Geraci, M.W.; Willson, T.M.; Dey, S.K.; DuBois, R.N. Prostacyclin-mediated activation of peroxisome proliferator-activated receptor delta in colorectal cancer. *Proc Natl Acad Sci U S A*, **2000**, *97(24)*, 13275-13280.

[371] Yoshinaga, M.; Taki, K.; Somada, S.; Sakiyama, Y.; Kubo, N.; Kaku, T.; Tsuruta, S.; Kusumoto, T.; Sakai, H.; Nakamura, K.; Takayanagi, R.; Muto, Y. The expression of both peroxisome proliferator-activated receptor delta and cyclooxygenase-2 in tissues is associated with poor prognosis in colorectal cancer patients. *Dig Dis Sci*, **2011**, *56(4)*, 1194-1200.

[372] Park, B.H.; Vogelstein, B.; Kinzler, K.W. Genetic disruption of PPARdelta decreases the tumorigenicity of human colon cancer cells. *Proc Natl Acad Sci U S A*, **2001**, *98(5)*, 2598-2603.

[373] He, T.C.; Chan, T.A.; Vogelstein, B.; Kinzler, K.W. PPARdelta is an APC-regulated target of nonsteroidal anti-inflammatory drugs. *Cell*, **1999**, *99(3)*, 335-345.

[374] Daikoku, T.; Tranguch, S.; Chakrabarty, A.; Wang, D.; Khabele, D.; Orsulic, S.; Morrow, J.D.; Dubois, R.N.; Dey, S.K. Extracellular signal-regulated kinase is a target of cyclooxygenase-1-peroxisome proliferator-activated receptor-delta signaling in epithelial ovarian cancer. *Cancer Res*, **2007**, *67(11)*, 5285-5292.

[375] Ouyang, N.; Williams, J.L.; Rigas, B. NO-donating aspirin isomers downregulate peroxisome proliferator-activated receptor (PPAR)delta expression in APC(min/+) mice proportionally to their tumor inhibitory effect: Implications for the role of PPARdelta in carcinogenesis. *Carcinogenesis*, **2006**, *27(2)*, 232-239.

[376] Shao, J.; Sheng, H.; DuBois, R.N. Peroxisome proliferator-activated receptors modulate K-Ras-mediated transformation of intestinal epithelial cells. *Cancer Res*, **2002**, *62(11)*, 3282-3288.

[377] Wang, D.; Wang, H.; Shi, Q.; Katkuri, S.; Walhi, W.; Desvergne, B.; Das, S.K.; Dey, S.K.; DuBois, R.N. Prostaglandin E(2) promotes colorectal adenoma growth via transactivation of the nuclear peroxisome proliferator-activated receptor delta. *Cancer Cell*, **2004**, *6(3)*, 285-295.

[378] Gupta, R.A.; Wang, D.; Katkuri, S.; Wang, H.; Dey, S.K.; DuBois, R.N. Activation of nuclear hormone receptor peroxisome proliferator-activated receptor-delta accelerates intestinal adenoma growth. *Nat Med*, **2004**, *10(3)*, 245-247.

[379] Wang, D.; Wang, H.; Guo, Y.; Ning, W.; Katkuri, S.; Wahli, W.; Desvergne, B.; Dey, S.K.; DuBois, R.N. Crosstalk between peroxisome proliferator-activated receptor delta and VEGF stimulates cancer progression. *Proc Natl Acad Sci U S A*, **2006**, *103(50)*, 19069-19074.

[380] Zuo, X.; Peng, Z.; Moussalli, M.J.; Morris, J.S.; Broaddus, R.R.; Fischer, S.M.; Shureiqi, I. Targeted genetic disruption of peroxisome proliferator-activated receptor-delta and colonic tumorigenesis. *J Natl Cancer Inst*, **2009**, *101(10)*, 762-767.

[381] Barak, Y.; Liao, D.; He, W.; Ong, E.S.; Nelson, M.C.; Olefsky, J.M.; Boland, R.; Evans, R.M. Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. *Proc Natl Acad Sci U S A*, **2002**, *99(1)*, 303-308.

[382] Zhu, B.; Bai, R.; Kennett, M.J.; Kang, B.H.; Gonzalez, F.J.; Peters, J.M. Chemoprevention of chemically induced skin tumorigenesis by ligand activation of peroxisome proliferator-activated receptor-beta/delta and inhibition of cyclooxygenase 2. *Mol Cancer Ther*, **2010**, *9(12)*, 3267-3277.

[383] Harman, F.S.; Nicol, C.J.; Marin, H.E.; Ward, J.M.; Gonzalez, F.J.; Peters, J.M. Peroxisome proliferator-activated receptor-delta attenuates colon carcinogenesis. *Nat Med*, **2004**, *10(5)*, 481-483.

[384] Reed, K.R.; Sansom, O.J.; Hayes, A.J.; Gescher, A.J.; Winton, D.J.; Peters, J.M.; Clarke, A.R. PPARdelta status and Apc-mediated tumourigenesis in the mouse intestine. *Oncogene*, **2004**, *23(55)*, 8992-8996.

