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Regulation of Skeletal Muscle Physiology and Metabolism by Peroxisome Proliferator-Activated Receptor δ

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***Abstract*——Agonists directed against the α and γ isoforms of the peroxisome proliferator-activated receptors (PPARs) have become important for the respective treatment of hypertriglyceridemia and insulin resistance associated with metabolic disease. PPARδ is the least well characterized of the three PPAR isoforms. Skeletal muscle insulin resistance is a primary risk factor for the development of type 2 diabetes. There is increasing evidence that PPARδ is an important regulator of skeletal muscle metabolism, in particular, muscle lipid oxidation, highlighting the potential utility of this isoform as a drug target. In addition, PPARδ seems to be a key regulator of skeletal muscle fiber type and a possible mediator of the adaptations noted in skeletal muscle in response to exercise. In this review we summarize the current status regarding the regulation, and the metabolic effects, of PPARδ in skeletal muscle.**

I. Introduction

Skeletal muscle constitutes up to 50% of total body mass, making it the largest organ in the body. By sheer volume, skeletal muscle metabolism affects the metabolic budget of the whole organism. Indeed, skeletal muscle plays an important role in the regulation of electrolytes such as potassium (Clausen, 1986) and calcium (Levy, 1999), nutrients such as glucose (Sinacore and Gulve, 1993), and pH (Juel, 1996); in addition, it provides the largest reserve of protein (Rennie et al., 2004). The metabolic requirements of skeletal muscle are also highly variable—the working contracting muscle is a high consumer of ATP. Skeletal muscle metabolism is also under hormonal control. In the basal (fasting and resting) condition, approximately 80% of blood glucose is metabolized in an insulin-independent manner by the brain, gut, and red blood cells, whereas insulin-sensitive tissues (skeletal muscle and fat) require only small quantities. However, after insulin stimulation, skeletal muscle accounts for 75% of glucose utilization (DeFronzo et al., 1981; Baron et al., 1988; DeFronzo, 1988). Skeletal muscle is also a primary site of insulin resistance in the context of metabolic disease, in particular, type 2 diabetes and obesity (DeFronzo, 1988; Bouzakri et al., 2005).

Skeletal muscle is a uniquely plastic tissue and adapts in response to both use and disuse. In response to an increased work load (for example, high-resistance strength training), the muscle used will increase in both size and strength (Hawley and Zierath, 2004; Hawley and Holloszy, 2009). In contrast, muscle disuse (such as injury-induced immobilization or bed rest) results in muscle weakness and atrophy (Harridge, 2007). These responses are localized to the muscle performing the work (or the muscle that has been immobilized), highlighting the idea that local signals within the muscle are likely to be important for this regulation. In addition, systemic factors, including nutritional status and hormones, affect muscle size (Harridge, 2007; Rennie, 2007). Exercise training also leads to changes in the metabolic phenotype of the muscle. In response to endurance exercise, the number of mitochondria in muscle increases (Holloszy and Booth, 1976; Holloszy and Coyle, 1984), resulting in an increased capacity of the muscle to sustain aerobic metabolism. In parallel with the increased number of mitochondria, exercise training also leads to increased expression of the insulin-sensitive glucose transporter, GLUT4. Trained muscle derives more of the energy required from fat and less from carbohydrate compared with untrained muscle during submaximal work (work performed below the maximal oxygen utilization capacity). A detailed understanding of the molecular regulation of skeletal muscle metabolism may reveal novel therapeutic targets in the treatment of metabolic disorders. The purpose of this review is to highlight the role that the nuclear receptor PPARδ plays in skeletal muscle.

II. Peroxisome Proliferator-Activated Receptor Family

PPARs[1] are ligand-dependent nuclear receptors that belong to the superfamily of nuclear transcription factors. These transcription factors share structural and functional similarities; to date, the superfamily consists of 48 members in humans and 49 in mice (Bookout et al., 2006). PPARδ, also known as PPARβ or NR1C2, is one of three PPAR isotypes that together constitute group C in subfamily 1 of the superfamily of nuclear receptors (Nuclear Receptors Nomenclature Committee, 1999). The other two members are PPARα or NR1C1 and PPARγ or NR1C3. The PPARs share a high degree of functional and structural similarities, but they are encoded by distinct single-copy genes located on different chromosomes. The human *PPARD* is located at chromosomal region 6p21.2-p21.1 and consists of nine exons (Skogs-

