

Distinct but complementary contributions of PPAR isotypes to energy homeostasis

Vanessa Dubois, Jérôme Eeckhoutte, Philippe Lefebvre, and Bart Staels

University of Lille, INSERM, CHU Lille, Institut Pasteur de Lille, U1011-EGID, Lille, France.

Peroxisome proliferator-activated receptors (PPARs) regulate energy metabolism and hence are therapeutic targets in metabolic diseases such as type 2 diabetes and non-alcoholic fatty liver disease. While they share anti-inflammatory activities, the PPAR isotypes distinguish themselves by differential actions on lipid and glucose homeostasis. In this Review we discuss the complementary and distinct metabolic effects of the PPAR isotypes together with the underlying cellular and molecular mechanisms, as well as the synthetic PPAR ligands that are used in the clinic or under development. We highlight the potential of new PPAR ligands with improved efficacy and safety profiles in the treatment of complex metabolic disorders.

Introduction

Metabolic syndrome (MetS) is a pathophysiologic condition characterized by increased visceral adiposity, dyslipidemia, prediabetes, and hypertension. This cluster of risk factors predisposes to type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) and increases the risk of microvascular complications and cardiovascular (CV) events. With the global increase in obesity, the prevalence of MetS has reached epidemic proportions. The pathophysiology of MetS and its comorbidities is complex and includes alterations in lipid and glucose metabolism accompanied by multi-organ inflammation; because of this complexity, current treatments address the individual components (1).

Over the last decades, the PPARs, which are members of the nuclear receptor superfamily of transcription factors (TFs), have been targeted to fight MetS and its complications. Three PPAR isotypes with different tissue distribution, ligand specificity, and metabolic regulatory activities exist in mammals: PPAR α (NR1C1), PPAR β/δ (NR1C2), and PPAR γ (NR1C3). PPARs regulate many metabolic pathways upon activation by endogenous ligands, such as fatty acids (FAs) and derivatives, or synthetic agonists, which bind to the ligand-binding domain of the receptor, triggering a conformational change. Subsequent recruitment of coactivators to the PPAR/retinoid X receptor heterodimer assembled at specific DNA response elements called PPAR response elements (PPREs) results in transactivation of target genes. In addition, PPAR activation attenuates the expression of pro-inflammatory genes, mostly through transrepressive mechanisms (2). This Review focuses on the metabolic effects of PPAR isotypes as well as synthetic PPAR ligands that are currently used in the clinic or are under development.

Endogenous PPAR ligands

PPARs are activated by FAs and their derivatives, and the level of physiologic receptor activation depends on the balance between ligand production and inactivation. Endogenous PPAR

ligands originate from three main sources: diet, de novo lipogenesis (DNL), and lipolysis, all of which are processes that integrate changes in nutritional status and circadian rhythms (3). PPARs control these metabolic processes to maintain metabolic flexibility, a prerequisite for the preservation of health.

Dietary lipids regulate PPAR activity, as evidenced by the increased target gene expression of PPAR α in liver (4) and PPAR β/δ in skeletal muscle (SKM) (5) upon high-fat diet (HFD) feeding in mice. Tissue-specific deficiency of FA synthase — a key enzyme in DNL — impairs PPAR α activity and identifies DNL as another source of PPAR ligands (6, 7). PPAR α ligands originating from DNL are not only simple FAs but include more complex molecules such as phosphatidylcholines (8). Lipolysis is a third source of endogenous PPAR activators. Angiotensin-like (ANGPTL) proteins are secreted glycoproteins that inhibit lipoprotein lipase (LPL), thereby controlling the plasma lipid pool according to lipid availability and cellular fuel demand. ANGPTL4 expression is induced in several tissues including adipose tissue, liver, and SKM by circulating FAs via PPARs, leading to inhibition of LPL and decreased plasma triglyceride-derived FA uptake, thus forming a negative feedback loop (9). Intracellular lipolysis also provides PPAR ligands. Deficiency of adipose triglyceride lipase, which lipolyzes lipid droplet triglycerides, decreases PPAR target gene expression in various tissues (10–13). Ligand availability is also modulated by FA degradation in peroxisomes, which are regulated by PPARs (14). Thus, PPAR activity relies on a careful balance between ligand production and degradation to meet fluctuating energy demands.

Contrasting metabolic effects of ligand-activated PPAR α and PPAR γ

Although they share similarities in function and mechanism of action, PPAR isotypes display important physiologic and pharmacologic differences. This section discusses the clinical and genetic evidence of contrasting PPAR α and PPAR γ effects, and sheds light on the cellular and molecular mechanisms underlying these differences.

Clinical effects of PPAR α and PPAR γ activation. Fibrates are synthetic PPAR α ligands used to treat dyslipidemia. Except for

Conflict of interest: B. Staels is an advisor for Genfit SA.

Reference information: *J Clin Invest.* 2017;127(4):1202–1214.

<https://doi.org/10.1172/JCI88894>.

the weak pan-agonist bezafibrate, all clinically used fibrates are specific activators of PPAR α . Fibrate outcome trials such as the Helsinki Heart Study (HHS) (15), Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (16), Bezafibrate Infarction Prevention (BIP) (17), Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (18), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) (19) consistently show beneficial effects on plasma lipids, particularly in normalizing the typical MetS dyslipidemia characterized by an “atherogenic lipid triad” (high LDL cholesterol [LDL-C] and triglycerides, low HDL cholesterol [HDL-C]). Fibrate therapy significantly decreases triglycerides and increases HDL-C, whereas LDL-C decreases except in patients with severe hypertriglyceridemia and low baseline LDL-C. Fibrate therapy, however, does not change circulating FA concentrations (20). Although both the FIELD and ACCORD trials showed a trend towards decreased CV risk (primary endpoint) in T2D, post-hoc and meta-analysis revealed that dyslipidemic patients (high triglyceride and low HDL-C levels) show the highest CV reduction (21, 22). Fibrates do not improve glucose homeostasis in people with T2D (18, 19, 23). However, PPAR α activation improves glucose homeostasis in prediabetic patients (24) and may prevent conversion of prediabetes to overt T2D. Fibrates exert few adverse effects. Most compounds induce mild hypercreatininemia and hyperhomocysteinemia, but these effects are pharmacodynamic markers of PPAR α activation rather than indicators of renal dysfunction (25). Hepatic carcinogenesis has been observed in rodents treated with fibrates but not in humans or non-human primates, likely due to lower peroxisome and peroxisomal β -oxidation levels in human liver (26).

Thiazolidinediones (TZDs, also referred to as glitazones), synthetic PPAR γ ligands, are anti-diabetic drugs with potent insulin-sensitizing effects that confer long-term glycemic control (27). However, their clinical use has been challenged due to side effects such as body weight gain, edema, and bone fractures (2). The increase in body weight upon TZD administration is due to PPAR γ -dependent white adipose tissue (WAT) expansion (28) and fluid retention caused by PPAR γ activation in the kidney collecting ducts (29). The increased fracture risk in TZD-treated patients results from a PPAR γ -driven rebalancing of bone remodeling in favor of net bone loss. Indeed, PPAR γ activation in bone marrow stimulates mesenchymal progenitor differentiation into the adipocyte lineage, suppressing osteoblast and hence bone formation through pathways involving protein phosphatase PP5 (30, 31). Moreover, pharmacologic, but not physiologic, PPAR γ activation promotes osteoclast formation thereby increasing bone resorption (32, 33). Rosiglitazone and pioglitazone increase plasma levels of the insulin-sensitizing adipokine adiponectin (2). They also increase HDL-C and reduce circulating FA levels (34), but have differential effects on triglyceride and LDL-C levels and CV risk. Pioglitazone, a full PPAR γ agonist with modest PPAR α -activating properties (35), lowers triglycerides, increases HDL-C, and reduces CV events in people with T2D (36) or who are insulin resistant (37). In contrast, the pure PPAR γ agonist rosiglitazone does not decrease CV risk in people with T2D but does increase both HDL-C and LDL-C (38). Hence, the beneficial effects of pioglitazone on triglycerides and CV events are likely due to combined PPAR α and PPAR γ activation. In summary, activation of PPAR α

improves the lipid profile, whereas activation of PPAR γ improves glycemic control and insulin sensitivity.

Genetic evidence of contrasting PPAR α and PPAR γ functions. The different phenotypes of patients carrying SNPs and mutations in PPAR α or PPAR γ coding sequences highlight their contrasting functions. PPAR α variants are associated with perturbations of lipid metabolism (39) and CV risk (40). PPAR α SNPs also associate with conversion from impaired glucose tolerance to T2D (41). PPAR α gene variation also influences the age of onset and progression of T2D (42). In contrast, dominant-negative mutations in the ligand-binding domain of PPAR γ result in severe insulin resistance (43). Accordingly, rare variants in PPAR γ with decreased adipogenic properties are associated with increased T2D risk (44). GWAS have also revealed an association between PPAR γ SNPs and T2D, although not all studies concur (45, 46). A recently developed functional assay identified PPAR γ variants with altered PPAR γ function (47). SNPs within DNA recognition motifs for PPAR γ or cooperating factors that alter PPAR γ recruitment to chromatin modulate the response to anti-diabetic drugs (48). Additionally, SNPs in PPAR γ DNA-binding sites are highly enriched among SNPs associated with triglyceride and HDL-C levels in GWAS (48). Taken together, these genetic data confirm the functional dichotomy between PPAR α and PPAR γ in humans, underscoring the effects of PPAR α on lipid metabolism and conversion from impaired glucose tolerance to T2D and the role of PPAR γ in T2D and the regulation of glucose homeostasis.