[385] Yang, L.; Zhang, H.; Zhou, Z.G.; Yan, H.; Adell, G.; Sun, X.F. Biological Function and Prognostic Significance of Peroxisome Proliferator-Activated Receptor {delta} in Rectal Cancer. *Clin Cancer Res*, **2011**, *17(11)*, 3760-3770.

[386] Chen, L.C.; Hao, C.Y.; Chiu, Y.S.; Wong, P.; Melnick, J.S.; Brotman, M.; Moretto, J.; Mendes, F.; Smith, A.P.; Bennington, J.L.; Moore, D.; Lee, N.M. Alteration of gene expression in normal-appearing colon mucosa of APC(min) mice and human cancer patients. *Cancer Res*, **2004**, *64(10)*, 3694-3700.

[387] Karin, M. Inflammation and cancer: the long reach of Ras. *Nat Med*, **2005**, *11(1)*, 20-21.

[388] Berger, J.; Moller, D.E. The mechanisms of action of PPARs. *Annu Rev Med*, **2002**, *53*, 409-435.

[389] Varet, J.; Vincent, L.; Mirshahi, P.; Pille, J.V.; Legrand, E.; Opolon, P.; Mishal, Z.; Soria, J.; Li, H.; Soria, C. Fenofibrate inhibits angiogenesis in vitro and in vivo. *Cell Mol Life Sci*, **2003**, *60(4)*, 810-819.

[390] Panigrahy, D.; Kaipainen, A.; Huang, S.; Butterfield, C.E.; Barnes, C.M.; Fannon, M.; Laforme, A.M.; Chaponis, D.M.; Folkman, J.; Kieran, M.W. PPARalpha agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition. *Proc Natl Acad Sci U S A*, **2008**, *105(3)*, 985-990.

[391] Grabacka, M.; Plonka, P.M.; Urbanska, K.; Reiss, K. Peroxisome proliferator-activated receptor alpha activation decreases metastatic potential of melanoma cells in vitro via down-regulation of Akt. *Clin Cancer Res*, **2006**, *12(10)*, 3028-3036.

[392] Grabacka, M.; Placha, W.; Plonka, P.M.; Pajak, S.; Urbanska, K.; Laidler, P.; Slominski, A. Inhibition of melanoma metastases by fenofibrate. *Arch Dermatol Res*, **2004**, *296(2)*, 54-58.

[393] Kasai, T.; Miyauchi, K.; Yokoyama, T.; Aihara, K.; Daida, H. Efficacy of peroxisome proliferative activated receptor (PPAR)-alpha ligands, fenofibrate, on intimal hyperplasia and constrictive remodeling after coronary angioplasty in porcine models. *Atherosclerosis*, **2006**, *188(2)*, 274-280.

[394] Blann, A.D.; Belgore, F.M.; Constans, J.; Conri, C.; Lip, G.Y. Plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and atherosclerosis and the effects of fluvastatin or fenofibrate. *Am J Cardiol*, **2001**, *87(10)*, 1160-1163.

[395] Panigrahy, D.; Singer, S.; Shen, L.Q.; Butterfield, C.E.; Freedman, D.A.; Chen, E.J.; Moses, M.A.; Kilroy, S.; Duensing, S.; Fletcher, C.; Fletcher, J.A.; Hlatky, L.; Hahnfeldt, P.; Folkman, J.; Kaipainen, A. PPARgamma ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis. *J Clin Invest*, **2002**, *110(7)*, 923-932.

[396] Inoue, K.; Kawahito, Y.; Sano, H.; Takano, H.; Yoshikawa, T. New diagnostic tool for tumor angiogenesis. *Chest*, **2003**, *123(3)*, 966-967.

[397] Bishop-Bailey, D.; Hla, T. Endothelial cell apoptosis induced by the peroxisome proliferator-activated receptor (PPAR) ligand 15-deoxy-Delta12, 14-prostaglandin J2. *J Biol Chem*, **1999**, *274(24)*, 17042-17048.

[398] Ferruzzi, P.; Ceni, E.; Tarocchi, M.; Grappone, C.; Milani, S.; Galli, A.; Fiorelli, G.; Serio, M.; Mannelli, M. Thiazolidinediones inhibit growth and invasiveness of the human adrenocortical cancer cell line H295R. *J Clin Endocrinol Metab*, **2005**, *90(3)*, 1332-1339.

[399] Han, S.; Rivera, H.N.; Roman, J. Peroxisome proliferator-activated receptor-gamma ligands inhibit alpha5 integrin gene transcription in non-small cell lung carcinoma cells. *Am J Respir Cell Mol Biol*, **2005**, *32(4)*, 350-359.

[400] Mueller, E.; Sarraf, P.; Tontonoz, P.; Evans, R.M.; Martin, K.J.; Zhang, M.; Fletcher, C.; Singer, S.; Spiegelman, B.M. Terminal differentiation of human breast cancer through PPARγ. *Mol. Cell.*, **1998**, *1*, 465-470.