[1] Abbreviations: AMPK, AMP-activated protein kinase; bezafibrate, 2-(4-{2-[(4-chlorobenzoyl)amino]ethyl}phenoxy)-2-methylpropanoic acid; BMI, body mass index; clofibrate, ethyl 2-(4-chlorophenoxy)-2-methylpropanoate; FABP, fatty acid-binding protein; fenofibrate, propan-2-yl 2-{4-[(4-chlorophenyl)carbonyl]phenoxy}-2-methylpropanoate; gemfibrozil, 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid; GW0742, 4-[2-(3-fluoro-4-trifluoromethyl-phenyl)-4-methyl-thiazol-5-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid; GW501516, 2-[2-methyl-4-([4-methyl-2-[4-(trifluoromethyl)phenyl)-1,3-thiazol-5-yl]methylsulfanyl]phenoxy]acetic acid; GW610742X, 3-(4-(3-(4-chloro-2-phenoxyphenoxy)butoxy)-2-ethylphenyl)propionic acid; GWAS, genome-wide association studies; HDL, high-density lipoprotein; L-165041, [4-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenoxy]acetic acid; LBD, ligand-binding domain; MAFbx, muscle atrophy F-box; MBX-8025, {2-methyl-4-[5-methyl-2-(4-trifluoromethyl-phenyl)-2*H*-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid; MHC, myosin heavy chain; MuRF1, muscle ring finger 1; PDC, pyruvate dehydrogenase complex; PDK, pyruvate dehydrogenase kinase; PGC1α, PPARγ coactivator 1α; PPAR, peroxisome proliferator-activated receptors; PPRE, peroxisomal proliferator response element; RA, retinoic acid; RXR, retinoid X receptor; SMRT, silencing mediator for retinoic acid and thyroid hormone receptor; SNP, single-nucleotide polymorphism.

berg et al., 2000), whereas the human *PPARA* comprises eight exons and is localized at chromosomal region 22q12-q13.1 (Sher et al., 1993; Auboeuf et al., 1997). The human *PPARG* has nine exons and is located on chromosome 3p25 (Fajas et al., 1997). PPARγ is the only PPAR that has two distinct full-length translated isoforms (Fajas et al., 1997). However, several splice variants, including truncated dominant-negative isoforms, have been detected for the three PPARs, the physiological roles of these splice variants need to be further elucidated (Fajas et al., 1997; Palmer et al., 1998; Gervois et al., 1999; Chew et al., 2003; Sabatino et al., 2005; Kim et al., 2006; Lundell et al., 2007).

A. Tissue Distribution

PPARδ is ubiquitously expressed and acts as an important nutritional metabolic sensor and regulator (Barish et al., 2006). Mice lacking PPARδ from genetic ablation have a number of developmental abnormalities. These include placental defects resulting in fewer births than would be expected by mendelian ratio, decreased adipose mass, defective myelination, and altered inflammatory responses (Peters et al., 2000; Tan et al., 2001; Barak et al., 2002). PPARδ has also been demonstrated to be involved in many different biological activities such as lipid and lipoprotein metabolism (Leibowitz et al., 2000; Oliver et al., 2001; Sprecher et al., 2007; Risérus et al., 2008), skeletal muscle lipid oxidation (Wang et al., 2004), inflammation (Tan et al., 2001), neuronal differentiation (Saluja et al., 2001; Cimini et al., 2003), mitochondrial respiration (Luquet et al., 2003; Wang et al., 2004), thermogenesis (Guardiola-Diaz et al., 1999), determination of skeletal muscle fiber type (Wang et al., 2004), keratinocyte differentiation, and wound healing (Tan et al., 2004). PPARα is mainly expressed in the liver, kidney, heart, and skeletal muscle, where high amounts of fatty acids are metabolized (Abbott, 2009). PPARγ is primarily expressed in adipose tissue promoting adipogenesis and lipid storage, but it is also expressed in the intestine and macrophages (Tontonoz et al., 1994; Lehrke and Lazar, 2005; Abbott, 2009).

In this review, we limit our scope to PPARδ-mediated effects in skeletal muscle. In skeletal muscle, PPARδ has a higher expression than PPARα, PPARγ expression being very low (Braissant et al., 1996; Muoio et al., 2002; de Lange et al., 2004). PPARδ also shows a higher expression in oxidative type I muscle fibers compared with glycolytic type II muscle fibers (Wang et al., 2004).

