PPARδ: a dagger in the heart of the metabolic syndrome

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Obesity is a growing threat to global health by virtue of its association with insulin resistance, glucose intolerance, hypertension, and dyslipidemia, collectively known as the metabolic syndrome or syndrome X. The nuclear receptors PPARα and PPARγ are therapeutic targets for hypertriglyceridemia and insulin resistance, respectively, and drugs that modulate these receptors are currently in clinical use. More recent work on the less-described PPAR isotype PPARδ has uncovered a dual benefit for both hypertriglyceridemia and insulin resistance, highlighting the broad potential of PPARδ in the treatment of metabolic disease. PPARδ enhances fatty acid catabolism and energy uncoupling in adipose tissue and muscle, and it suppresses macrophage-derived inflammation. Its combined activities in these and other tissues make it a multifaceted therapeutic target for the metabolic syndrome with the potential to control weight gain, enhance physical endurance, improve insulin sensitivity, and ameliorate atherosclerosis.

Introduction

The prevalence of adult obesity has increased an alarming 75% since 1980, rendering a third of men and women obese in the US (1). This unabated rise has spawned proportionate increases in obesity-associated metabolic disorders, including glucose intolerance, insulin resistance, dyslipidemia, and hypertension, that are well-established risk factors for cardiovascular disease. Known as the metabolic syndrome or syndrome X, this dangerous cluster of pathologies accounts for 6–7% of all-cause mortality and is an expanding health threat. In fact, it is predicted that life expectancy will plateau or decline in the US within the first half of this century because of the magnitude of obesity-associated conditions and the increased rates of obesity in younger populations, particularly children (2, 3). The global obesity problem will require complex solutions, including public health efforts to diminish portion sizes, improve food choices, increase physical activity levels, and raise public awareness. In addition to social and behavioral changes, however, pharmacological interventions to diminish diabetic and cardiovascular complications of the metabolic syndrome are urgently needed.

The pathophysiology underlying the metabolic syndrome is incompletely understood, but insulin resistance appears to be an important component (4, 5). Insulin resistance is marked by hyperinsulinemia, enhanced hepatic gluconeogenesis, and impaired insulin-stimulated glucose uptake into skeletal muscle and fat. Elevated levels of circulating FFAs, associated with obesity and insulin resistance, increase fat accumulation in insulin target tissues and contribute to defective insulin action. Indeed, intramuscular fat, based on NMR spectroscopy, correlates strongly with insulin resistance (6). Obese adipose tissue–derived inflammation and altered adipokine secretion may also inhibit insulin signals and affect systemic metabolism (7). The resulting hyperglycemia, dyslipidemia, and hypertension of the metabolic syndrome cause endothelial dysfunction and hasten atherogenesis. Monocyte-derived macrophages are recruited to the vascular wall, where uptake of modified LDL cholesterol drives their development into so-called foam cells. These cholesterol-loaded macrophages elaborate inflammatory mediators and matrix remodeling enzymes, begetting further inflammation and the formation of complex atherosclerotic lesions through interactions and recruitment of vascular cells, T cells, and additional macrophages (8). Ultimately, such changes put metabolic syndrome patients at high risk for heart attack and stroke (9).

PPARs: lipid sensors and transcriptional switches

The identification of PPARs as molecular targets for drugs to treat hypertriglyceridemia and type 2 diabetes mellitus has fueled interest in their biology and potential as targets to treat the metabolic syndrome. PPARs are members of the nuclear receptor superfamily of ligand-inducible transcription factors. They form heterodimers with retinoid X receptors (RXRs) and bind to consensus DNA sites composed of direct repeats (DRs) of hexameric DNA sequences separated by 1 bp (DR1). In the absence of ligand, PPAR-RXR heterodimers recruit corepressors and associated histone deacetylases and chromatin-modifying enzymes, silencing transcription by so-called active repression (10–12). Ligand binding induces a conformational change in PPAR-RXR complexes, releasing repressors in exchange for coactivators. Ligand-activated complexes recruit the basal transcriptional machinery, resulting in enhanced gene expression. Unlike classical endocrine receptors that bind to high-affinity glandular hormones, PPARs bind to lower-affinity ligands generated from dietary fat or intracellular metabolism. In keeping with their roles as lipid sensors, ligand-activated PPARs turn on feed-forward metabolic cascades to regulate lipid homeostasis via the transcription of genes involved in lipid metabolism, storage, and transport. Additionally, PPARs may suppress inflammation through mechanisms involving the release of antiinflammatory factors or the stabilization of repressive complexes at inflammatory gene promoters (13, 14).

Three PPAR isotypes exist in mammals: α (NR1C1), γ (NR1C3), and δ (also known as β or NR1C2). PPARα was the first PPAR to be identified and was demonstrated to be the target of hypolipidemic fibrate drugs and carcinogens that cause peroxisome pro-

Nonstandard abbreviations used: APC, adenomatous polyposis coli; BCL-6, B cell lymphoma-6; DR, direct repeat; MCP-1, monocyte chemoattractant protein-1; RXR, retinoid X receptor; UCP, uncoupling protein; VP16, viral protein 16.