[401] Jiang, C.; Ting, A.T.; Seed, B. PPARγ agonists inhibit production of monocyte inflammatory cytokines. *Nature*, **1998**, *391(6662)*, 82-86.

[402] Yuan, J.; Takahashi, A.; Masumori, N.; Uchida, K.; Hisasue, S.; Kitamura, H.; Itoh, N.; Tsukamoto, T. Ligands for peroxisome proliferator-activated receptor gamma have potent antitumor effect against human renal cell carcinoma. *Urology*, **2005**, *65(3)*, 594-599.

[403] Fauconnet, S.; Lascombe, I.; Chabannes, E.; Adessi, G.L.; Desvergne, B.; Wahli, W.; Bittard, H. Differential regulation of vascular endothelial growth factor expression by peroxisome proliferator-activated receptors in bladder cancer cells. *J Biol Chem*, **2002**, *277(26)*, 23534-23543.

[404] Haslmayer, P.; Thalhammer, T.; Jager, W.; Aust, S.; Steiner, G.; Ensinger, C.; Obrist, P. The peroxisome proliferator-activated receptor gamma ligand 15-deoxy-Delta12,14-prostaglandin J2 induces vascular endothelial growth factor in the hormone-independent prostate cancer cell line PC 3 and the urinary bladder carcinoma cell line 5637. *Int J Oncol*, **2002**, *21(4)*, 915-920.

[405] Masuda, T.; Wada, K.; Nakajima, A.; Okura, M.; Kudo, C.; Kadowaki, T.; Kogo, M.; Kamisaki, Y. Critical role of peroxisome proliferator-activated receptor gamma on anoikis and invasion of squamous cell carcinoma. *Clin Cancer Res*, **2005**, *11(11)*, 4012-4021.

[406] Schaefer, K.L.; Wada, K.; Takahashi, H.; Matsuhashi, N.; Ohnishi, S.; Wolfe, M.M.; Turner, J.R.; Nakajima, A.; Borkan, S.C.; Saubermann, L.J. Peroxisome proliferator-activated receptor gamma inhibition prevents adhesion to the extracellular matrix and induces anoikis in hepatocellular carcinoma cells. *Cancer Res*, **2005**, *65(6)*, 2251-2259.

[407] Luconi, M.; Mangoni, M.; Gelmini, S.; Poli, G.; Nesi, G.; Francalanci, M.; Pratesi, N.; Cantini, G.; Lombardi, A.; Pepi, M.; Ercolino, T.; Serio, M.; Orlando, C.; Mannelli, M. Rosiglitazone impairs proliferation of human adrenocortical cancer: preclinical study in a xenograft mouse model. *Endocr Relat Cancer*, **2010**, *17(1)*, 169-177.

[408] Bren-Mattison, Y.; Van Putten, V.; Chan, D.; Winn, R.; Geraci, M.W.; Nemenoff, R.A. Peroxisome proliferator-activated receptor-gamma (PPAR(gamma)) inhibits tumorigenesis by reversing the undifferentiated phenotype of metastatic non-small-cell lung cancer cells (NSCLC). *Oncogene*, **2005**, *24(8)*, 1412-1422.

[409] Huang, H.; Campbell, S.C.; Bedford, D.F.; Nelius, T.; Veliceasa, D.; Shroff, E.H.; Henkin, J.; Schneider, A.; Bouck, N.; Volpert, O.V. Peroxisome proliferator-activated receptor gamma ligands improve the antitumor efficacy of thrombospondin peptide ABT510. *Mol Cancer Res*, **2004**, *2(10)*, 541-550.

[410] Ohta, K.; Endo, T.; Haraguchi, K.; Hershman, J.M.; Onaya, T. Ligands for peroxisome proliferator-activated receptor gamma inhibit growth and induce apoptosis of human papillary thyroid carcinoma cells. *J Clin Endocrinol Metab*, **2001**, *86(5)*, 2170-2177.

[411] Papadaki, I.; Mylona, E.; Giannopoulou, I.; Markaki, S.; Keramopoulos, A.; Nakopoulou, L. PPARgamma expression in breast cancer: clinical value and correlation with ERbeta. *Histopathology*, **2005**, *46(1)*, 37-42.

[412] Jiang, W.G.; Douglas-Jones, A.; Mansel, R.E. Expression of peroxisome-proliferator activated receptor-gamma (PPARgamma) and the PPARgamma co-activator, PGC-1, in human breast cancer correlates with clinical outcomes. *Int J Cancer*, **2003**, *106(5)*, 752-757.

[413] Oyama, T.; Toyota, K.; Waku, T.; Hirakawa, Y.; Nagasawa, N.; Kasuga, J.I.; Hashimoto, Y.; Miyachi, H.; Morikawa, K. Adaptability and selectivity of human peroxisome proliferator-activated receptor (PPAR) pan agonists revealed from crystal structures. *Acta crystallographica. Section D, Biological crystallography*, **2009**, *65(Pt 8)*, 786-795.