Cellular and molecular mechanisms underlying PPAR α and PPAR γ functions. The function of PPAR α (Figure 1) is best characterized in the liver, where it regulates genes involved in lipid and plasma lipoprotein metabolism during the nutritional transition phases (49, 50). During fasting, PPAR α increases hepatic uptake and mitochondrial transport of FA originating from adipose tissue lipolysis through transcriptional upregulation of FA transport proteins and carnitine palmitoyltransferases. PPAR α induces expression of mitochondrial acyl-CoA dehydrogenases, hence stimulating hepatic FA oxidation (FAO) and increasing acetyl-CoA production. Upon prolonged fasting, acetyl-CoA is preferentially converted into ketone bodies to provide energy for extrahepatic tissues. PPAR α also upregulates mitochondrial hydroxymethylglutaryl-CoA synthase (HMGCS), a rate-limiting ketogenesis enzyme (51, 52). Glucagon receptor signaling (53) and the IRE1 α /XBPI pathway (54) cooperate with PPAR α to control metabolic pathways during fasting. In the fed state, PPAR α coordinates DNL to supply FAs, which are stored as hepatic triglycerides and used in periods of starvation. A crucial step in DNL is the citrate-malate shuttle, which controls the efflux of acetyl-CoA from the mitochondria to the cytosol, where it serves as a precursor for FA synthesis. Citrate carrier, an essential component of this shuttle system, is a direct PPAR α target gene in hepatocytes (55). Additionally, PPAR α increases protein levels of the lipogenic factor SREBP1c by promoting proteolytic cleavage of its precursor (56), hence stimulating transcription of its target genes (57). In these postprandial conditions, mTORC1, activated through the insulin-dependent PI3K pathway, inhibits PPAR α -mediated hepatic ketogenesis (58). Thus, PPAR α contributes to the maintenance of metabolic flexibility by adapting fuel utilization to fuel availability, and its expression decreases in conditions of metabolic inflexi-

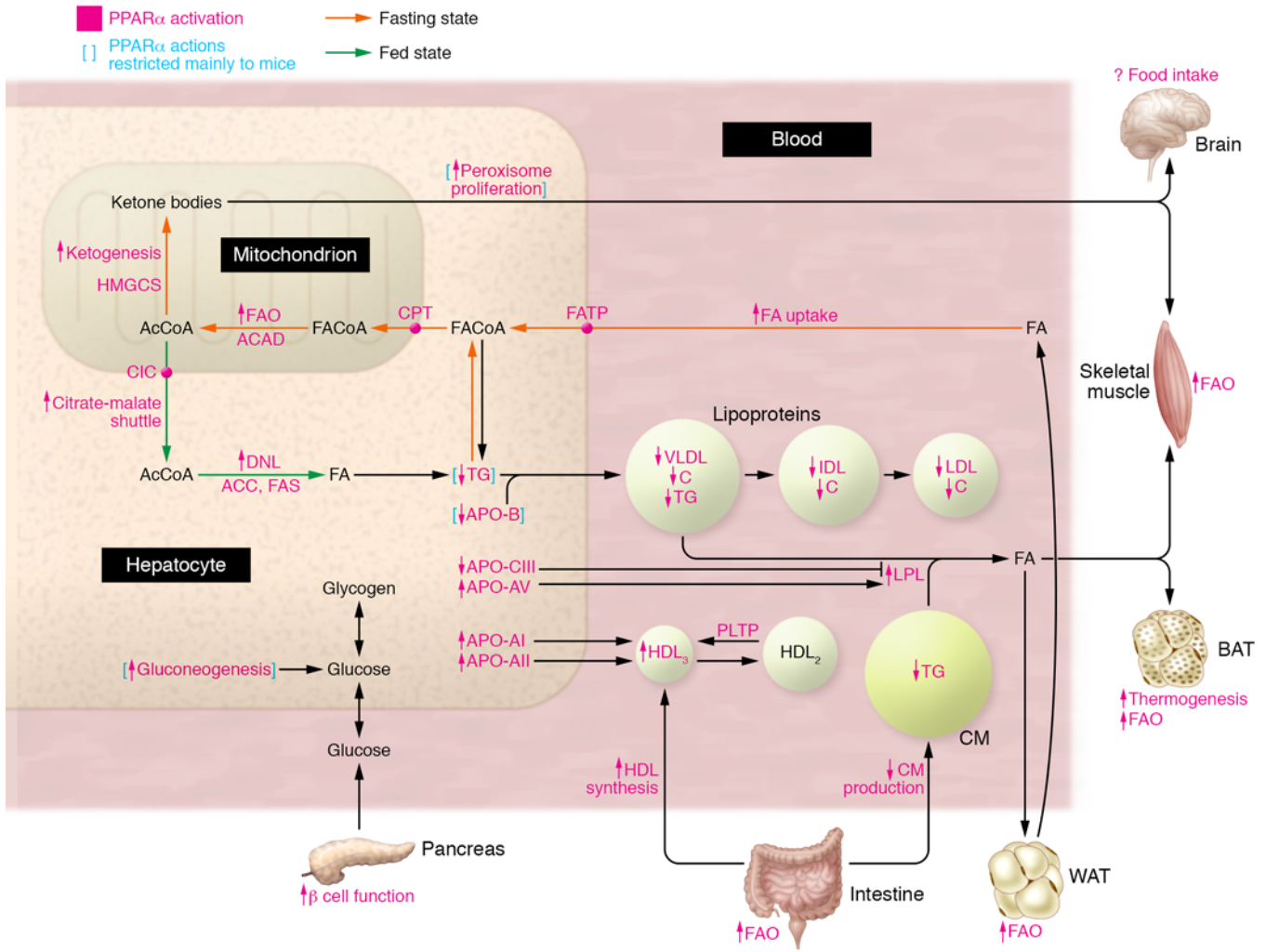


Figure 1. PPARα activation stimulates FA and triglyceride metabolism. During fasting (yellow), FAs released from WAT are taken up by the liver and transported to mitochondria, where FAO takes place, to produce acetyl-CoA (AcCoA), which can be further converted to ketone bodies and serve as fuel for peripheral tissues. In the fed state (green), acetyl-CoA is shuttled to the cytosol, where DNL takes place. The effects of PPARα activation and PPARα target genes are indicated in pink. FAO is also stimulated by PPARα in WAT and SKM. By regulating hepatic apolipoprotein synthesis, PPARα activation decreases plasma levels of triglycerides (TG) and LDL-C and increases HDL-C. PPARα also acts on BAT, gut, and pancreas, but its central effects are unclear. Blue brackets indicate PPARα actions that are mainly restricted to mice and do not occur (e.g., peroxisome proliferation, reduced liver fat content) or occur to a lesser extent (e.g., reduced APO-B production) in humans. ACAD, acyl-CoA dehydrogenase; ACC, acetyl-CoA carboxylase; CM, chylomicron; CPT, carnitine palmitoyltransferase; FAcCoA, fatty acyl-CoA; FAS, fatty acid synthase; FATP, fatty acid transport protein.

bility such as NAFLD (59). PPARα activity is also dysregulated by microRNA-10b (60), microRNA-21 (61), and JNK (62), all of which are upregulated in NAFLD.

PPARα activation reduces plasma triglyceride-rich lipoproteins by enhancing FA uptake and FAO and increasing the activity of LPL, which hydrolyzes lipoprotein triglycerides. PPARα stimulation of LPL enzyme activity is both direct, through PPRE-dependent activation of *LPL* (63), as well as indirect, through decreasing the expression of the LPL inhibitor and pro-atherogenic APO-CIII (64, 65) and increasing the expression of the LPL activator APO-AV (66). Reduced VLDL production contributes to the triglyceride-lowering effects of PPARα activation mainly in rodents and, likely to a lesser extent, in humans. Interestingly, a SNP in the *TM6SF7* gene reduces VLDL production and lowers circulating triglyceride levels while promoting hepatic steatosis

(67), an effect not observed in PPARα agonist-treated patients (68). In line with this, administration of fenofibrate to people with MetS increases the fractional catabolic rate of VLDL-APOB, intermediate-density lipoprotein-APOB (IDL-APOB), and LDL-APOB without affecting VLDL-APOB production (69). The rise in plasma HDL-C upon PPARα activation is linked to increased synthesis of major HDL-C constituents, apolipoproteins APO-AI and APO-AII (70), and induction of phospholipid transfer protein (PLTP) (71). Of note, differences between rodents and humans with respect to apolipoprotein regulation exist, as APO-AI and APO-AV are direct positive PPARα target genes in human but not murine liver (49). Through FAO, PPARα activation leads to energy dissipation not only in the liver but also in SKM (72) and WAT (73). In brown adipose tissue (BAT) PPARα stimulates lipid oxidation as well as thermogenesis in synergy with PPARγ coactiva-

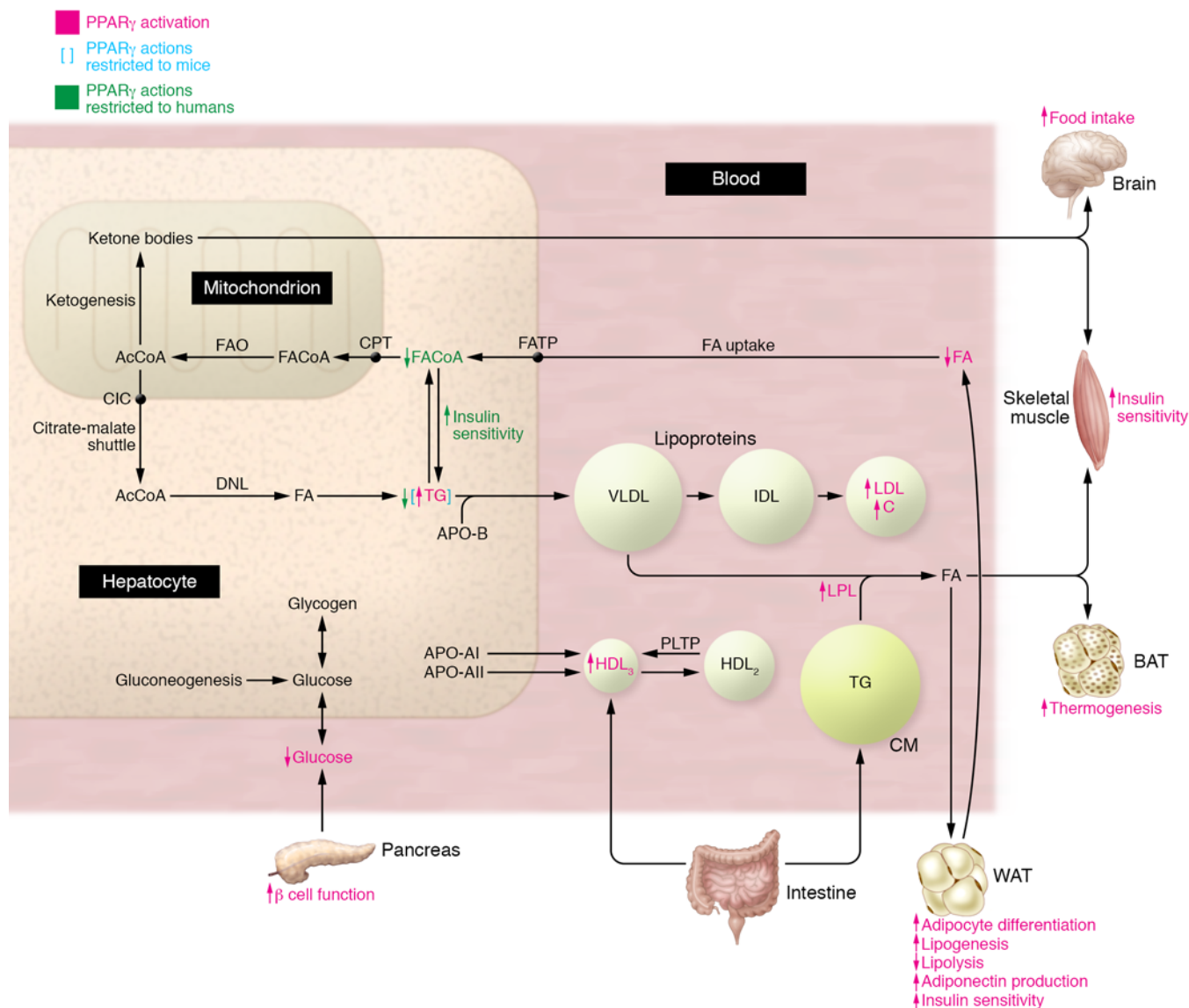


Figure 2. PPAR γ activation increases whole-body insulin sensitivity. In WAT, PPAR γ activation (effects are indicated in pink) enhances FA uptake and storage, lipogenesis, and adipogenesis (lipid steal action). PPAR γ activation lowers circulating FA levels, alleviating lipotoxicity and increasing insulin sensitivity. PPAR γ agonism induces adiponectin production by WAT, further enhancing insulin sensitivity and lowering blood glucose. PPAR γ also exerts metabolic effects on BAT, brain, and pancreas. Increased hepatic steatosis upon PPAR γ activation occurs in mice but not in humans (blue brackets), who display increased hepatic insulin sensitivity due to reduced FA flux from WAT.

tor-1 α (PGC1A) (74). While PPAR α activation reduces weight gain in rodents (73), there is no evidence of PPAR α effects on body mass in humans (18, 19).