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liferation in rodent livers, where PPARα is abundantly expressed (15). Subsequent cloning efforts identified the γ and δ isotypes. PPARγ is expressed predominantly in adipose tissue, and to a lesser extent in macrophages, muscle, and liver. It has received considerable attention since the mid-1990s, when it was found to be the molecular target of insulin-sensitizing, antidiabetic drugs known as thiazolidinediones (16, 17). PPARδ remained an enigma for almost a decade after its cloning in 1992 (18–20). Its near-ubiquitous tissue expression raised early speculation that it may serve a "general housekeeping role" (20). More recently, receptor knockouts revealed multiple developmental and homeostatic abnormalities in *PPAR*δ-null mice, including placental defects causing frequent embryonic lethality, decreased adipose mass, myelination defects, altered skin inflammatory responses, and impaired wound healing (21–23). These findings, along with discoveries aided by the development of high-affinity PPARδ agonists and additional genetic models, have instead revealed PPARδ as a key regulator with the potential to therapeutically target multiple aspects of the metabolic syndrome. This Review will cover the cellular and systemic effects of PPARδ action, with special emphasis on its role in the metabolic syndrome.

PPARδ ligands

X-ray crystallography studies of PPARδ revealed an exceptionally large ligand-binding pocket of approximately 1,300 Å^3, similar to that of PPARγ but much larger than the pockets of other nuclear receptors (24, 25). The increased dimension is believed to accommodate the binding of various fatty acids or other amphipathic acids to PPARδ via hydrogen bonds and hydrophobic interactions (24). Several 14- to 18-carbon saturated fatty acids as well as 16- to 20-carbon polyunsaturated fatty acids are suggested to bind PPARδ based on ligand screens and competition binding assays, with affinities in the micromolar range (24, 26–28). Similar concentrations of synthetic and naturally occurring eicosanoids including prostaglandin A_1, iloprost, 15d-J2, and carbaprostacyclin serve as effective PPARδ activators (26). Which fatty acids or eicosanoids are physiological ligands of PPARδ remains unsettled. However, VLDL particle–derived fatty acids enhance the expression of PPARδ target genes in a receptor-dependent manner, suggesting that a variety of VLDL-delivered fatty acids could serve as endogenous receptor agonists (29). Alternatively, combinatorial chemistry and structure-based drug design have facilitated the development of synthetic agonists with nanomolar affinities for PPARδ, although none is currently marketed for clinical use in humans.

PPARδ in lipoprotein metabolism

A hallmark of the metabolic syndrome is dyslipidemia, marked by elevated triglycerides and low levels of HDL cholesterol. HDL is a driving force in the process of reverse cholesterol transport, reclaiming excess peripheral tissue cholesterol to the liver for excretion. Accordingly, low levels of HDL are associated with an increased risk of coronary artery disease and cardiovascular death in afflicted patients, while overexpression of apoA-I, the major apolipoprotein composing HDL particles, retards atherogenesis in animal models (30–32). Despite clear therapeutic need, currently marketed cholesterol-modifying drugs raise serum HDL levels only modestly.

High-affinity PPARδ ligands have revealed an important role for PPARδ in lipoprotein metabolism. Treatment of insulin-resistant obese rhesus monkeys with the PPARδ-selective agonist GW501516 resulted in a dramatic 79% increase in HDL-C, a 56% decrease in triglycerides, and a 29% decrease in LDL cholesterol (33). The profound increase in HDL cholesterol levels correlated with an increase in number, not size, of HDL particles and was accompanied by increased serum levels of the HDL-associated apolipoproteins apoA-I, apoA-II, and apoC-III (33). In addition, fasting insulin levels declined by up to 48% in the PPARδ drug–treated animals (33). Obese and nonobese mice similarly develop an increase of up to 50% in HDL cholesterol levels when treated with PPARδ agonists (34, 35). The mechanism by which PPARδ activation raises HDL cholesterol levels remains to be elucidated, but studies to date indi-

Table 1
PPARδ gene targets in fat and muscle tissues

Brown fat	White fat	Skeletal muscle	Cardiac muscle
Fatty acid transport and oxidation *LCAS* (39), *VLCAS* (39), ACOX1 (39), *m-CPT1* (39), *LCAD* (39), *VLCAD* (39), *HSL* (39)	Thermogenesis *UCP1* (39)	Fatty acid transport and oxidation *Heart fatty acid–binding protein* (48), *fatty acid transport protein/CD36* (48), *m-CPT1* (40,48), *PDK4* (40,48,50), *HMGCS2* (48), *thiolase* (48), *LCAD* (48)	Fatty acid transport and oxidation *l-CPT1* (68), *m-CPT1* (68), *thiolase* (68), *UCP3* (68), *LCAD* (68), *MCAD* (68), *PDK4* (68), *VLCAD* (68), *ACOX1* (68)
Thermogenesis *UCP1* (39), *UCP3* (39)		Oxidative metabolism *Succinate dehydrogenase* (49, 60), *citrate synthase* (49, 60)	
		Mitochondrial respiration and thermogenesis *Cytochrome c* (40,48), *cytochrome oxidase II* (40), *cytochrome oxidase IV* (40), *UCP2* (40,48), *UCP3* (40,48)	
		Slow-twitch fibers *Myoglobin* (40), *troponin I slow* (40)	