[414] Pettersson, I.; Ebdrup, S.; Havranek, M.; Pihera, P.; Korinek, M.; Mogensen, J.P.; Jeppesen, C.B.; Johansson, E.; Sauerberg, P. Design of a partial PPARdelta agonist. *Bioorganic & medicinal chemistry letters*, **2007**, *17(16)*, 4625-4629.

[415] Lin, C.H.; Peng, Y.H.; Coumar, M.S.; Chittimalla, S.K.; Liao, C.C.; Lyn, P.C.; Huang, C.C.; Lien, T.W.; Lin, W.H.; Hsu, J.T.; Cheng, J.H.; Chen, X.; Wu, J.S.; Chao, Y.S.; Lee, H.J.; Juo, C.G.; Wu, S.Y.; Hsieh, H.P. Design and structural analysis of novel pharmacophores for potent and selective peroxisome proliferator-activated receptor gamma agonists. *Journal of medicinal chemistry*, **2009**, *52(8)*, 2618-2622.

[416] Ye, J.M.; Doyle, P.J.; Iglesias, M.A.; Watson, D.G.; Cooney, G.J.; Kraegen, E.W. Peroxisome proliferator-activated receptor (PPAR)-alpha activation lowers muscle lipids and improves insulin sensitivity in high fat-fed rats: comparison with PPAR-gamma activation. *Diabetes*, **2001**, *50(2)*, 411-417.

[417] Chou, C.J.; Haluzik, M.; Gregory, C.; Dietz, K.R.; Vinson, C.; Gavrilova, O.; Reitman, M.L. WY14,643, a peroxisome proliferator-activated receptor alpha (PPARalpha) agonist, improves hepatic and muscle steatosis and reverses insulin resistance in lipoatrophic A-ZIP/F-1 mice. *J Biol Chem*, **2002**, *277(27)*, 24484-24489.

[418] Kubota, N.; Terauchi, Y.; Miki, H.; Tamemoto, H.; Yamauchi, T.; Komeda, K.; Satoh, S.; Nakano, R.; Ishii, C.; Sugiyama, T.; Eto, K.; Tsubamoto, Y.; Okuno, A.; Murakami, K.; Sekihara, H.; Hasegawa, G.; Naito, M.; Toyoshima, Y.; Tanaka, S.; Shiota, K.; Kitamura, T.; Fujita, T.; Ezaki, O.; Aizawa, S.; Kadowaki, T.; et al. PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. *Mol Cell*, **1999**, *4(4)*, 597-609.

[419] Medina-Gomez, G.; Gray, S.L.; Yetukuri, L.; Shimomura, K.; Virtue, S.; Campbell, M.; Curtis, R.K.; Jimenez-Linan, M.; Blount, M.; Yeo, G.S.; Lopez, M.; Seppanen-Laakso, T.; Ashcroft, F.M.; Oresic, M.; Vidal-Puig, A. PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism. *PLoS Genet*, **2007**, *3(4)*, e64.

[420] Matsusue, K.; Haluzik, M.; Lambert, G.; Yim, S.H.; Gavrilova, O.; Ward, J.M.; Brewer, B., Jr.; Reitman, M.L.; Gonzalez, F.J. Liver-specific disruption of PPARgamma in leptin-deficient mice improves fatty liver but aggravates diabetic phenotypes. *J Clin Invest*, **2003**, *111(5)*, 737-747.

[421] Gavrilova, O.; Haluzik, M.; Matsusue, K.; Cutson, J.J.; Johnson, L.; Dietz, K.R.; Nicol, C.J.; Vinson, C.; Gonzalez, F.J.; Reitman, M.L. Liver peroxisome proliferator-activated receptor γ contributes to hepatic steatosis, triglyceride clearance, and regulation of body fat mass. *J. Biol. Chem.*, **2003**, *278(36)*, 34268-34276.

[422] Kleemann, R.; Verschuren, L.; de Rooij, B.J.; Lindeman, J.; de Maat, M.M.; Szalai, A.J.; Princen, H.M.; Kooistra, T. Evidence for anti-inflammatory activity of statins and PPARalpha activators in human C-reactive protein transgenic mice in vivo and in cultured human hepatocytes in vitro. *Blood*, **2004**, *103(11)*, 4188-4194.

[423] Xu, J.; Storer, P.D.; Chavis, J.A.; Racke, M.K.; Drew, P.D. Agonists for the peroxisome proliferator-activated receptor-alpha and the retinoid X receptor inhibit inflammatory responses of microglia. *J Neurosci Res*, **2005**, *81(3)*, 403-411.

[424] Staels, B.; Koenig, W.; Habib, A.; Merval, R.; Lebret, M.; Torra, I.P.; Delerive, P.; Fadel, A.; Chinetti, G.; Fruchart, J.C.; Najib, J.; Maclouf, J.; Tedgui, A. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. *Nature*, **1998**, *393(6687)*, 790-793.