The inability of fibrates to improve glucose homeostasis in people with T2D (18, 19) may result from several mechanisms. Glucose handling in liver and peripheral tissues is reduced as a consequence of increased FAO (75). PPAR α activation also reduces pyruvate kinase (PK) and induces PDK4 expression in the liver, decreases glycolysis, and enhances gluconeogenesis in mice (76). As discussed above, clinical and genetic data have revealed a role for PPAR α in preventing conversion from impaired glucose tolerance to overt T2D. This effect of PPAR α might stem from pancreatic β cell protection from lipotoxicity (77) and decreases in insulin clearance mediated by the biliary glycoprotein CEACAM1 (78).

PPAR γ is highly expressed in WAT, where it controls FA uptake and lipogenesis. Target genes contributing to this activity include FA binding protein-4 and the FA translocase CD36 (79). Additionally, PPAR γ is a master regulator of white adipocyte differentiation. Multiple TFs including the glucocorticoid receptor (GR) and STAT5A cooperatively induce PPAR γ during adipogenesis (28), while other TFs such as C/EBP α cooperate with PPAR γ to stimulate genomic binding and transcription of target genes (80), thereby regulating both housekeeping and adipocyte-specific functions (81). These PPAR γ -mediated changes in gene expression are preceded by chromatin remodeling involving both adipocyte-specific TFs such as C/EBP β (82) as well as ubiquitous TFs such as CCCTC-binding factor (CTCF) (83). Interestingly, promotion of adipogenesis by the mTORC1 complex occurs through stimu-

lation of PPAR γ translation (84) and transcriptional activity (85), which contrasts with the inhibitory effect of mTORC1 on PPAR α (discussed above) (58).

In contrast to WAT, PPAR γ target genes in BAT encode thermogenic proteins and inducers of mitochondrial biogenesis such as PGC1A and uncoupling protein-1 (UCP1, also known as thermogenin). PPAR γ promotes brown adipocyte differentiation, but additional TFs including PPAR α are required to switch on their thermogenic program (74).

PPAR γ enhances whole body insulin sensitivity through multiple mechanisms (Figure 2). By augmenting WAT expandability, PPAR γ shifts lipids from liver and SKM to WAT, thereby indirectly increasing glucose utilization in liver and peripheral tissues. As a result of this “lipid stealing,” lipotoxicity, which impairs insulin signaling, is alleviated. PPAR γ also regulates the expression of adipocyte hormones that modulate liver and SKM insulin sensitivity such as adiponectin and leptin (86, 87). Results of a Mendelian randomization study refuted a causal role for adiponectin in CV disease (88), which may explain why pure PPAR γ agonists, such as rosiglitazone, are not cardioprotective. Finally, PPAR γ activation improves pancreatic β cell function and survival by preventing FA-induced impairment of insulin secretion (77) and enhancing the unfolded protein response (89). Thus, whereas PPAR α activation leads to energy dissipation, activation of PPAR γ stimulates energy storage in WAT, thereby sensitizing liver and peripheral tissues to insulin.

The contrasting mechanisms of action of PPAR α and PPAR γ are also illustrated by their opposite function on hepatic lipid metabolism. Reduced hepatic steatosis due to increased FAO in hepatocytes occurs upon PPAR α activation in rodent models of NAFLD (90, 91), while PPAR γ activation in rodents (but not humans) increases liver fat accumulation by enhancing hepatic expression of PPAR γ -dependent genes involved in lipogenesis (79, 92). Interestingly, hepatic PPAR γ expression levels determine liver steatosis: mice with low hepatic PPAR γ expression are resistant to diet-induced development of fatty liver when treated with rosiglitazone, whereas liver steatosis is exacerbated in obese mice expressing high hepatic levels of PPAR γ (93). In mice, PPAR γ expression in liver is regulated by the dimeric AP-1 protein complex, thereby controlling hepatic steatosis (94). However, in humans with NAFLD, PPAR γ expression is unaltered (59) and TZD treatment decreases hepatic steatosis, likely due to decreased FA flux from WAT to liver (95, 96).

Energy homeostasis is also regulated by inter-organ communications involving the brain and the gut. Neuronal PPAR γ deletion in mice diminishes food intake and energy expenditure, thus reducing weight gain upon HFD feeding, suggesting that brain PPAR γ exerts hyperphagic effects and promotes obesity (97). Similarly, central PPAR α activation may also increase food intake (6), although not all studies concur (98). In the intestine, PPAR α activation suppresses postprandial hyperlipidemia by enhancing intestinal epithelial cell FAO (99). Furthermore, intestinal PPAR α activation reduces cholesterol esterification, suppresses chylomicron production, and increases HDL synthesis by enterocytes (100).

Molecular basis for differential activities of PPAR α and PPAR γ . The exact mechanisms through which the different PPAR isotypes — which share similar DNA-binding motifs — bind and regulate

different genes remain to be established. Several explanations and hypotheses have been put forward. First, PPAR α is predominantly expressed in the liver, whereas PPAR γ expression is highest in WAT (2). The different PPARs emerged during evolution from gene duplications, but subsequent sequence variations of their promoters and 3'-UTRs have contributed to acquisition of differential expression patterns and functions (101). Tissue-specific chromatin and TF environments also play a role by restricting PPAR recruitment to selective enhancers and therefore specifying PPAR target genes (28). This is illustrated by the tissue-specific PPAR γ cisomes in white adipocytes and macrophages, both of which express high PPAR γ levels. The macrophage-specific PPAR γ cisome is defined by the pioneer TF PU.1 (102), which induces nucleosome remodeling and histone modifications, promoting the recruitment of additional TFs (103). In white adipocytes, however, these macrophage-specific binding regions are marked with repressive histone modifications, thus disabling PPAR γ binding (104). Furthermore, PPAR γ cisomes differ between white adipocyte depots (epididymal vs. inguinal) in association with depot-specific gene expression patterns (105).

Nutritional status also contributes to differential PPAR regulation. PPAR α is a metabolic sensor, switching its activity from coordination of lipogenesis in the fed state to promotion of FA uptake and FAO during a fasting state (49). PPAR α activation during fasting involves PGC1 α coactivator induction by the fasting-induced TF EB (106). In addition to PPAR α itself (107), circadian transcription of genes encoding acyl-CoA thioesterases coordinates cyclic intracellular production of FA ligands (108). The TF CREBH, a circadian regulator of hepatic lipid metabolism, rhythmically interacts with PPAR α and regulates its activity (109). Adjustment of PPAR α transcriptional activity to nutritional status is also controlled by kinases phosphorylating PPAR α or its coregulators. In the fed state, PPAR α activity is enhanced through insulin-activated MAPK and glucose-activated PKC, while glucagon-activated PKA and AMPK increase PPAR α signaling in fasting (49). Moreover, the fasting response is co-controlled by PPAR α and GR α , which show extensive chromatin colocalization and interact to induce lipid metabolism genes upon prolonged fasting through genomic AMPK recruitment (110). Conversely, GR β antagonizes glucocorticoid signaling during fasting via inhibition of GR α and PPAR α , thus increasing inflammation and hepatic lipid accumulation (111).

PPAR γ activity is higher in the fed state, in line with its role in lipid synthesis and storage. PPAR γ activity in WAT is repressed during fasting via mechanisms involving SIRT1 (112) or AMPK (113). In mice, the amplitude of hepatic circadian clock gene expression is reduced by HFD feeding (114), whereas circadian rhythmicity of PPAR γ and genes containing the PPAR γ binding site is induced (115). Thus, the HFD-induced transcriptional reprogramming relies at least in part on changes in expression, oscillation pattern, and chromatin recruitment of PPAR γ . Gut microbiota, which also exhibit circadian activity (116), are drivers of HFD-induced hepatic transcriptional reprogramming by PPAR γ in mice (117). Nutritional status also links PPARs to FGF21 signaling, as fasting increases PPAR α -dependent FGF21 expression in liver, further enhancing FAO and ketogenesis (118). In WAT, PPAR γ induces FGF21 expression (119), where it acts as an autocrine factor in the fed state, regulating PPAR γ activity through

a feedforward mechanism (120). In the pancreas, PPAR γ agonism reverses high glucose-induced islet dysfunction by enhancing FGF21 signaling (121). FGF1 is also induced by PPAR γ in WAT, and the PPAR γ /FGF1 axis is critical for maintaining metabolic homeostasis and insulin sensitization (122).

Combating inflammation: a shared function of PPAR α and PPAR γ

MetS is accompanied by a low-grade inflammatory state in different metabolic tissues — termed meta-inflammation — characterized by increased secretion of pro-inflammatory chemokines and cytokines, many of which (including TNF- α , IL-1, and IL-6) influence lipid metabolism and insulin resistance (123). Besides differentially regulating lipid and glucose metabolism, PPAR α and PPAR γ also counter inflammation. However, the anti-inflammatory effects of PPAR α and PPAR γ activation are likely distinct due to differences in tissue and cell type expression.

In WAT, fenofibrate and rosiglitazone reduce the expression of several pro-inflammatory mediators, including IL-6 and the chemokines CXCL10 and MCP1 (124). PPAR γ also inhibits pro-inflammatory cytokine production by WAT-resident macrophages and modulates macrophage polarization (125). Although innate immune cells such as macrophages were initially thought to be the main drivers of WAT inflammation and metabolic dysregulation, important roles of the adaptive immune system, including WAT Tregs, have recently emerged (126). PPAR γ acts as a molecular orchestrator of WAT Treg accumulation, phenotype, and function (127, 128). Indeed, the WAT Treg transcriptome alterations in obese mice depend on PPAR γ phosphorylation by cyclin-dependent kinase 5 (CDK5) (127). In addition, PPAR γ expression in WAT Tregs is necessary for complete restoration of insulin sensitivity in obese mice upon pioglitazone treatment (128). On the other hand, activation of CD4⁺ T cells is accompanied by mTORC1-dependent PPAR γ induction and enhanced expression of FA uptake genes, enabling rapid T cell proliferation and optimal immune responses (129). PPAR α and PPAR γ also modulate the inflammatory response in liver and vascular wall (130, 131).