References are shown in parentheses. *ACOX1*, *acyl-CoA oxidase*; *HMGCS2*, *3-hydroxy-3-methylglutaryl-CoA synthase 2*; *HSL*, *hormone-sensitive lipase*; *LCAD*, *long-chain acyl-CoA dehydrogenase*; *LCAS*, *long-chain acyl-CoA synthetase*; *l-CPT1*, *liver carnitine palmitoyltransferase 1*; *MCAD*, *medium-chain fatty acyl-CoA decarboxylase*; *m-CPT1*, *muscle carnitine palmitoyltransferase 1*; *PDK4*, *pyruvate dehydrogenase kinase 4*; *VLCAD*, *very-long-chain acyl-CoA dehydrogenase*; *VLCAS*, *very-long-chain acyl-CoA synthetase*.

cate that expression of the reverse cholesterol transporter ABCA1 is enhanced in some tissues upon exposure to PPARδ agonists, including human and mouse macrophages as well as human intestinal cells and fibroblasts (33, 35). Additional work suggests that PPARδ activation reduces intestinal cholesterol absorption via downregulation of the *Niemann-Pick C1–like 1 gene* (*NPC1L1*) (35). NPC1L1 is a key mediator of intestinal cholesterol absorption and a putative target for the clinically used cholesterol absorption inhibitor ezetimibe. In light of these findings, PPARδ drugs are now in clinical trial for the treatment of human dyslipidemia.

PPARδ action in adipose tissue

Once viewed as a bland storage depot, adipose tissue has emerged as a dynamic endocrine organ (7). Adiposity correlates with insulin resistance and is believed by some to be of primacy in the metabolic syndrome (36). Even mild weight loss may improve serum lipid profiles, glycemic control, and hypertension, yet currently available weight-loss drugs are of limited effectiveness (37, 38).

Genetic models and ligand treatment studies have uncovered powerful regulatory functions for PPARδ in adipose tissue metabolism and weight control. Using a gain-of-function strategy, transgenic mice encoding a constitutively active viral protein 16–PPARδ fusion (VP16-PPARδ) expressed under the enhancer-promoter region of the *adipose tissue–specific adipocyte fatty acid–binding protein* (*aP2*) gene were developed (39). On a standard chow diet, these fat-specific VP16-PPARδ mice had 20% reduced body weights, 40% reduced inguinal fat pad masses, decreased adipocyte triglyceride accumulation, and reduced circulating FFAs and triglycerides compared to that of control littermates on the same diet (39). Moreover, in the context of high-fat diet or genetically predisposed obesity, fat-specific VP16-PPARδ expression protected against weight gain, adipocyte hypertrophy, hypertriglyceridemia, and steatosis (39). Transcriptional analysis of brown fat in fat-specific VP16-PPARδ mice revealed upregulation of genes involved in triglyceride hydrolysis (*hormone-sensitive lipase*), fatty acid oxidation (*long-chain acyl-CoA synthetase*, *very-long-chain acyl-CoA synthetase*, *acyl-CoA oxidase*), and uncoupling of oxidative phosphorylation (*uncoupling protein-1* and *-3*) (39). *Uncoupling protein-1* (*UCP1*) expression was likewise elevated in white adipose tissue (Table 1). Conversely, *PPAR*δ-null mice are more susceptible to weight gain and have blunted expression of brown fat *UCP1* on a high-fat diet (39). These genetic models collectively suggest that activation of PPARδ protects against obesity.

Importantly, PPARδ ligands mimic the effects of expression of a constitutively active PPARδ transgene. Administration of the synthetic PPARδ agonist GW501516 to genetically obese (*db/db*) mice reduced intracellular triglyceride accumulation in the brown fat and liver, analogous to the effects of VP16-PPARδ (39). Moreover, PPARδ agonists enhanced β-oxidation in 3T3-L1 preadipocytes by 50% (39). Most importantly, PPARδ ligands retard weight gain in models of high-fat diet–induced obesity (39, 40). These results suggest that PPARδ synthetic drugs may be therapeutic as antiobesity agents. Short-term (4-month) treatment of obese rhesus monkeys with variable doses of GW501516 did not affect body weight, however, so it remains to be determined whether long-term administration of PPARδ drugs will control body weight in monkeys and humans (33).