[425] Letavernier, E.; Perez, J.; Joye, E.; Bellocq, A.; Fouqueray, B.; Haymann, J.P.; Heudes, D.; Wahli, W.; Desvergne, B.; Baud, L. Peroxisome proliferator-activated receptor beta/delta exerts a strong protection from ischemic acute renal failure. *J Am Soc Nephrol*, **2005**, *16(8)*, 2395-2402.

[426] Ding, G.; Cheng, L.; Qin, Q.; Frontin, S.; Yang, Q. PPARdelta modulates lipopolysaccharide-induced TNFalpha inflammation signaling in cultured cardiomyocytes. *J Mol Cell Cardiol*, **2006**, *40(6)*, 821-828.

[427] Niino, M.; Iwabuchi, K.; Kikuchi, S.; Ato, M.; Morohashi, T.; Ogata, A.; Tashiro, K.; Onoe, K. Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by an agonist of peroxisome proliferator-activated receptor-gamma. *J Neuroimmunol*, **2001**, *116(1)*, 40-48.

[428] Kobayashi, T.; Notoya, K.; Naito, T.; Unno, S.; Nakamura, A.; Martel-Pelletier, J.; Pelletier, J.P. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, reduces the progression of experimental osteoarthritis in guinea pigs. *Arthritis Rheum*, **2005**, *52(2)*, 479-487.

[429] Boileau, C.; Martel-Pelletier, J.; Fahmi, H.; Mineau, F.; Boily, M.; Pelletier, J.P. The peroxisome proliferator-activated receptor gamma agonist pioglitazone reduces the development of cartilage lesions in an experimental dog model of osteoarthritis: in vivo protective effects mediated through the inhibition of key signaling and catabolic pathways. *Arthritis Rheum*, **2007**, *56(7)*, 2288-2298.

[430] Kume, S.; Uzu, T.; Araki, S.; Sugimoto, T.; Isshiki, K.; Chin-Kanasaki, M.; Sakaguchi, M.; Kubota, N.; Terauchi, Y.; Kadowaki, T.; Haneda, M.; Kashiwagi, A.; Koya, D. Role of altered renal lipid metabolism in the development of renal injury induced by a high-fat diet. *J Am Soc Nephrol*, **2007**, *18(10)*, 2715-2723.

[431] Raikwar, H.P.; Muthian, G.; Rajasingh, J.; Johnson, C.; Bright, J.J. PPARgamma antagonists exacerbate neural antigen-specific Th1 response and experimental allergic encephalomyelitis. *J Neuroimmunol*, **2005**, *167(1-2)*, 99-107.

[432] Dewald, O.; Sharma, S.; Adrogue, J.; Salazar, R.; Duerr, G.D.; Crapo, J.D.; Entman, M.L.; Taegtmeyer, H. Downregulation of peroxisome proliferator-activated receptor-alpha gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity. *Circulation*, **2005**, *112(3)*, 407-415.

[433] Xu, Y.; Lu, L.; Greyson, C.; Rizeq, M.; Nunley, K.; Wyatt, B.; Bristow, M.R.; Long, C.S.; Schwartz, G.G. The PPAR-alpha activator fenofibrate fails to provide myocardial protection in ischemia and reperfusion in pigs. *Am J Physiol Heart Circ Physiol*, **2006**, *290(5)*, H1798-1807.

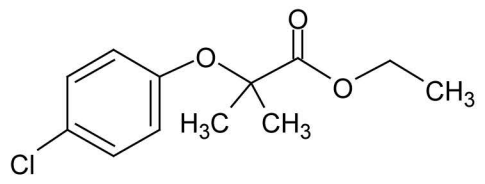
[434] Xu, Y.; Lu, L.; Greyson, C.; Lee, J.; Gen, M.; Kinugawa, K.; Long, C.S.; Schwartz, G.G. Deleterious effects of acute treatment with a peroxisome proliferator-activated receptor-gamma activator in myocardial ischemia and reperfusion in pigs. *Diabetes*, **2003**, *52(5)*, 1187-1194.

[435] Hu, Q.; Zhang, X.J.; Zhang, C.; Zhao, Y.X.; He, H.; Liu, C.X.; Feng, J.B.; Jiang, H.; Yang, F.L.; Zhang, C.X.; Zhang, Y. Peroxisome proliferator-activated receptor-gamma1 gene therapy attenuates atherosclerosis and stabilizes plaques in apolipoprotein E-deficient mice. *Hum Gene Ther*, **2008**, *19(3)*, 287-299.

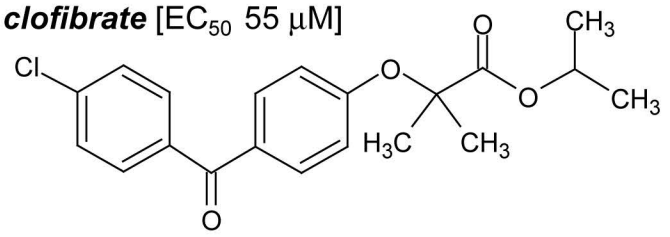
[436] Read, W.L.; Baggstrom, M.Q.; Fracasso, P.M.; Govindan, R. A phase I study of bexarotene and rosiglitazone in patients with refractory cancers. *Chemotherapy*, **2008**, *54(3)*, 236-241.