Inhibition of pro-inflammatory gene expression is the main process underlying the anti-inflammatory properties of PPAR α and PPAR γ . Several mechanisms have been proposed for transcriptional repression by PPARs that are not mutually exclusive. These include direct physical interaction of PPAR α or PPAR γ with several pro-inflammatory TFs including AP-1 and NF- κ B (132, 133). Repression of inflammation independently of direct PPAR α DNA binding results in anti-inflammatory and anti-fibrotic effects in a mouse model of non-alcoholic steatohepatitis (NASH) (134). In addition to this PPRE-independent transrepression mechanism, interaction between NF- κ B and PPRE-bound PPAR α also occurs, leading to repression of TNF- α -mediated upregulation of complement C3 gene expression and protein secretion during acute inflammation (135). Moreover, simultaneous activation of PPAR α and GR α increases the repression of NF- κ B-driven genes, thereby decreasing cytokine production (136). Transcriptional repression of pro-inflammatory genes by PPAR γ may include ligand-activated PPAR γ sumoylation, which targets the receptor to corepressor complexes assembled at inflammatory gene promoters. This prevents promoter recruitment of the proteasome machinery that

normally mediates the inflammatory signal-dependent removal of corepressor complexes required for gene activation. As a result, these complexes are not cleared from the promoters and inflammatory genes are maintained in a repressed state (137). In addition to downregulating the expression of pro-inflammatory genes, PPAR α (138) and PPAR γ (139) also suppress inflammation by upregulating genes with anti-inflammatory properties, such as IL-1Ra, suggesting a possible cooperation between PPAR-dependent transactivation and transrepression to counter inflammation.

The anti-inflammatory properties of PPAR α likely contribute to the improved lobular inflammation and hepatocellular ballooning observed in NAFLD patients treated with pioglitazone (140) or elafibranor (141), a dual PPAR α / β / δ agonist. Pioglitazone reduces hepatic steatosis in NAFLD patients (140), likely due to PPAR γ activation. The pure PPAR γ agonist rosiglitazone also lowers liver fat in humans (96), whereas the pure PPAR α agonist fenofibrate does not (68). Administration of fenofibrate to people with dyslipidemia lowers plasma levels of atypical deoxysphingolipids (142), which increase upon the transition from simple steatosis to NASH (143). Thus, activation of both PPAR α and PPAR γ appears to be beneficial in human NAFLD, although the underlying mechanisms clearly differ. Whereas the effects of PPAR α agonism on inflammation and ballooning are due to direct PPAR α activation in the liver, the effects of PPAR γ on hepatic steatosis are likely mediated by indirect mechanisms such as suppression of FA flux to the liver; this is in line with the low expression and absence of PPAR γ induction in human fatty liver (59).

PPAR β / δ , the clinically enigmatic third PPAR

Selective synthetic PPAR β / δ agonists are not yet clinically available; however, beneficial effects of PPAR β / δ activation on various MetS components have been reported and include both differences and similarities to PPAR α and PPAR γ , such as reduced inflammation (144–146).

PPAR β / δ variants are associated with cholesterol metabolism (147), insulin sensitivity (148), T2D risk (149), and CV risk (40). In obese men, administration of the synthetic PPAR β / δ agonist GW501516 lowers liver fat content and plasma levels of insulin, FAs, triglycerides, and LDL-C (150). These beneficial effects on plasma lipids are also observed in overweight patients treated with seladelpar (MBX-8025), a novel PPAR β / δ agonist (151). Thus, PPAR β / δ agonism combines the metabolic effects of PPAR α and PPAR γ activation on lipid metabolism and glucose homeostasis, respectively. Preclinical studies support this conclusion, as the administration of GW501516 to overweight monkeys (152) or obese rats (153) lowered serum LDL-C and raised HDL-C while improving insulin sensitivity.

PPAR β / δ activation protects from diet-induced or genetically induced obesity in mice by increasing energy expenditure (154). In BAT, activation of PPAR β / δ induces the expression of thermogenic genes, including UCP1, and FAO genes (154). PPAR β / δ agonism also promotes FAO in SKM (155), WAT (156), and liver (157). PPAR β / δ in brain controls energy expenditure, as neuron-specific PPAR β / δ deletion increases susceptibility to diet-induced obesity (158). Thus, similar to PPAR α , PPAR β / δ activation induces energy dissipation. Interestingly, both isotypes crosstalk in liver, where PPAR β / δ stimulates the production of the PPAR α

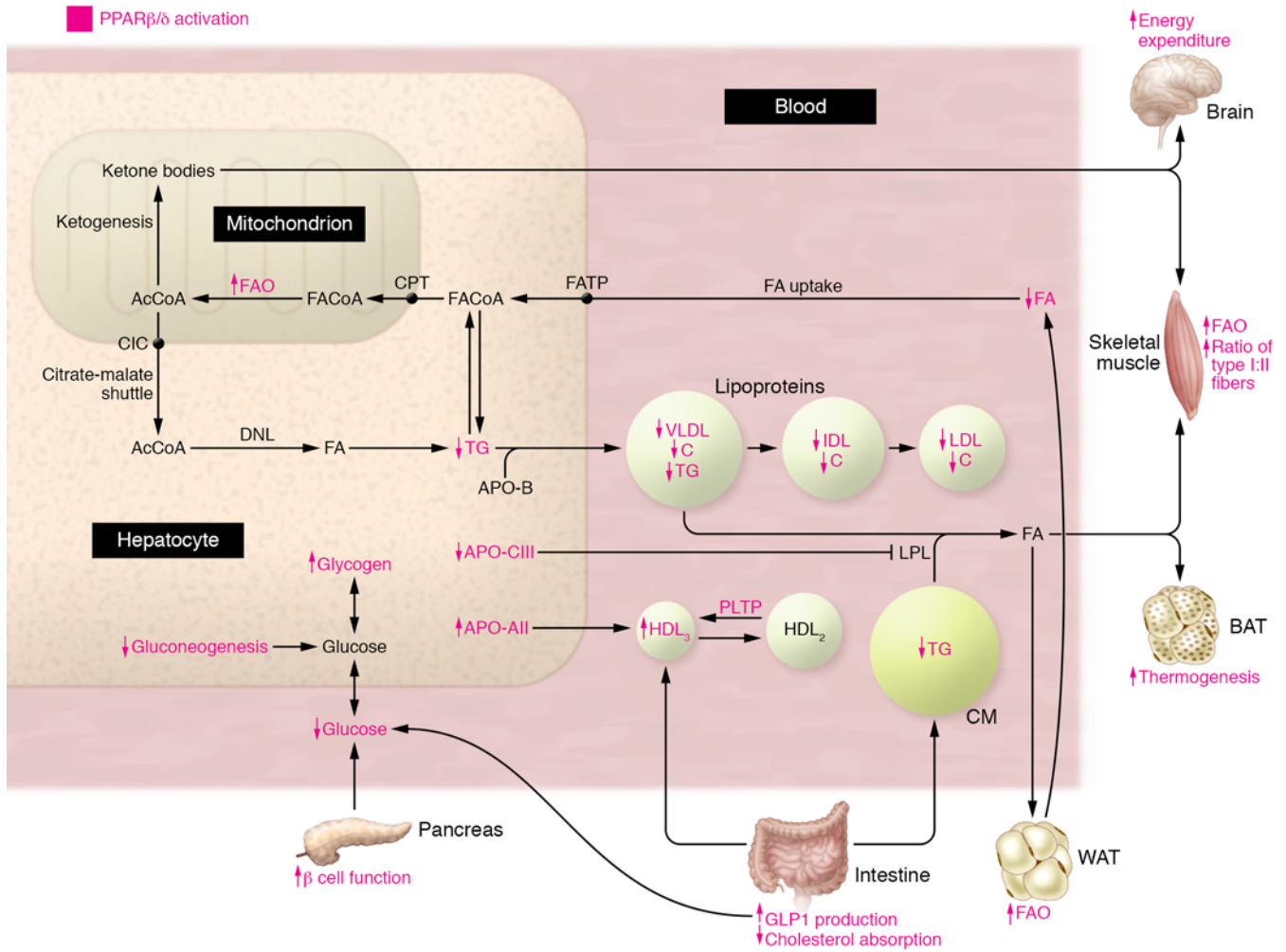


Figure 3. PPARβ/δ activation enhances glucose and lipid homeostasis. In SKM, PPARβ/δ activation (effects are indicated in pink) favors fiber type switching toward type I oxidative fibers, which have a higher glucose-handling capacity compared with type II fibers. PPARβ/δ also augments FAO in SKM, liver, and WAT and enhances hepatic glucose metabolism and pancreatic β cell function. PPARβ/δ activation decreases FAs, triglycerides, and LDL-C and increases HDL-C levels in blood. Metabolic effects of PPARβ/δ agonism also take place in brain and gut.

ligand 16:0/18:0-phosphatidylcholine as well as PPARα expression and DNA-binding activity, thereby increasing hepatic FAO (159). Enhanced FAO upon PPARβ/δ activation contributes to its plasma lipid-lowering effects, together with decreased cholesterol absorption (160) and increased trans-intestinal cholesterol efflux (161). PPARβ/δ also raises HDL-C by increasing hepatic APO-AII (162) and PLTP (163) expression.

PPARβ/δ agonism improves insulin sensitivity through several mechanisms (Figure 3). In SKM, PPARβ/δ activation favors fiber type switching, from type II fast-twitch glycolytic to type I slow-twitch oxidative fibers (164), via mechanisms involving PGC1α (165) and an estrogen-related receptor γ/microRNA regulatory circuit (166), thereby improving glucose handling (167). The type I fiber fraction is reduced in people with T2D (168), which may contribute to altered glucose homeostasis. Mice with myocyte-selective PPARβ/δ deficiency exhibit decreased type I fiber count, which precedes the development of a diabetic phenotype (165). PPARβ/δ also improves glucose handling and insulin sensitivity in the liver. GW501516 treatment suppresses hepatic glucose output

and enhances glucose disposal by increasing glucose flux through the pentose phosphate pathway (169). Liver-restricted PPARβ/δ overexpression reduces fasting glucose levels and stimulates hepatic glycogen production via upregulation of glucose utilization pathways (170). Additionally, stress-induced JNK signaling is reduced, contributing to improved hepatic insulin sensitivity (170). PPARβ/δ agonism promotes pancreatic β cell mitochondrial function and ATP production, thereby improving glucose-stimulated insulin secretion (171). Furthermore, PPARβ/δ increases intestinal production of the incretin glucagon-like peptide 1 (GLP1) (172).