PPARδ action in skeletal muscle

Skeletal muscle is a key metabolic tissue, accounting for approximately 80% of insulin-stimulated glucose uptake. It is composed of heterogeneous myofibers that differ in their metabolic and contractile properties, including oxidative slow-twitch (type I), mixed oxidative/glycolytic fast-twitch (type IIA), and glycolytic fast-twitch (type IIB) forms (41). Oxidative myofibers preferentially express enzymes that oxidize fatty acids and contain slow isoforms of contractile proteins, whereas glycolytic myofibers predominantly metabolize glucose and are composed of fast contractile protein isoforms (41, 42). Skeletal muscle is highly plastic, adapting to environmental challenges by regulating the composition of slow- and fast-twitch myofibers. Interventions including endurance exercise, physical inactivity, and metabolic diseases such as type 2 diabetes mellitus can induce the *trans*-differentiation of myofibers (43). This process involves changes in the expression of metabolic and contractile proteins within the myofiber and is influenced by transcription factors including NFAT, FOXO1, and myogenin (43–46).

*PPAR*δ is expressed in skeletal muscle at 10- and 50-fold higher levels compared with *PPAR*α and *PPAR*γ, respectively, and it is preferentially found in oxidative rather than glycolytic myofibers (47, 48). Consistent with a role for PPARδ in the maintenance or formation of oxidative fibers, targeted expression of constitutively active PPARδ (VP16-PPARδ) in rodent skeletal muscle increases the proportion of oxidative slow-twitch fibers in predominantly fast-twitch muscle (48). The observed PPARδ-mediated reprogramming of muscle fiber involves the increased expression of genes related to fatty acid oxidation, mitochondrial respiration, oxidative metabolism, and slow-twitch contractile apparatus (48). Skeletal muscle–specific overexpression of wild-type PPARδ induces some features of fiber type remodeling, such as enhanced skeletal muscle oxidative enzyme expression and activity, but fiber type switching is not observed (49). This difference may be due to reduced transcriptional activity of the wild-type PPARδ transgene relative to VP16-PPARδ. Indeed, the former presumably requires endogenous receptor ligands, such as fatty acids and prostaglandins, for activation, and these may be present at limiting concentrations or may activate at reduced potency relative to the constitutively active VP16 transactivation domain. PPARδ-mediated regulation of gene expression has also been confirmed pharmacologically. Treatment of rodents with a synthetic PPARδ agonist increases the expression of all of the aforementioned classes of skeletal muscle genes, including those involved in fatty acid oxidation, mitochondrial respiration, oxidative metabolism, and slow-twitch contractile apparatus (40, 48). Similarly, activation of PPARδ in cultured skeletal muscle L6 myotubes and C2C12 cells increases the expression of genes related to oxidative metabolism (40, 50, 51). A complete roster of genes regulated by PPARδ in skeletal muscle is provided in Table 1.

PPARδ's regulation of metabolic and fiber type status has several physiological implications. First, the presence of an increased proportion of oxidative slow-twitch fibers is predicted to decrease skeletal muscle fatigability. For example, increased endurance in marathon runners is linked to a higher proportion of oxidative slow-twitch fibers in their skeletal muscles. Mice with muscle-specific VP16-PPARδ transgenes have strikingly higher treadmill endurance capacity, running twice as long and far as wild-type mice (48). Second, oxidative fibers have a tremendous impact on fatty acid homeostasis. Both obesity and insulin resistance are linked to a decrease in the proportion of oxidative slow-twitch fibers in skeletal muscle (52–56). Muscle-specific VP16-PPARδ transgenic mice, which have a higher proportion of oxidative slow-twitch fibers, are resistant to high-fat diet–induced obesity (48). Activation of PPARδ during high-fat feeding increases disposal of

lipid in skeletal muscles, preventing the storage of excess fat in adipocytes and weight gain (39, 40, 49). This metabolic remodeling of skeletal muscle may also be responsible for the insulin-sensitizing effects of PPARδ agonists in high-fat diet–induced and genetic models of obesity (39, 40). Interestingly, in vitro studies also show that PPARδ agonist treatment of cultured human skeletal muscle increases insulin-independent glucose uptake (57).

Given the important role of PPARδ in skeletal muscle, regulation of its activity by pre- and posttranslational modification is physiologically relevant. Luquet et al. demonstrated that endurance training with 3 weeks of swimming increases the expression of PPARδ mRNA and protein in rodent skeletal muscle (49). In addition, a single exhaustive bout of cycling increases PPARδ mRNA and protein expression within 3 hours after completion of exercise in humans (58, 59). Fasting also increases PPARδ expression in skeletal muscle, and it is proposed that PPARδ mediates the fasting-dependent rise in skeletal muscle fatty acid oxidation (60). To our knowledge, changes in the expression of muscle PPARδ during instances of positive energy balance, such as obesity, have not been measured. In addition to pretranslational modification, muscle PPARδ protein may be subject to posttranslational modifications, as multiple intracellular signaling molecules such as protein kinase A and MAPK phosphorylate PPARδ and increase its transcriptional activity in vitro (61–63). Like PPARδ, MAPK, calcium/calmodulin–dependent kinase, and adenosine monophosphate–activated protein kinase are each activated by exercise in skeletal muscle, and future work will be important to determine interconnections between these factors (64–66).