A

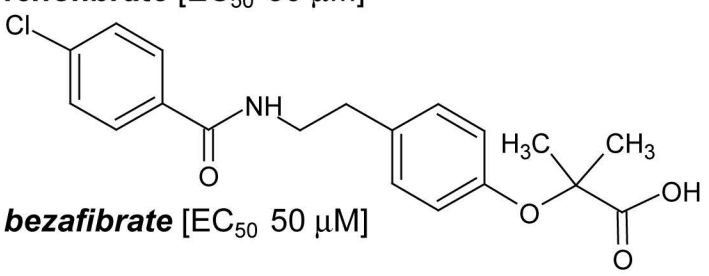
PPARα agonists



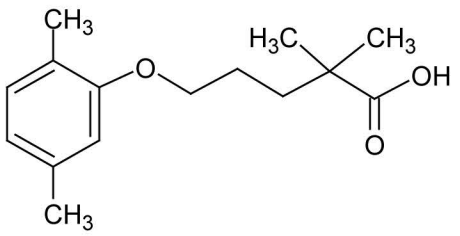
clofibrate [EC_{50} 55 μM]



fenofibrate [EC_{50} 30 μM]

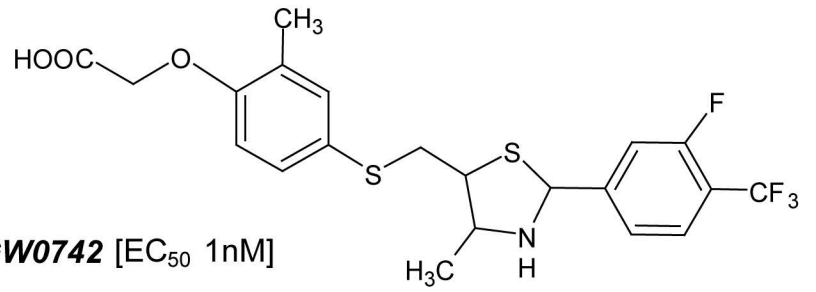


bezafibrate [EC_{50} 50 μM]



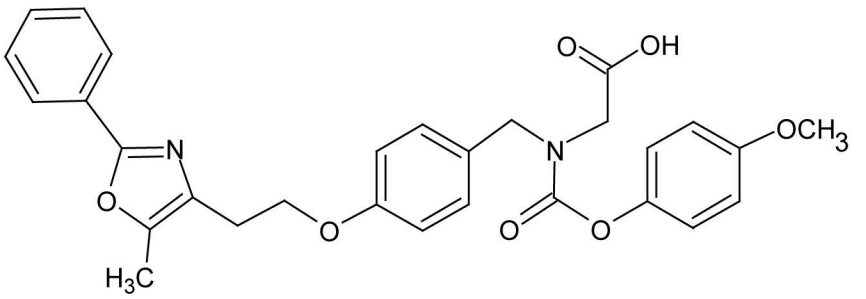
gemfibrozil [EC_{50} 190 μM]

PPARβ/δ agonist

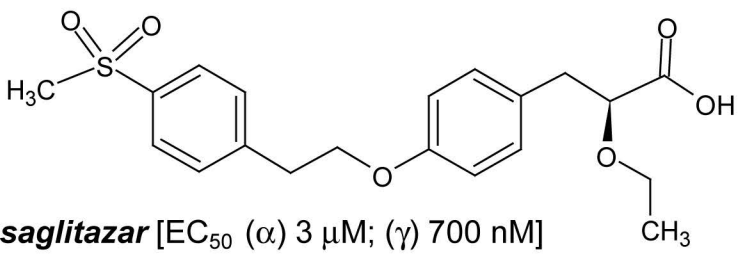


GW0742 [EC_{50} 1nM]

PPARα/PPARγ dual agonists

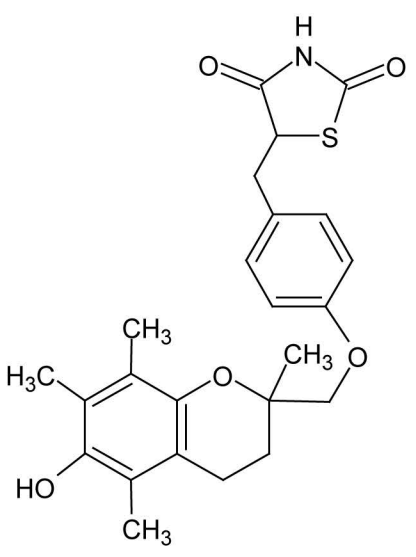


muraglitazar [EC_{50} (α) 4 μM; (γ) 150 nM]