In summary, the mechanisms underlying the metabolic effects of PPARβ/δ resemble those of PPARα, which promotes energy dissipation, as opposed to PPARγ, which promotes energy storage. PPARβ/δ normalizes plasma lipids through enhanced FAO in several tissues, coupled to actions on hepatic apolipoprotein metabolism and intestinal cholesterol homeostasis. In contrast to PPARα and similar to PPARγ, activation of PPARβ/δ enhances insulin sensitivity. The mechanisms underlying PPARβ/δ-mediated improvement in glucose handling are not similar to PPARγ, but

Table 1. Selective PPAR modulators

Compound	Reported effects	Status
PPARα agonists		
Pemafibrate (K-877)	Improved lipid profile in patients with dyslipidemia (175)	Phase 3 CV outcome trial ongoing for treatment of dyslipidemia
LY518674	Increased cholesterol efflux in patients with MetS (191)	Discontinued
PPARγ agonists		
INT131	Improved glucose tolerance in people with T2D (176)	Phase 2 trial ongoing for treatment of T2D
PPARβ/δ agonists		
GW501516	Improved lipid profile and insulin sensitivity in overweight monkeys (152) and obese rats (153)	Discontinued
Seladelpar (MBX-8025)	Improved lipid profile and insulin sensitivity in overweight patients with dyslipidemia (151, 181)	Phase 2 trial ongoing for treatment of hyperlipidemia

instead involve PPAR β / δ -specific actions on SKM fiber type distribution, hepatic glucose metabolism, and pancreatic islet function.

Current state of PPAR-targeted therapies

Currently used PPAR agonists display weak potencies (PPAR α) or are associated with important side effects (PPAR γ). Optimization of therapeutic efficacy may be achieved through the development of selective PPAR modulators that retain the beneficial effects of PPAR activation while diminishing unwanted side effects (ref. 173 and Table 1). The selective PPAR α agonist pemafibrate (K-877) (174) exhibited greater lipid modifying efficacy than fenofibrate in a phase 2 trial, with little or no effect on serum creatinine and homocysteine levels (175). This compound is undergoing a phase 3 CV prevention trial, PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients), in patients with high triglyceride and low HDL-C levels. The non-T2D PPAR γ modulator INT131, which improves glucose tolerance in people with T2D without adverse effects on body weight or hemodilution (176), is in phase 2 development. Several compounds that are not direct PPAR γ agonists but that inhibit CDK5-mediated PPAR γ phosphorylation also exert anti-diabetic

activities in obese mice (177–180); whether this will eventually translate to clinical efficacy is unclear. The PPAR β / δ agonist seladelpar (MBX-8025) decreases plasma triglycerides, increases HDL-C, and improves insulin sensitivity and liver function in overweight people with dyslipidemia (151, 181).

Dual PPAR agonists (which activate two PPAR isotypes) and pan-PPAR agonists (which activate all three PPARs) have been developed with the goal of combining the beneficial effects of each receptor isotype (Table 2). The pan-agonist chiglitazar (CS038) improves lipid profiles and insulin sensitivity without increasing body weight in animal models of obesity (182). IVA337, a pan-agonist that prevents and reverses skin fibrosis (183), is currently entering phase 2 trials for the treatment of NASH. Many dual PPAR α / γ agonists, termed glitazars, showed improved efficacy on glucose and lipid metabolism in clinical trials, although safety concerns often halted further development (184). Two phase 3 trials with saroglitazar showed improved glucose and lipid profiles in patients with diabetic dyslipidemia compared with pioglitazone (185) or placebo (186). In contrast to the other PPAR γ -dominant glitazars, saroglitazar predominantly activates PPAR α with only moderate PPAR γ agonism, which may explain the lack of typical

Table 2. Dual and pan-PPAR agonists

Compound	Reported effects	Status
Pan-PPAR agonists		
Chiglitazar	Improved lipid profile and insulin resistance in obese mice (182)	Phase 3 trial ongoing for treatment of T2D
IVA337	Improved skin fibrosis in rodents (183)	Phase 2 trial ongoing for treatment of NASH
Dual PPARα/γ agonists		
Saroglitazar	Improved glucose and lipid profiles in patients with dyslipidemia (185, 186)	Marketed in India for dyslipidemia; phase 3 trial ongoing for treatment of T2D
DSP-8658	Improved glucose and lipid profiles in obese mice (192)	Discontinued
Dual PPARβ(δ)/γ agonists		
DB959	Improved glucose and lipid profiles in obese mice (193)	Discontinued
Dual PPARα/β(δ) agonists		
Elafibranor (GFT505)	Improved hepatic steatosis, inflammation, and fibrosis in rodent models of NASH (90) and in patients with NASH (141); improved lipid profile and insulin sensitivity in patients with dyslipidemia or prediabetes (187) and in obese individuals (188)	Phase 3 trial ongoing for treatment of NASH

PPAR γ side effects. Elafibranor (GFT505), a dual PPAR $\alpha/\beta(\delta)$ agonist, demonstrated protective effects against hepatic steatosis, inflammation, and fibrosis in animal models of NAFLD/NASH (90). In phase 2a trials, elafibranor improved lipid and glucose profiles in dyslipidemic and prediabetic patients (187) and obese individuals (188). The GOLDEN-505 phase 2b study in people with NASH showed that elafibranor treatment induces NASH resolution without worsening fibrosis in a higher proportion of patients compared with placebo (141). The drug was well tolerated and improved glucose homeostasis and CV risk profile, and has since entered phase 3 development for NASH (the RESOLVE-IT trial; NCT02704403).

PPARs are still valuable targets for metabolic diseases

Over the last decades, market withdrawals and failed drug development programs have cast doubts on the clinical value of PPAR-activating compounds. However, this issue is not black and white. The pure PPAR γ agonist rosiglitazone as well as dual PPAR agonists with predominant PPAR γ -activating properties all displayed important adverse effects that led to restricted use or halted development. However, most of these side effects were either drug specific and hence off-target (189) or related to excessive PPAR γ activation. Several fibrate trials, including FIELD and ACCORD, failed to meet the primary endpoint of reduced CV risk; however, such negative outcomes are likely linked to inappropriate patient selection, since subgroup analyzes revealed significant CV risk reduction in those patients with marked dyslipidemia upon trial enrolment (21). Furthermore, in several of these

fibrate trials, including BIP and FIELD, the proportion of patients who received statin therapy was unbalanced between placebo and treatment groups. Correction for this nonrandomized statin drop-in in the FIELD study estimated that fenofibrate reduces relative CV risk by 19% (190).

It has become increasingly clear that PPAR α and PPAR γ agonism display contrasting metabolic effects with different mechanisms of action. Whereas PPAR β/δ agonism is more related to PPAR α , subtle differences exist (e.g., in regulation of glucose homeostasis). These findings are in line with the enhanced metabolic actions and improved safety profiles of novel compounds such as dual PPAR $\alpha/\beta(\delta)$ ligands, which target both lipid (via PPAR α and PPAR β/δ) and glucose (via PPAR β/δ) abnormalities in people with MetS without displaying PPAR γ -related adverse effects. Altogether, we are convinced that targeting PPARs in metabolic disorders remains a valuable and promising approach with a future ahead.

Acknowledgments

BS is a member of the Institut Universitaire de France. This work was supported by grants from the European Genomic Institute for Diabetes (grant ANR-10-LABX-46), the European Commission (RESOLVE contract FP7-305707), and the Fondation de France and Fondation pour la Recherche Médicale (contract DEQ20150331724).

Address correspondence to: Bart Staels, Institut Pasteur de Lille, 1 rue du Professeur Calmette, 59019 Lille, France. Phone: 33.3.20.87.78.25; E-mail: bart.staels@pasteur-lille.fr.

- O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev*. 2015;16(1):1-12.
- Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat Rev Endocrinol*. 2017;13(1):36-49.
- Woller A, Duez H, Staels B, Lefranc M. A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function. *Cell Rep*. 2016;17(4):1087-1097.
- Patsouris D, Reddy JK, Müller M, Kersten S. Peroxisome proliferator-activated receptor alpha mediates the effects of high-fat diet on hepatic gene expression. *Endocrinology*. 2006;147(3):1508-1516.
- Garcia-Roves P, et al. Raising plasma fatty acid concentration induces increased biogenesis of mitochondria in skeletal muscle. *Proc Natl Acad Sci U S A*. 2007;104(25):10709-10713.
- Chakravarthy MV, et al. Brain fatty acid synthase activates PPARalpha to maintain energy homeostasis. *J Clin Invest*. 2007;117(9):2539-2552.
- Chakravarthy MV, et al. "New" hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. *Cell Metab*. 2005;1(5):309-322.
- Chakravarthy MV, et al. Identification of a physiologically relevant endogenous ligand for PPAR α in liver. *Cell*. 2009;138(3):476-488.
- Dijk W, Kersten S. Regulation of lipid metabolism by angiopoietin-like proteins. *Curr Opin Lipidol*. 2016;27(3):249-256.
- Haemmerle G, et al. ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR- α and PGC-1. *Nat Med*. 2011;17(9):1076-1085.
- Jha P, et al. Role of adipose triglyceride lipase (PNPLA2) in protection from hepatic inflammation in mouse models of steatohepatitis and endotoxemia. *Hepatology*. 2014;59(3):858-869.
- Biswas D, Ghosh M, Kumar S, Chakrabarti P. PPAR α -ATGL pathway improves muscle mitochondrial metabolism: implication in aging. *FASEB J*. 2016;30(11):3822-3834.
- Schreiber R, et al. Hypophagia and metabolic adaptations in mice with defective ATGL-mediated lipolysis cause resistance to HFD-induced obesity. *Proc Natl Acad Sci U S A*. 2015;112(45):13850-13855.
- Fan CY, Pan J, Usuda N, Yeldandi AV, Rao MS, Reddy JK. Steatohepatitis, spontaneous peroxisome proliferation and liver tumors in mice lacking peroxisomal fatty acyl-CoA oxidase. Implications for peroxisome proliferator-activated receptor alpha natural ligand metabolism. *J Biol Chem*. 1998;273(25):15639-15645.
- Manninen V, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;85(1):37-45.
- Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341(6):410-418.
- Bezafibrate Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. *Circulation*. 2000;102(1):21-27.
- Keech A, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366(9500):1849-1861.
- ACCORD Study Group, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563-1574.
- Vega GL, Cater NB, Hadzadeh DR, Meguro S, Grundy SM. Free fatty acid metabolism during fenofibrate treatment of the metabolic syndrome. *Clin Pharmacol Ther*. 2003;74(3):236-244.
- Scott R, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care*. 2009;32(3):493-498.
- Jun M, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375(9729):1875-1884.
- Black RN, Ennis CN, Young IS, Hunter SJ, Atkin-