PPARδ action in cardiac muscle

Fatty acid oxidation is the primary source of energy in the postnatal heart (67). Impaired fatty acid oxidation and a shift to reliance on glucose metabolism are hallmarks of myocardial diseases such as cardiac hypertrophy and congestive heart failure (67). As in skeletal muscle, PPARδ is a critical regulator of fatty acid oxidation in cardiac tissue. Cheng et al. showed that cardiac-specific deletion of *PPAR*δ suppresses the expression of oxidative genes (68). This leads to impaired fatty acid oxidation and a reciprocal increase in glucose oxidation, along with fat accumulation in cardiomyocytes (68). Moreover, PPARδ-selective agonists increase fatty acid oxidation via the induction of oxidative genes in isolated neonatal as well as adult rat cardiomyocytes (69) (Table 1). The PPARδ-dependent maintenance of basal fatty acid oxidation is crucial for normal cardiac mechanics. *PPAR*δ-null hearts are characterized by decreased rates of contraction and relaxation, increased left ventricular end-diastolic pressure, and decreased cardiac output, factors associated with the onset of cardiac failure (68). Indeed, mice with cardiac-specific deletion of *PPAR*δ develop age-dependent cardiac lipotoxicity, cardiac hypertrophy, end-stage dilated cardiomyopathy, and decreased survival (68). The protective role of PPARδ in the heart has been confirmed by in vitro studies showing that PPARδ agonists attenuate phenylephrine-induced cardiac hypertrophy. While phenylephrine suppresses fatty acid oxidation in cardiomyocytes, concomitant activation of PPARδ reverses these effects (70). Although PPARδ may directly increase the transcription of fatty acid oxidative genes, at least 1 study suggests that effects could also be indirect. Planavila and colleagues showed that PPARδ interacts with and blocks NF-κB–mediated suppression of fatty acid oxidation in cardiomyocytes (71). PPARδ-dependent antagonism of NF-κB could be particularly important during sepsis, when endotoxins decrease cardiac fatty acid oxidation and initiate cardiac failure (71, 72).

PPARδ action in macrophage biology and atherosclerosis

Atherosclerosis is a chronic inflammatory process within the arterial wall that results from the interaction between modified lipoproteins, macrophages, T cells, ECs, and VSMCs (8). It is a major source of morbidity and mortality in the Western world, particularly for patients with the metabolic syndrome. Numerous studies have identified roles for the nuclear receptors PPARγ and liver X receptor-α/β in macrophage cholesterol homeostasis, inflammatory signaling, and atherosclerosis. Like these related receptors, PPARδ is expressed by macrophages, in which its functions and implications for atherosclerosis have been studied.

*Influence of PPAR*δ *on macrophage cholesterol homeostasis.* Macrophage cholesterol homeostasis is influenced by PPARγ and the liver X receptors, but whether PPARδ plays a role remains controversial. Oliver et al. showed that treatment of THP-1 human monocytes with the high-affinity agonist GW501516 increased the expression of *ABCA1*, a critical reverse cholesterol transporter, and doubled apoA-I–specific cholesterol efflux (33). Opposing these results, Vosper et al. found that treatment with a different PPARδ drug promoted lipid accumulation in human macrophages exposed to oxidized LDL or THP-1 cells exposed to serum (73). Although PPARδ ligand treatment increased apoA-I–specific cholesterol efflux, as reported by Oliver et al., total efflux was diminished (73). *ABCA1* was induced, but so too were the cholesterol uptake receptors *CD36* and *SR-A* and the lipid storage–related genes *AFABP* (*aP2*) and *adipophilin* (73). Moreover, the cholesterol efflux gene *apoE* was repressed (73). These aggregate effects were presumed to contribute to lipid accrual in human macrophages. Alternatively, Lee et al. reported that neither genetic loss of PPARδ nor treatment with the PPARδ agonist GW501516 influenced cholesterol efflux or accumulation in murine macrophages (13). Li et al. similarly demonstrated no overall effect of the PPARδ agonist GW0742 on mouse macrophage cholesterol accumulation, uptake, or apoA-I–dependent efflux, although slightly enhanced cholesterol degradation was observed (74). Taken together, these data suggest that PPARδ does not significantly affect macrophage cholesterol metabolism in the mouse, but additional work to decipher a potential contribution of PPARδ to human macrophage cholesterol metabolism is needed given the mixed reports described to date.

*Role of PPAR*δ *in atherogenic inflammation.* An in vivo role for PPARδ in atherosclerosis was first described using a genetic loss-of-function approach (13). Atherosclerosis-prone LDL receptor–null mice were transplanted with *PPAR*δ-deficient bone marrow and fed a high-cholesterol diet. After 8 weeks, vascular lesions in *PPAR*δ-null recipients were at least 50% smaller than those of wild-type recipient controls (13). There were no differences in cholesterol levels between experimental groups (13). However, *PPAR*δ-null macrophages expressed decreased levels of inflammatory mediators including *monocyte chemoattractant protein-1* (*MCP-1*), *IL-1*β, and *MMP-9*, while macrophages overexpressing PPARδ produced increased levels of inflammatory markers (13). Notably, PPARδ ligands inhibited inflammatory gene expression in wild-type macrophages, mimicking the suppressed inflammation elicited in *PPAR*δ-null cells. Binding studies identified an interaction between PPARδ and the inflammatory suppressor protein B cell lymphoma-6 (BCL-6), which is released from PPARδ in a ligand-dependent man-