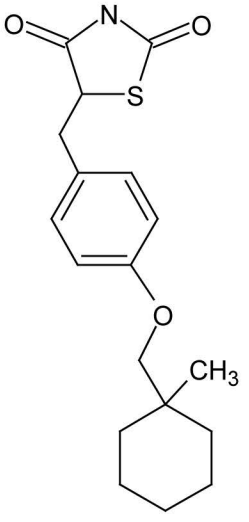


tesaglitazar [EC_{50} (α) 3 μM; (γ) 700 nM]

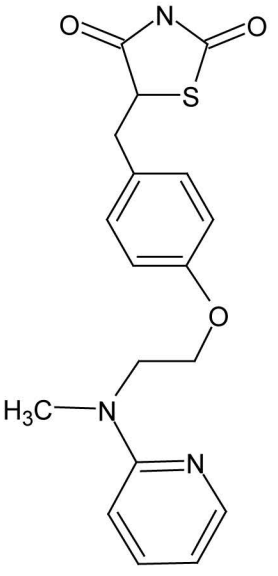
PPARγ agonists



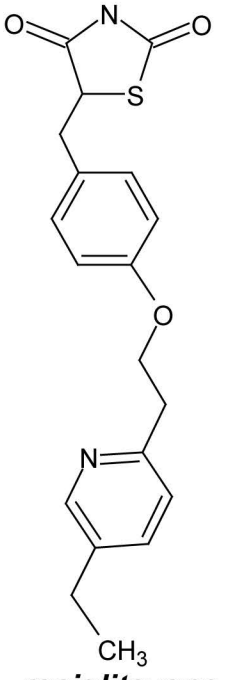
troglitazone
[EC_{50} 550 nM]



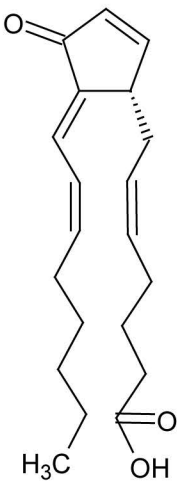
ciglitazone
[EC_{50} 3 μM]



pioglitazone
[EC_{50} 580 nM]



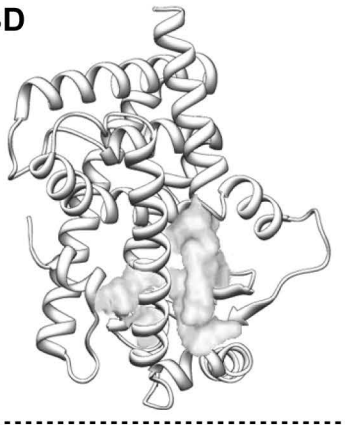
rosiglitazone
[EC_{50} 43 nM]



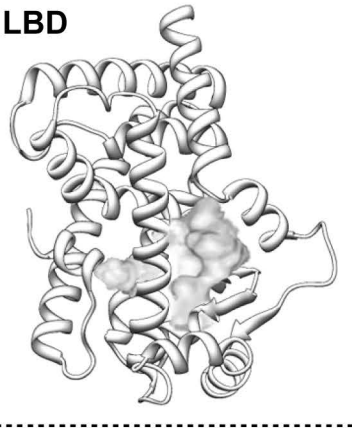
15d-PGJ2
[EC_{50} 2 μM]

B

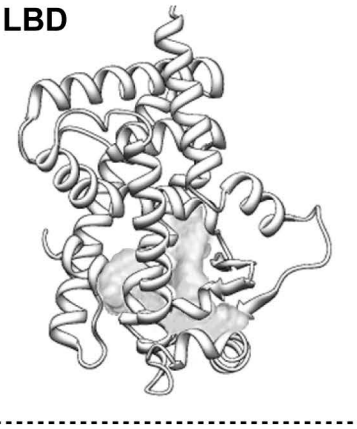
PPARα LBD



PPARβ/δ LBD



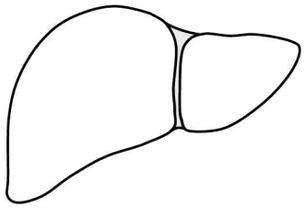
PPARγ LBD



cardiovascular system

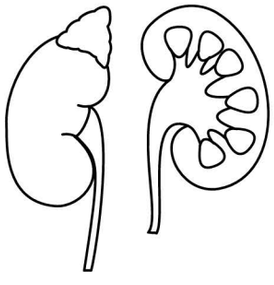
- PPARs are expressed in the heart, vascular smooth muscle cells, endothelial cells and the renin-angiotensin-aldosterone system
- PPARs have anti-atherogenic benefits
- PPARs control cardiac lipid and glucose metabolism
- PPARγ and PPARα reduce hypertension

liver



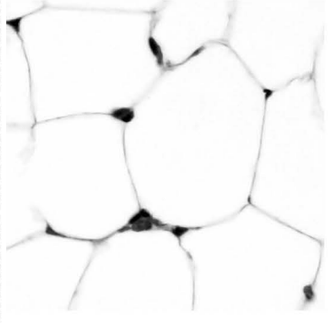
- PPARs are expressed in the liver
- PPARγ increases glycogen storage and lipogenesis
- PPARα increases gluconeogenesis and fatty acid utilization
- PPARβ/δ maintains anti-inflammatory phenotype of Kupffer cells
- TZDs improve liver insulin sensitivity, thus attenuating T2DM