- son AB, Bell PM. The peroxisome proliferator-activated receptor alpha agonist fenofibrate has no effect on insulin sensitivity compared to atorvastatin in type 2 diabetes mellitus; a randomised, double-blind controlled trial. *J Diabetes Complicat.* 2014;28(3):323-327.
24. Krysiak R, Gdula-Dymek A, Bachowski R, Okopien B. Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes. *Diabetes Care.* 2010;33(10):2266-2270.
25. Bonds DE, et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) experience. *Diabetologia.* 2012;55(6):1641-1650.
26. Bentley P, Calder I, Elcombe C, Grasso P, Stringer D, Wiegand HJ. Hepatic peroxisome proliferation in rodents and its significance for humans. *Food Chem Toxicol.* 1993;31(11):857-907.
27. Kahn SE, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
28. Lefterova MI, Haakonsson AK, Lazar MA, Mandrup S. PPAR γ and the global map of adipogenesis and beyond. *Trends Endocrinol Metab.* 2014;25(6):293-302.
29. Zhang H, Zhang A, Kohan DE, Nelson RD, Gonzalez FJ, 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.
30. Akune T, et al. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J Clin Invest.* 2004;113(6):846-855.
31. Stechschulte LA, Ge C, Hinds TD, Sanchez ER, Franceschi RT, Lecka-Czernik B. Protein phosphatase PP5 controls bone mass and the negative effects of rosiglitazone on bone through reciprocal regulation of PPAR γ (Peroxisome Proliferator-activated Receptor γ) and RUNX2 (Runt-related Transcription Factor 2). *J Biol Chem.* 2016;291(47):24475-24486.
32. Wan Y, Chong LW, Evans RM. PPAR- γ regulates osteoclastogenesis in mice. *Nat Med.* 2007;13(12):1496-1503.
33. Zou W, et al. PPAR- γ regulates pharmacological but not physiological or pathological osteoclast formation. *Nat Med.* 2016;22(11):1203-1205.
34. Deeg MA, et al. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. *Diabetes Care.* 2007;30(10):2458-2464.
35. Sakamoto J, et al. Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun.* 2000;278(3):704-711.
36. Dormandy JA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. *Lancet.* 2005;366(9493):1279-1289.
37. Kernan WN, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med.* 2016;374(14):1321-1331.
38. Home PD, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009;373(9681):2125-2135.
39. Fan W, Shen C, Wu M, Zhou ZY, Guo ZR. Association and interaction of PPAR α , δ , and γ gene polymorphisms with low-density lipoprotein-cholesterol in a Chinese Han population. *Genet Test Mol Biomarkers.* 2015;19(7):379-386.
40. Qian Y, et al. Association between peroxisome proliferator-activated receptor-alpha, delta, and gamma polymorphisms and risk of coronary heart disease: a case-control study and meta-analysis. *Medicine (Baltimore).* 2016;95(32):e4299.
41. Andrulionyte L, Kuulasmaa T, Chiasson JL, Laakso M, STOP-NIDDM Study Group. Single nucleotide polymorphisms of the peroxisome proliferator-activated receptor- α gene (PPARA) influence the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes.* 2007;56(4):1181-1186.
42. Flavell DM, et al. Peroxisome proliferator-activated receptor alpha gene variation influences age of onset and progression of type 2 diabetes. *Diabetes.* 2005;54(2):582-586.
43. Barroso I, et al. Dominant negative mutations in human PPAR γ associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature.* 1999;402(6764):880-883.
44. Majithia AR, et al. Rare variants in PPAR γ with decreased activity in adipocyte differentiation are associated with increased risk of type 2 diabetes. *Proc Natl Acad Sci U S A.* 2014;111(36):13127-13132.
45. Scott LJ, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science.* 2007;316(5829):1341-1345.
46. Villegas R, et al. Genetic variation and insulin resistance in middle-aged Chinese men [published online ahead of print August 7, 2015]. *Ann Hum Genet.* <https://doi.org/10.1111/ahg.12124>.
47. Majithia AR, et al. Prospective functional classification of all possible missense variants in PPAR γ . *Nat Genet.* 2016;48(12):1570-1575.
48. Soccio RE, et al. Genetic variation determines PPAR γ function and anti-diabetic drug response in vivo. *Cell.* 2015;162(1):33-44.
49. Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPAR α action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *J Hepatol.* 2015;62(3):720-733.
50. Montagner A, et al. Liver PPAR α is crucial for whole-body fatty acid homeostasis and is protective against NAFLD. *Gut.* 2016;65(7):1202-1214.
51. Kersten S. Integrated physiology and systems biology of PPAR α . *Mol Metab.* 2014;3(4):354-371.
52. Janssen AW, et al. The impact of PPAR α activation on whole genome gene expression in human precision cut liver slices. *BMC Genomics.* 2015;16:760.
53. Longuet C, et al. The glucagon receptor is required for the adaptive metabolic response to fasting. *Cell Metab.* 2008;8(5):359-371.
54. Shao M, et al. Hepatic IRE1 α regulates fasting-induced metabolic adaptive programs through the XBP1s-PPAR α axis signalling. *Nat Commun.* 2014;5:3528.
55. Damiano F, Gnani GV, Siculella L. Citrate carrier promoter is target of peroxisome proliferator-activated receptor α and γ in hepatocytes and adipocytes. *Int J Biochem Cell Biol.* 2012;44(4):659-668.
56. Knight BL, et al. A role for PPAR α in the control of SREBP activity and lipid synthesis in the liver. *Biochem J.* 2005;389(pt 2):413-421.
57. Patel DD, Knight BL, Wiggins D, Humphreys SM, Gibbons GF. Disturbances in the normal regulation of SREBP-sensitive genes in PPAR α -deficient mice. *J Lipid Res.* 2001;42(3):328-337.
58. Sengupta S, Peterson TR, Laplante M, Oh S, Sabatini DM. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. *Nature.* 2010;468(7327):1100-1104.
59. Francque S, et al. PPAR α gene expression correlates with severity and histological treatment response in patients with non-alcoholic steatohepatitis. *J Hepatol.* 2015;63(1):164-173.
60. Zheng L, Lv GC, Sheng J, Yang YD. Effect of miRNA-10b in regulating cellular steatosis level by targeting PPAR- α expression, a novel mechanism for the pathogenesis of NAFLD. *J Gastroenterol Hepatol.* 2010;25(1):156-163.
61. Loyer X, et al. Liver microRNA-21 is overexpressed in non-alcoholic steatohepatitis contributes to the disease in experimental models by inhibiting PPAR α expression [published online ahead print September 3, 2015]. *Gut.* <https://doi.org/10.1136/gutjnl-2014-308883>.
62. Vernia S, et al. The PPAR α -FGF21 hormone axis contributes to metabolic regulation by the hepatic JNK signaling pathway. *Cell Metab.* 2014;20(3):512-525.
63. Schoonjans K, et al. PPAR α and PPAR γ activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J.* 1996;15(19):5336-5348.
64. Staels B, et al. Fibrates downregulate apolipoprotein C-III expression independent of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism for the hypolipidemic action of fibrates. *J Clin Invest.* 1995;95(2):705-712.
65. TG HDL Working Group of the Exome Sequencing Project, National Heart, Lung, Blood Institute, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med.* 2014;371(1):22-31.
66. Vu-Dac N, et al. Apolipoprotein A5, a crucial determinant of plasma triglyceride levels, is highly responsive to peroxisome proliferator-activated receptor α activators. *J Biol Chem.* 2003;278(20):17982-17985.
67. Dongiovanni P, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. *Hepatology.* 2015;61(2):506-514.
68. Fernández-Miranda C, Pérez-Carreras M, Colina F, López-Alonso G, Vargas C, Solís-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis.* 2008;40(3):200-205.
69. Watts GF, et al. Differential regulation of lipoprotein kinetics by atorvastatin and fenofibrate in