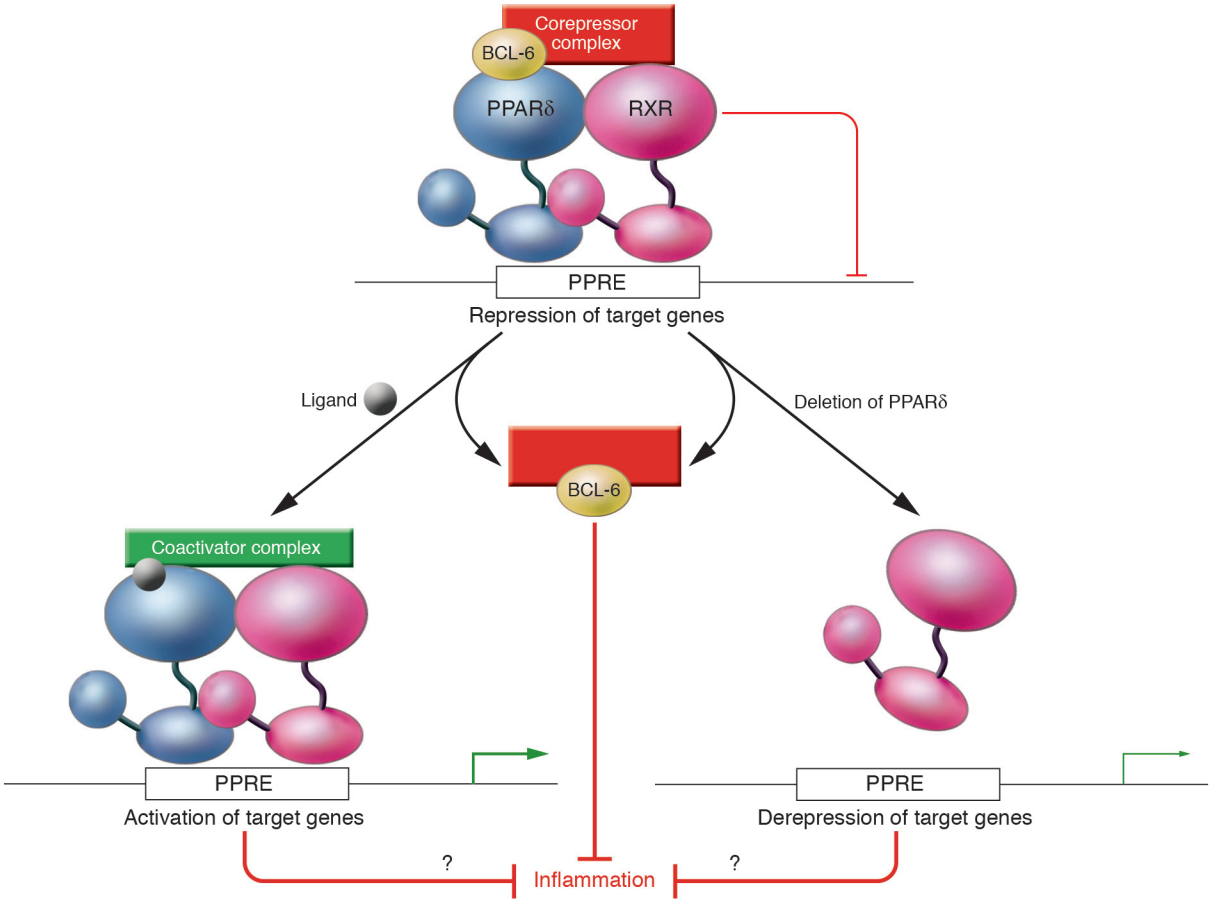


Figure 1

PPARδ: an inflammatory switch. In the absence of ligand, PPARδ-RXR heterodimers bind to consensus PPAR DNA response elements (PPREs) and repress target gene expression by recruiting corepressors and associated repressive proteins including B cell lymphoma-6 (BCL-6) (top). Upon addition of PPARδ ligand (bottom left), PPARδ-RXR heterodimers undergo a conformational shift. This dismisses the corepressor complex, including BCL-6, in exchange for a complex of coactivator proteins and results in enhanced PPARδ target gene expression. BCL-6, an inflammatory suppressor protein, is thereby liberated to repress inflammatory gene expression. Genetic deletion of PPARδ also releases BCL-6 and repressor complexes from PPARδ target gene promoters, rendering BCL-6 available to suppress inflammation (bottom right). It is unknown whether the expression of direct PPARδ target genes (bottom left and right) has antiinflammatory effects. Target gene expression may occur either by ligand-induced transcriptional activation (large green arrow) or more modestly by transcriptional derepression (small green arrow).

ner (13). Thus, genetic loss of PPARδ or the addition of PPARδ ligands frees a negative regulator of inflammation within the macrophage (13). This "inflammatory switch" model predicts that PPARδ ligands, as with genetic deletion of PPARδ, should ameliorate inflammation (Figure 1) (13). Whether direct genetic targets of PPARδ have antiinflammatory effects is unknown (Figure 1). Additional in vitro studies confirm that PPARδ ligands are antiinflammatory, suppressing the expression of LPS-induced proinflammatory genes, including iNOS and COX2 (13, 75).