B. Peroxisome Proliferator-Activated Receptor Structure and Function

PPARs are predominantly nuclear and regulate transcription by heterodimerizing with the retinoid X receptor (RXR) as shown in Fig. 1. The receptor complex binds to a peroxisomal proliferator response element (PPRE) located in the regulatory region of a gene and binds to DNA in the absence of ligands (Feige et al., 2005). The heterodimer is permissive because it can activate transcription in response to only one ligand binding to its specific receptor (i.e., either 9-*cis*-retinoic acid or a PPAR ligand), but activation by both ligands results in an enhanced induction of gene expression (Kliewer et al., 1992). The PPRE consists of two direct repeats of the consensus sequence AGGTCA separated by a single nucleotide, which constitutes a DR-1 motif (Kliewer et al., 1992). Functional PPREs are typically located in the promoter or other regulatory regions of target genes, but it has been reported that PPREs can be located in the

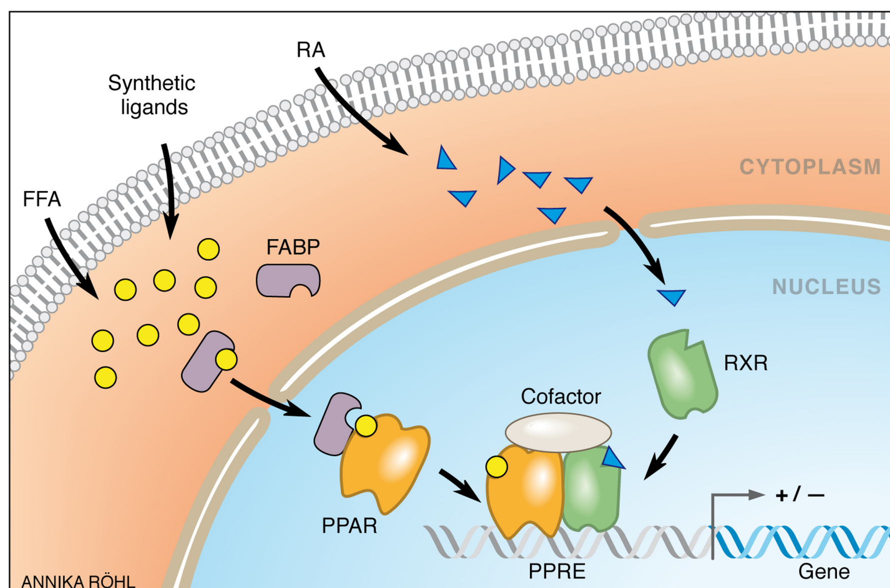

FIG. 1. PPARδ structure and function. PPARδ forms a heterodimer with the RXR and regulates the transcription of genes harboring a PPAR response element. Effects are further modified by specific interactions with cofactors. FABPs may bind and deliver ligands to PPARδ. A number of possible ligands are depicted, including free fatty acids (FFA), synthetic ligands, and the RXR ligand RA.

5′-transcribed region of specific target genes (Kim and Ahn, 2004). PPAR binds 5′ of RXR on the DR-1 motif and the 5′-flanking sequence conveys the selectivity of binding between different PPAR isotypes (Juge-Aubry et al., 1997). Functional PPREs have been found in regulatory regions of genes involved in lipid and glucose homeostasis, inflammation, wound healing, cell proliferation, and differentiation.

The PPAR receptors have four functional domains: A/B, C, D, and E/F (Fig. 2). The N-terminal A/B domain contains a ligand-independent activation function. This region is not well conserved between the PPAR isotypes. The C domain comprises the DNA binding region, which is highly conserved among the PPARs, and it consists of two zinc-finger-like structures with α-helical DNA binding motifs. The D domain includes the hinge region, which is important regarding interaction with cofactors and preservation of the functional structure of the nuclear receptor (Dowell et al., 1997; Miyamoto et al., 2001; Tomaru et al., 2006). The well-conserved E/F domain consists of the ligand-binding domain (LBD) including the ligand-dependent activation function (AF-2). This region is important for RXR heterodimerization and interaction with coactivators (Nolte et al., 1998; Schulman et al., 1998). The LBD is composed of 13 α-helices and a small four-stranded β-sheet forming a very large Y-shaped cavity that is mainly hydrophobic. The cavity of the PPARs is larger than those found in other nuclear receptors, and the entrance of the binding pocket is very flexible, which might explain the ability to bind a range of endogenous and synthetic lipophilic ligands (Nolte et al., 1998; Uppenberg et al., 1998; Xu et al., 1999; Cronet et al., 2001). Hydrogen bonds between the AF-2 helix and carboxylate groups of endogenous or synthetic ligands are formed whereby the AF-2 helix is folded against the LBD and stabilized, thus enabling binding of coactivator proteins. This conformational change results in release of corepressor proteins that inhibit transcriptional activation (Dowell et al., 1999).