- subjects with the metabolic syndrome. *Diabetes*. 2003;52(3):803-811.
70. Vu-Dac N, et al. Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. *J Clin Invest*. 1995;96(2):741-750.
 71. Bouly M, et al. Induction of the phospholipid transfer protein gene accounts for the high density lipoprotein enlargement in mice treated with fenofibrate. *J Biol Chem*. 2001;276(28):25841-25847.
 72. Muoio DM, et al. Peroxisome proliferator-activated receptor- α regulates fatty acid utilization in primary human skeletal muscle cells. *Diabetes*. 2002;51(4):901-909.
 73. Goto T, et al. Activation of peroxisome proliferator-activated receptor- α stimulates both differentiation and fatty acid oxidation in adipocytes. *J Lipid Res*. 2011;52(5):873-884.
 74. Seale P. Transcriptional regulatory circuits controlling brown fat development and activation. *Diabetes*. 2015;64(7):2369-2375.
 75. Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. *Am J Physiol Endocrinol Metab*. 2009;297(3):E578-E591.
 76. Peeters A, Baes M. Role of PPAR α in hepatic carbohydrate metabolism. *PPAR Res*. 2010;2010:572405.
 77. Lalloyer F, et al. Peroxisome proliferator-activated receptor α improves pancreatic adaptation to insulin resistance in obese mice and reduces lipotoxicity in human islets. *Diabetes*. 2006;55(6):1605-1613.
 78. Ramakrishnan SK, et al. Fenofibrate decreases insulin clearance and insulin secretion to maintain insulin sensitivity. *J Biol Chem*. 2016;291(46):23915-23924.
 79. Morán-Salvador E, et al. Role for PPAR γ in obesity-induced hepatic steatosis as determined by hepatocyte- and macrophage-specific conditional knockouts. *FASEB J*. 2011;25(8):2538-2550.
 80. Madsen MS, Siersbæk R, Boergesen M, Nielsen R, Mandrup S. Peroxisome proliferator-activated receptor γ and C/EBP α synergistically activate key metabolic adipocyte genes by assisted loading. *Mol Cell Biol*. 2014;34(6):939-954.
 81. Oger F, et al. Peroxisome proliferator-activated receptor γ regulates genes involved in insulin/insulin-like growth factor signaling and lipid metabolism during adipogenesis through functionally distinct enhancer classes. *J Biol Chem*. 2014;289(2):708-722.
 82. Siersbæk R, et al. Molecular architecture of transcription factor hotspots in early adipogenesis. *Cell Rep*. 2014;7(5):1434-1442.
 83. Dubois-Chevalier J, et al. A dynamic CTCF chromatin binding landscape promotes DNA hydroxymethylation and transcriptional induction of adipocyte differentiation. *Nucleic Acids Res*. 2014;42(17):10943-10959.
 84. Le Bacquer O, et al. Elevated sensitivity to diet-induced obesity and insulin resistance in mice lacking 4E-BP1 and 4E-BP2. *J Clin Invest*. 2007;117(2):387-396.
 85. Kim JE, Chen J. regulation of peroxisome proliferator-activated receptor- γ activity by mammalian target of rapamycin and amino acids in adipogenesis. *Diabetes*. 2004;53(11):2748-2756.
 86. Yu JG, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes*. 2002;51(10):2968-2974.
 87. Kallen CB, Lazar MA. Antidiabetic thiazolidinediones inhibit leptin (ob) gene expression in 3T3-L1 adipocytes. *Proc Natl Acad Sci U S A*. 1996;93(12):5793-5796.
 88. Borges MC, et al. Role of adiponectin in coronary heart disease risk: a Mendelian Randomization Study. *Circ Res*. 2016;119(3):491-499.
 89. Maganti AV, et al. Peroxisome proliferator-activated receptor- γ activation augments the β -cell unfolded protein response and rescues early glycemic deterioration and β cell death in non-obese diabetic mice. *J Biol Chem*. 2016;291(43):22524-22533.
 90. Staels B, et al. Hepatoprotective effects of the dual peroxisome proliferator-activated receptor α/δ agonist, GFT505, in rodent models of non-alcoholic fatty liver disease/nonalcoholic steatohepatitis. *Hepatology*. 2013;58(6):1941-1952.
 91. Ip E, Farrell G, Hall P, Robertson G, Leclercq I. Administration of the potent PPAR α agonist, Wy-14,643, reverses nutritional fibrosis and steatohepatitis in mice. *Hepatology*. 2004;39(5):1286-1296.
 92. Wolf Greenstein A, Majumdar N, Yang P, Subbaiah PV, Kineman RD, Cordoba-Chacon J. Hepatocyte-specific, PPAR γ -regulated mechanisms to promote steatosis in adult mice. *J Endocrinol*. 2017;232(1):107-121.
 93. Gao M, Ma Y, Alsaggar M, Liu D. Dual outcomes of rosiglitazone treatment on fatty liver. *AAPS J*. 2016;18(4):1023-1031.
 94. Hasenfuss SC, Bakiri L, Thomsen MK, Williams EG, Auwerx J, Wagner EF. Regulation of steatohepatitis and PPAR γ signaling by distinct AP-1 dimers. *Cell Metab*. 2014;19(1):84-95.
 95. Sanyal AJ, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362(18):1675-1685.
 96. Ratziu V, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology*. 2008;135(1):100-110.
 97. Lu M, et al. Brain PPAR- γ promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. *Nat Med*. 2011;17(5):618-622.
 98. Fu J, et al. Oleyethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR- α . *Nature*. 2003;425(6953):90-93.
 99. Kimura R, Takahashi N, Goto T, Murota K, Kawada T. Activation of peroxisome proliferator-activated receptor- α (PPAR α) in proximal intestine improves postprandial lipidemia in obese diabetic KK-Ay mice. *Obes Res Clin Pract*. 2013;7(5):e353-e360.
 100. Colin S, et al. Activation of intestinal peroxisome proliferator-activated receptor- α increases high-density lipoprotein production. *Eur Heart J*. 2013;34(32):2566-2574.
 101. Zhou T, et al. Evolutionary pattern and regulation analysis to support why diversity functions existed within PPAR gene family members. *Biomed Res Int*. 2015;2015:613910.
 102. Lefterova MI, et al. Cell-specific determinants of peroxisome proliferator-activated receptor γ function in adipocytes and macrophages. *Mol Cell Biol*. 2010;30(9):2078-2089.
 103. Heinz S, et al. Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. *Mol Cell*. 2010;38(4):576-589.
 104. Dispirito JR, Fang B, Wang F, Lazar MA. Pruning of the adipocyte peroxisome proliferator-activated receptor γ cisrome by hematopoietic master regulator PU.1. *Mol Cell Biol*. 2013;33(16):3354-3364.
 105. Siersbæk MS, et al. Genome-wide profiling of peroxisome proliferator-activated receptor γ in primary epididymal, inguinal, and brown adipocytes reveals depot-selective binding correlated with gene expression. *Mol Cell Biol*. 2012;32(17):3452-3463.
 106. Settembre C, et al. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. *Nat Cell Biol*. 2013;15(6):647-658.
 107. Yang X, et al. Nuclear receptor expression links the circadian clock to metabolism. *Cell*. 2006;126(4):801-810.
 108. Gachon F, et al. Proline- and acidic amino acid-rich basic leucine zipper proteins modulate peroxisome proliferator-activated receptor α (PPAR α) activity. *Proc Natl Acad Sci U S A*. 2011;108(12):4794-4799.
 109. Zheng Z, et al. CREBH couples circadian clock with hepatic lipid metabolism. *Diabetes*. 2016;65(11):3369-3383.
 110. Ratman D, et al. Chromatin recruitment of activated AMPK drives fasting response genes co-controlled by GR and PPAR α . *Nucleic Acids Res*. 2016;44(22):10539-10553.
 111. Marino JS, Stechschulte LA, Stec DE, Nestor-Kalinowski A, Coleman S, Hinds TD. Glucocorticoid receptor β induces hepatic steatosis by augmenting inflammation and inhibition of the peroxisome proliferator-activated receptor (PPAR) α . *J Biol Chem*. 2016;291(50):25776-25788.
 112. Picard F, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR- γ . *Nature*. 2004;429(6993):771-776.
 113. Kajita K, et al. Effect of fasting on PPAR γ and AMPK activity in adipocytes. *Diabetes Res Clin Pract*. 2008;81(2):144-149.
 114. Hatori M, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab*. 2012;15(6):848-860.
 115. Eckel-Mahan KL, et al. Reprogramming of the circadian clock by nutritional challenge. *Cell*. 2013;155(7):1464-1478.
 116. Liang X, Bushman FD, FitzGerald GA. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. *Proc Natl Acad Sci U S A*. 2015;112(33):10479-10484.
 117. Murakami M, Tognini P, Liu Y, Eckel-Mahan KL, Baldi P, Sassone-Corsi P. Gut microbiota directs PPAR γ -driven reprogramming of the liver circadian clock by nutritional challenge. *EMBO Rep*. 2016;17(9):1292-1303.
 118. Inagaki T, et al. Endocrine regulation of the fasting response by PPAR α -mediated induction of fibroblast growth factor 21. *Cell Metab*. 2007;5(6):415-425.
 119. Zhang X, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes*.