PPARδ ligands as therapeutics for atherosclerosis. Whether PPARδ ligands are therapeutic for atherosclerosis remains controversial; ligand studies have yielded mixed results. To date, 2 published reports have examined the effects of PPARδ agonists in mouse models of atherosclerosis. In a study by Li et al., male *LDLR*$^{-/-}$ mice fed an atherogenic diet (containing 1.25% cholesterol) and treated with 5 mg/kg/d of the high-affinity PPARδ agonist GW0742 for 14 weeks had no significant changes in atherosclerotic lesion size. Despite this, serum triglyceride levels and vascular wall expression of inflammatory mediators including *IFN-γ*, *TNF-α*, *MCP-1*, *IL-1β*, *VCAM-1*, and *ICAM-1* were significantly diminished in drug-exposed animals (74). In contrast, Graham et al. reported that 16-week administration of GW0742 (6 or 60 mg/kg/d) to female *LDLR*$^{-/-}$ mice given an atherogenic diet (containing 0.25% cholesterol) inhibited atherosclerosis by approximately 30% (76). VLDL levels were significantly reduced in mice treated with lower doses of PPARδ agonist, but these changes were not recapitulated with the higher-dose regimen, and no other changes in serum lipid fractions were identified (76). As in the previously described study, Graham et al. found reduced expression of inflammatory genes including *MCP-1*, *TNF-α*, and *ICAM-1* within the aortae of PPARδ drug–treated mice (76). Serum levels of proinflammatory mediators including MCP-1, RANTES, IL-12, and soluble TNF-R1 were also suppressed in high-dose drug–treated animals (76). Compared with the study by Li et al., the efficacy achieved by Graham et al. could be due to use of higher drug doses, longer treatment duration, lower cholesterol supplementation, or female mice. It is possible that the antiatherosclerotic effects of PPARδ compounds require high doses, are more pronounced in advanced lesions or in the setting of modest

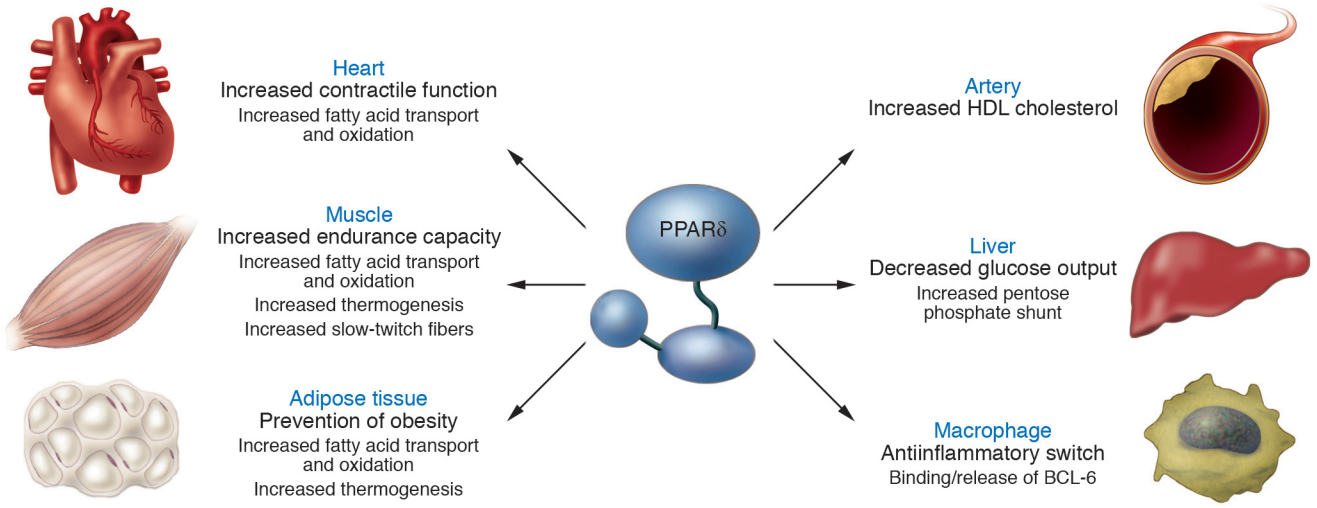


Figure 2
Therapeutic targets of PPARδ in the metabolic syndrome. Receptor activation improves multiple aspects of the metabolic syndrome through tissue- and cell-specific effects. In skeletal muscle, PPARδ regulates fatty acid transport and oxidation, thermogenesis, and the formation of slow-twitch muscle fibers, resulting in enhanced endurance performance. It likewise activates fatty acid transport and oxidation as well as thermogenesis in adipose tissue, retarding weight gain. PPARδ regulates the availability of BCL-6, an inflammatory suppressor protein released upon ligation of PPARδ, thereby functioning as an "antiinflammatory switch" to control macrophage-elicited inflammation and atherogenesis. In the liver, PPARδ activation suppresses glucose production by upregulating the pentose phosphate shunt. PPARδ activation also improves atherogenic dyslipidemia by raising serum HDL cholesterol levels via unclear mechanisms. Additionally, PPARδ activation in the heart enhances contractile function and may improve cardiomyopathy.