kidney



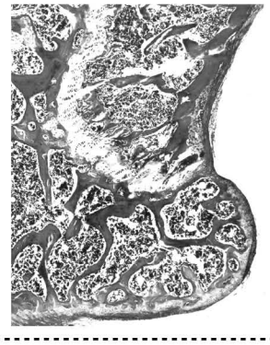
- PPARs are expressed in the kidney
- PPARs affect renal lipid and glucose metabolism
- PPARγ ligands have renoprotective effects by reducing renal inflammation and atherosclerosis
- PPARγ affects the renin-angiotensin-aldosterone system
- TZDs increase water resorbtion from the distal tubules

adipose tissue



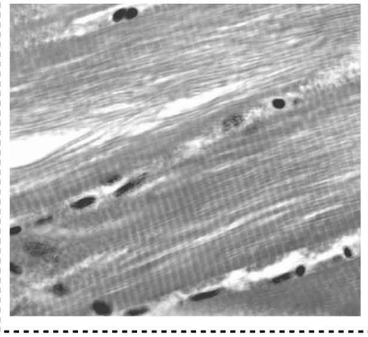
- PPARγ is required for adipocyte differentiation and adipose tissue stem cell dynamics
- PPARγ regulates genes related to lipogenesis, lipid storage, cholesterol and lipoprotein transport
- TZDs improve adipocyte insulin sensitivity and increase lipid deposition
- adipose tissue PPARγ level shows circadian oscillation

bone and cartilage



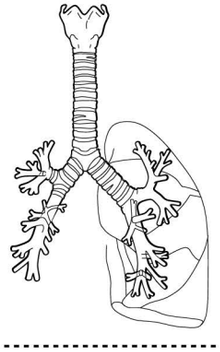
- anti-inflammatory actions of PPARγ alleviate osteoarthritis, having a chondroprotective effect
- osteoblast differentiation and survival are impaired by PPARγ activation
- PPARγ increases osteoclast activity
- TZDs increase bone adiposity and reduce bone mineral content

skeletal muscle



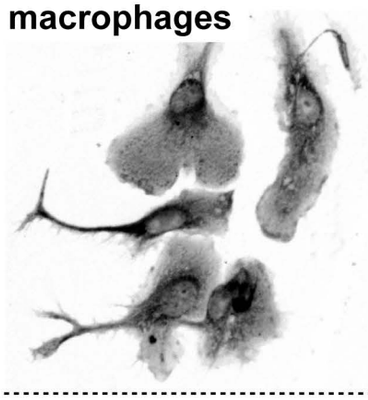
- PPARγ increases glucose uptake by the skeletal muscle and promotes glucose utilization; thus TZDs normalize glycemic control in T2DM
- PPARβ/δ improves glucose disposal to muscle
- PPARα enhances fatty acid oxidation

mucosal barriers and skin



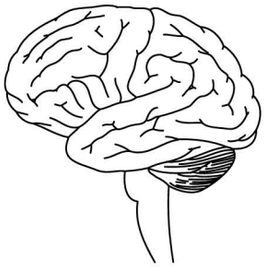
- PPARγ reduces chronic inflammation of the intestinal mucosa (in inflammatory bowel disease) and the skin (in psoriasis)
- PPARβ/δ increases T-cell activation and inflammation
- PPARγ is required for proper mucus production
- in cystic fibrosis PPARγ activation may reduce mucus obstruction and inflammation

macrophages



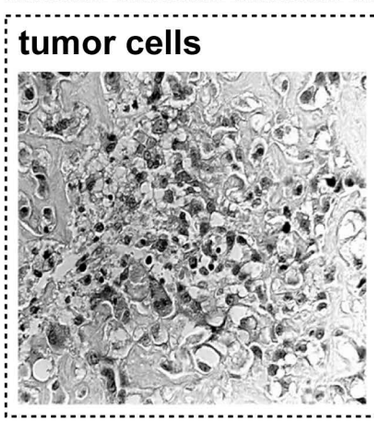
- inflammatory gene expression is controlled by PPARs
- PPARs promote anti-inflammatory macrophage phenotype
- PPARγ and PPAβ/δ are required for engulfment of apoptotic cells
- uptake of apoptotic cell debris mitigates inflammation in a PPAR-dependent manner
- PPARs control lipid handling

nervous system



- PPARs reduce oxidative damage and attenuate ischemic brain injury
- PPARs reduce glial activation and inflammation and protect against neuronal apoptosis in neurodegenerative diseases, such as Alzheimer disease, Parkinson disease and multiple sclerosis
- PPARγ activation may also reduce inflammatory hyperalgesia

tumor cells



- PPAR agonists arrest tumor growth through induction of apoptosis and/or cell-cycle arrest
- PPARα and PPARγ suppress tumor expansion through inhibition of angiogenesis
- PPARα and PPARγ prevent the development of inflammation-associated colorectal cancer