- 2008;57(5):1246–1253.
120. Dutchak PA, et al. Fibroblast growth factor-21 regulates PPAR γ activity and the anti-diabetic actions of thiazolidinediones. *Cell*. 2012;148(3):556–567.
 121. So WY, et al. High glucose represses β -klotho expression and impairs fibroblast growth factor 21 action in mouse pancreatic islets: involvement of peroxisome proliferator-activated receptor γ signaling. *Diabetes*. 2013;62(11):3751–3759.
 122. Jonker JW, et al. A PPAR γ -FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis. *Nature*. 2012;485(7398):391–394.
 123. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol*. 2011;11(2):98–107.
 124. Massaro M, et al. Therapeutic potential of the dual peroxisome proliferator activated receptor (PPAR) α/γ agonist aleglitazar in attenuating TNF- α -mediated inflammation and insulin resistance in human adipocytes. *Pharmacol Res*. 2016;107:125–136.
 125. Bouhrel MA, et al. PPAR γ activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. *Cell Metab*. 2007;6(2):137–143.
 126. Bapat SP, et al. Depletion of fat-resident Treg cells prevents age-associated insulin resistance. *Nature*. 2015;528(7580):137–141.
 127. Cipolletta D, Cohen P, Spiegelman BM, Benoist C, Mathis D. Appearance and disappearance of the mRNA signature characteristic of Treg cells in visceral adipose tissue: age, diet, and PPAR γ effects. *Proc Natl Acad Sci U S A*. 2015;112(2):482–487.
 128. Cipolletta D, et al. PPAR- γ is a major driver of the accumulation and phenotype of adipose tissue Treg cells. *Nature*. 2012;486(7404):549–553.
 129. Angela M, et al. Fatty acid metabolic reprogramming via mTOR-mediated inductions of PPAR γ directs early activation of T cells. *Nat Commun*. 2016;7:13683.
 130. Mansouri RM, Baugé E, Staels B, Gervois P. Systemic and distal repercussions of liver-specific peroxisome proliferator-activated receptor- α control of the acute-phase response. *Endocrinology*. 2008;149(6):3215–3223.
 131. Chinetti-Gbaguidi G, Staels B. Lipid ligand-activated transcription factors regulating lipid storage and release in human macrophages. *Biochim Biophys Acta*. 2009;1791(6):486–493.
 132. Delerive P, et al. Peroxisome proliferator-activated receptor alpha negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF- κ B and AP-1. *J Biol Chem*. 1999;274(45):32048–32054.
 133. Chung SW, et al. Oxidized low density lipoprotein inhibits interleukin-12 production in lipopolysaccharide-activated mouse macrophages via direct interactions between peroxisome proliferator-activated receptor- γ and nuclear factor- κ B. *J Biol Chem*. 2000;275(42):32681–32687.
 134. Pawlak M, et al. The transrepressive activity of peroxisome proliferator-activated receptor α is necessary and sufficient to prevent liver fibrosis in mice. *Hepatology*. 2014;60(5):1593–1606.
 135. Mogilenko DA, et al. Peroxisome proliferator-activated receptor α positively regulates complement C3 expression but inhibits tumor necrosis factor α -mediated activation of C3 gene in mammalian hepatic-derived cells. *J Biol Chem*. 2013;288(3):1726–1738.
 136. Bougarne N, et al. PPAR α blocks glucocorticoid receptor α -mediated transactivation but cooperates with the activated glucocorticoid receptor α for transrepression on NF- κ B. *Proc Natl Acad Sci U S A*. 2009;106(18):7397–7402.
 137. Pascual G, et al. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR- γ . *Nature*. 2005;437(7059):759–763.
 138. Stienstra R, et al. The Interleukin-1 receptor antagonist is a direct target gene of PPAR α in liver. *J Hepatol*. 2007;46(5):869–877.
 139. Meier CA, Chicheportiche R, Juge-Aubry CE, Dreyer MG, Dayer JM. Regulation of the interleukin-1 receptor antagonist in THP-1 cells by ligands of the peroxisome proliferator-activated receptor gamma. *Cytokine*. 2002;18(6):320–328.
 140. Belfort R, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 2006;355(22):2297–2307.
 141. Ratziu V, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor- α and - δ , induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. *Gastroenterology*. 2016;150(5):1147–1159.e5.
 142. Othman A, et al. Fenofibrate lowers atypical sphingolipids in plasma of dyslipidemic patients: a novel approach for treating diabetic neuropathy? *J Clin Lipidol*. 2015;9(4):568–575.
 143. Gorden DL, et al. Biomarkers of NAFLD progression: a lipidomics approach to an epidemic. *J Lipid Res*. 2015;56(3):722–736.
 144. Barroso E, et al. PPAR β/δ ameliorates fructose-induced insulin resistance in adipocytes by preventing Nrf2 activation. *Biochim Biophys Acta*. 2015;1852(5):1049–1058.
 145. Kang K, et al. Adipocyte-derived Th2 cytokines and myeloid PPARdelta regulate macrophage polarization and insulin sensitivity. *Cell Metab*. 2008;7(6):485–495.
 146. Odegaard JJ, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. *Cell Metab*. 2008;7(6):496–507.
 147. Skogsberg J, Kannisto K, Cassel TN, Hamsten A, Eriksson P, Ehrenborg E. Evidence that peroxisome proliferator-activated receptor delta influences cholesterol metabolism in men. *Arterioscler Thromb Vasc Biol*. 2003;23(4):637–643.
 148. Vääntinen M, et al. Single nucleotide polymorphisms in the peroxisome proliferator-activated receptor δ gene are associated with skeletal muscle glucose uptake. *Diabetes*. 2005;54(12):3587–3591.
 149. Andrulionyte L, Peltola P, Chiasson JL, Laakso M, STOP-NIDDM Study Group. Single nucleotide polymorphisms of PPARG in combination with the Gly482Ser substitution of PGC-1A and the Pro12Ala substitution of PPARG2 predict the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes*. 2006;55(7):2148–2152.
 150. Risérus U, et al. Activation of peroxisome proliferator-activated receptor (PPAR)delta promotes reversal of multiple metabolic abnormalities, reduces oxidative stress, and increases fatty acid oxidation in moderately obese men. *Diabetes*. 2008;57(2):332–339.
 151. Bays HE, et al. MBX-8025, a novel peroxisome proliferator receptor-delta agonist: lipid and other metabolic effects in dyslipidemic overweight patients treated with and without atorvastatin. *J Clin Endocrinol Metab*. 2011;96(9):2889–2897.
 152. Oliver WR, et al. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci U S A*. 2001;98(9):5306–5311.
 153. Li X, et al. Treatment with PPAR δ agonist alleviates non-alcoholic fatty liver disease by modulating glucose and fatty acid metabolic enzymes in a rat model. *Int J Mol Med*. 2015;36(3):767–775.
 154. Wang YX, et al. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell*. 2003;113(2):159–170.
 155. Tanaka T, et al. Activation of peroxisome proliferator-activated receptor delta induces fatty acid β -oxidation in skeletal muscle and attenuates metabolic syndrome. *Proc Natl Acad Sci U S A*. 2003;100(26):15924–15929.
 156. Roberts LD, Murray AJ, Menassa D, Ashmore T, Nicholls AW, Griffin JL. The contrasting roles of PPAR δ and PPAR γ in regulating the metabolic switch between oxidation and storage of fats in white adipose tissue. *Genome Biol*. 2011;12(8):R75.
 157. Bojic LA, et al. PPAR δ activation attenuates hepatic steatosis in Ldlr $^{-/-}$ mice by enhanced fat oxidation, reduced lipogenesis, and improved insulin sensitivity. *J Lipid Res*. 2014;55(7):1254–1266.
 158. Kocalis HE, et al. Neuron-specific deletion of peroxisome proliferator-activated receptor delta (PPAR δ) in mice leads to increased susceptibility to diet-induced obesity. *PLoS One*. 2012;7(8):e42981.
 159. Barroso E, et al. The PPAR β/δ activator GW501516 prevents the down-regulation of AMPK caused by a high-fat diet in liver and amplifies the PGC-1 α -Lipin 1-PPAR α pathway leading to increased fatty acid oxidation. *Endocrinology*. 2011;152(5):1848–1859.
 160. van der Veen JN, et al. Reduced cholesterol absorption upon PPARdelta activation coincides with decreased intestinal expression of NPC1L1. *J Lipid Res*. 2005;46(3):526–534.
 161. Vrnins CL, et al. Peroxisome proliferator-activated receptor delta activation leads to increased transintestinal cholesterol efflux. *J Lipid Res*. 2009;50(10):2046–2054.
 162. Thulin P, Glinghammar B, Skogsberg J, Lundell K, Ehrenborg E. PPAR δ increases expression of the human apolipoprotein A-II gene in human liver cells. *Int J Mol Med*. 2008;21(6):819–824.
 163. Chehaibi K, et al. PPAR- β/δ activation promotes phospholipid transfer protein expression. *Biochem Pharmacol*. 2015;94(2):101–108.
 164. Luquet S, et al. Peroxisome proliferator-activated receptor delta controls muscle development and oxidative capability. *FASEB J*. 2003;17(15):2299–2301.
 165. Schuler M, et al. PGC1alpha expression is controlled in skeletal muscles by PPAR β , whose ablation results in fiber-type switching, obesity, and type 2 diabetes. *Cell Metab*. 2006;4(5):407–414.
 166. Gan Z, et al. Nuclear receptor/microRNA circuitry links muscle fiber type to energy metabolism. *J Clin Invest*. 2013;123(6):2564–2575.

167. Albers PH, et al. Human muscle fiber type-specific insulin signaling: impact of obesity and type 2 diabetes. *Diabetes*. 2015;64(2):485-497.
168. Oberbach A, et al. Altered fiber distribution and fiber-specific glycolytic and oxidative enzyme activity in skeletal muscle of patients with type 2 diabetes. *Diabetes Care*. 2006;29(4):895-900.
169. Lee CH, et al. PPARdelta regulates glucose metabolism and insulin sensitivity. *Proc Natl Acad Sci U S A*. 2006;103(9):3444-3449.
170. Liu S, et al. Role of peroxisome proliferator-activated receptor δ/β in hepatic metabolic regulation. *J Biol Chem*. 2011;286(2):1237-1247.
171. Tang T, Abbott MJ, Ahmadian M, Lopes AB, Wang Y, Sul HS. Desnutrin/ATGL activates PPAR δ to promote mitochondrial function for insulin secretion in islet β cells. *Cell Metab*. 2013;18(6):883-895.
172. Daoudi M, et al. PPAR β/δ activation induces enteroendocrine L cell GLP-1 production. *Gastroenterology*. 2011;140(5):1564-1574.
173. Sahebkar A, Chew GT, Watts GF. New peroxisome proliferator-activated receptor agonists: potential treatments for atherogenic dyslipidemia and non-alcoholic fatty liver disease. *Expert Opin Pharmacother*. 2014;15(4):493-503.
174. Hennuyer N, et al. The novel selective PPAR α modulator (SPPARMa) pemafibrate improves dyslipidemia, enhances reverse cholesterol transport and decreases inflammation and atherosclerosis. *Atherosclerosis*. 2016;249:200-208.
175. Ishibashi S, et al. Effects of K-877, a novel selective PPAR α modulator (SPPARMa), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial. *Atherosclerosis*. 2016;249:36-43.
176. Dunn FL, Higgins LS, Fredrickson J, DePaoli AM, INT131-004 Study Group. Selective modulation of PPAR γ activity can lower plasma glucose without typical thiazolidinedione side-effects in patients with Type 2 diabetes. *J Diabetes Complicat*. 2011;25(3):151-158.
177. Banks AS, et al. An ERK/Cdk5 axis controls the diabetogenic actions of PPAR γ . *Nature*. 2015;517(7534):391-395.
178. Choi JH, et al. Thrap3 docks on phosphoserine 273 of PPAR γ and controls diabetic gene programming. *Genes Dev*. 2014;28(21):2361-2369.
179. Choi SS, et al. PPAR γ antagonist gleevec improves insulin sensitivity and promotes the browning of white adipose tissue. *Diabetes*. 2016;65(4):829-839.
180. Choi SS, et al. A novel non-agonist peroxisome proliferator-activated receptor γ (PPAR γ) ligand UHC1 blocks PPAR γ phosphorylation by cyclin-dependent kinase 5 (CDK5) and improves insulin sensitivity. *J Biol Chem*. 2014;289(38):26618-26629.
181. Choi YJ, et al. Effects of the PPAR- δ agonist MBX-8025 on atherogenic dyslipidemia. *Atherosclerosis*. 2012;220(2):470-476.
182. He BK, et al. In vitro and in vivo characterizations of Chiglitazar, a newly identified PPAR pan-agonist. *PPAR Res*. 2012;2012:546548.
183. Ruzehaji N, et al. Pan PPAR agonist IVA337 is effective in prevention and treatment of experimental skin fibrosis. *Ann Rheum Dis*. 2016;75(12):2175-2183.
184. Rosenson RS, Wright RS, Farkouh M, Plutzky J. Modulating peroxisome proliferator-activated receptors for therapeutic benefit? Biology, clinical experience, and future prospects. *Am Heart J*. 2012;164(5):672-680.
185. Pai V, et al. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of saroglitazar 2 and 4 mg compared to pioglitazone 45 mg in diabetic dyslipidemia (PRESS V). *J Diabetes Sci Technol*. 2014;8(1):132-141.
186. Jani RH, et al. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). *Diabetes Technol Ther*. 2014;16(2):63-71.
187. Cariou B, Zaïr Y, Staels B, Bruckert E. Effects of the new dual PPAR α/δ agonist GFT505 on lipid and glucose homeostasis in abdominally obese patients with combined dyslipidemia or impaired glucose metabolism. *Diabetes Care*. 2011;34(9):2008-2014.
188. Cariou B, et al. Dual peroxisome proliferator-activated receptor α/δ agonist GFT505 improves hepatic and peripheral insulin sensitivity in abdominally obese subjects. *Diabetes Care*. 2013;36(10):2923-2930.
189. Wright MB, Bortolini M, Tadayyon M, Bopst M. Minireview: Challenges and opportunities in development of PPAR agonists. *Mol Endocrinol*. 2014;28(11):1756-1768.
190. Staels B, Maes M, Zambon A. Fibrates and future PPAR α agonists in the treatment of cardiovascular disease. *Nat Clin Pract Cardiovasc Med*. 2008;5(9):542-553.
191. Khara AV, Millar JS, Ruotolo G, Wang MD, Rader DJ. Potent peroxisome proliferator-activated receptor- α agonist treatment increases cholesterol efflux capacity in humans with the metabolic syndrome. *Eur Heart J*. 2015;36(43):3020-3022.
192. Goto T, et al. Effects of DSP-8658, a novel selective peroxisome proliferator-activated receptors α/γ modulator, on adipogenesis and glucose metabolism in diabetic obese mice. *Exp Clin Endocrinol Diabetes*. 2015;123(8):492-499.
193. Delmedico MK, et al. DB959 is a novel, dual PPAR δ/γ agonist which controls glucose regulates triglycerides HDLc in animal models of T2D dyslipidemia. 69th Annual Scientific Sessions of the American Diabetes Association. June 5, 2009. Abstr. 365-OR.