cholesterol exposure, or are exerted in a sexually dimorphic manner, accounting for the discrepancy among published studies in the *LDLR*$^{-/-}$ mouse model. Hence, PPARδ ligands have antiinflammatory effects in vivo, but whether this is generally sufficient to inhibit atherogenesis will require additional studies.

Conclusion

PPARδ has emerged as a powerful metabolic regulator in diverse tissues including fat, skeletal muscle, and the heart. Its transcriptional program enhances fatty acid catabolism and energy uncoupling, resulting in decreased triglyceride stores, improved endurance performance, and enhanced cardiac contractility (Table 1), respectively. PPARδ receptor activation mitigates macrophage inflammatory responses and modulates lipoprotein metabolism to lower triglycerides and robustly raise HDL cholesterol. Additionally, recent studies reveal that PPARδ activation in the liver suppresses hepatic glucose output, contributing to improved glucose homeostasis (77). These aggregate effects suggest that high-affinity PPARδ synthetic drugs may uniquely target multiple components of the metabolic syndrome, including obesity, insulin resistance, hyperglycemia, dyslipidemia, and atherosclerosis, or other diseases such as cardiomyopathy (Figure 2).

As with any drug anticipated for chronic use in the treatment of metabolic disease, safety issues about PPARδ-targeted compounds have been raised. Particular attention has focused on a potential connection to carcinogenesis, since *PPAR*δ was reported as a downstream target of the oncogenic Wnt/adenomatous polyposis coli (APC)/β-catenin pathway (78). A recent study disputes this connection, and further studies to decipher a role for PPARδ in cancer have been inconsistent (21, 79–82). Experiments using *PPAR*δ-null mice demonstrated that PPARδ is genetically dispensable for colon polyp formation in both the Apc^{min} genetic mutant and chemically induced colon cancer mouse models, and colon polyp formation was exacerbated in the genetic absence of PPARδ (21, 79, 80). Alternatively, xenografts of human colon cancer cells showed decreased tumorigenesis in cells somatically deleted of PPARδ, and treatment of Apc^{min} mice with high doses of the PPARδ ligand GW501516 yielded increases in the number and size of intestinal polyps (81, 82). Whether these ligand effects are truly dependent on PPARδ has not been established, and study using a *PPAR*δ-null background is warranted. It is notable that synthetic PPARγ agonists, which have been extensively used in human subjects, enhance colon polyp formation in the Apc^{min} model yet have not been demonstrated to cause cancer in humans (83, 84). Similarly, PPARα activators cause hepatocarcinomas in rodents but fail to have such deleterious effects in humans. These findings cast doubt on the predictive power of mouse models to determine the human carcinogenicity of PPAR-targeted drugs. Nevertheless, additional toxicology work will be required before PPARδ compounds can be marketed for chronic clinical use.

Despite significant strides in understanding PPARδ, a number of questions remain. For example, based on primate studies, PPARδ agonists may have unprecedented potential to raise low HDL cholesterol levels, a problem not well addressed by currently marketed drugs for lipid disorders (33). How PPARδ produces these effects remains unclear, but the development and study of tissue-specific receptor knockouts may yield valuable insight. Indeed, further study of PPARδ could lead to important advances in understanding HDL biogenesis. With regard to obesity, the potent ability of PPARδ to drive adaptive thermogenesis is clearly protective in rodents, but whether its ability to upregulate metabolism will be effective in humans as in mice will require clinical study. In fact, studies in humans suggest that thermogenesis may be a minor mechanism in the prevention of obesity, and physical

activity–related energy expenditure may have a dominant impact (85). This raises a parallel question of whether PPARδ agonists, as with constitutive genetic activation of PPARδ in skeletal muscle, can drive the formation of oxidative myofibers and enhance physical activity endurance. Could PPARδ drugs used in combination with exercise be a key strategy to increase physical activity–related energy expenditure and overcome the sedentary lifestyle and poor cardiorespiratory fitness considered by some as identifying features of the metabolic syndrome (86)? Further study to define the potential of PPARδ-targeted drugs to treat cardiovascular disease, given the mixed available experimental data, is also needed. Finally, PPARδ is expressed in the brain, liver, β cells, VSMCs, and endothelium, each of which has connections to the metabolic syndrome; yet its functions in each of these tissues and cell types are virtually unexplored (21, 22, 87, 88). Unquestionably, a great deal of research will be needed to understand the tissue-specific effects of this near-ubiquitous receptor and its full potential to impact the metabolic syndrome and other disorders.

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