C. Ligands

Ligands that activate PPARs are all long-chain fatty acids or their derivatives, as well as specific synthetic compounds (Xu et al., 1999; Gervois et al., 2007). Endogenous substances that can activate PPAR include eicosanoids, leukotrienes, and prostaglandins, but the vitamin A metabolite retinoic acid has also been shown to be a ligand for PPARδ (Yu et al., 1995; Schug et al., 2007). Other endogenous substances that are able to act as PPAR ligands include 8(*S*)-hydroxyeicosatetraenoic acid and leukotriene B4, whereas 9-hydroxy-10,12-octadecadienoic acid, 13-hydroxy-9,11-octadecadienoic acid, and 15Δ-deoxy-12,14-prostaglandin J_2 activate PPARγ (Forman et al., 1995; Kliewer et al., 1995; Devchand et al., 1996; Kliewer et al., 1997; Nagy et al., 1998; Lin et al., 1999). Whether any of these metabolites is a physiologically relevant PPAR activator in vivo is still not clear.

Synthetic ligands with high specificity for each of the three PPAR isotypes have been developed. Different fibrate compounds such as gemfibrozil, bezafibrate, clofibrate, and fenofibrate are PPARα-specific agonists. Fibrates primarily lower the plasma triglyceride concentrations and are used to treat dyslipidemia and cardiovascular disease (Fruchart et al., 1999). Thiazolidinediones are potent and specific PPARγ ligands that are used as antidiabetic drugs. The thiazolidinediones delay the onset of type 2 diabetes because of their ability to reduce insulin resistance and ectopic fat accumulation (Lehmann et al., 1995; Mayerson et al., 2002; Gerstein et al., 2006). Regarding PPARδ-specific agents, no compounds are in clinical use, but two studies in humans have recently been published (Sprecher et al., 2007; Risérus et al., 2008) and are discussed in section IV.A.

PPAR selectivity for different endogenous ligands is determined by several factors. Comparing the the three-dimensional structures of the LBD reveals that PPARδ has the smallest cavity of the PPAR isotypes. Ligand specificity is determined by the shape complementarity between the cavity and the ligand (Xu et al., 2001).

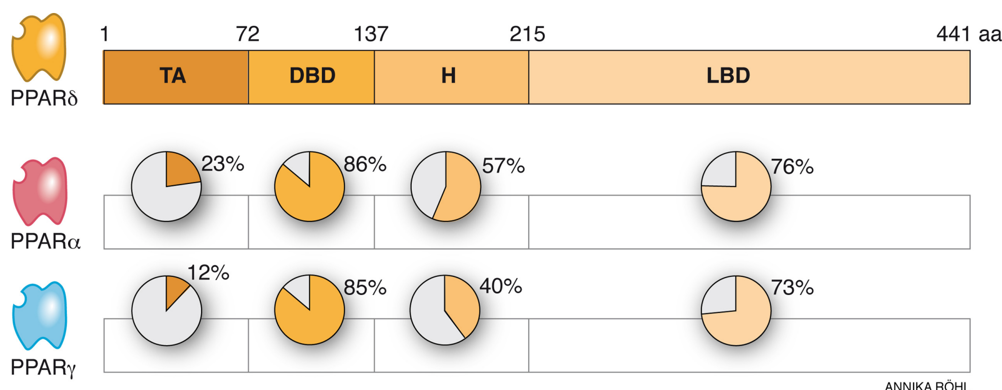

FIG. 2. Schematic representation of the functional domains in PPARs and similarity between isoforms. The N-terminal A/B domain contains ligand-independent transcriptional activation (TA). The C domain is the DNA binding domain (DBD). The D domain includes the hinge (H) region. The E/F domain consists of the LBD, including the ligand-dependent activation function, and RXR interaction.

Thus, a difference of a single amino acid in the PPARs has a remarkable impact on ligand selectivity. Because PPARs are bound to DNA, they need to have their ligands delivered to the nucleus. These transport mechanisms are poorly understood, but it has been shown that fatty acid-binding proteins (FABPs) can transport the ligands to specific PPARs (Fig. 1). The unliganded FABPs are cytosolic, but upon binding they are transferred to the nucleus and associated with a specific PPAR. FABP5 transfers ligands to PPARδ, whereas FABP3 and FABP4 shuttle them to PPARα and PPARγ, respectively (Tan et al., 2002; Schug et al., 2007). Although the FABPs bind various lipid metabolites with similar affinities, only a few specific ligands induce their nuclear localization depending on whether they can activate a specific PPAR (Gillilan et al., 2007). The importance of intracellular lipid binding proteins has been shown by studies of retinoic acid (RA). RA activates not only the RA receptor, which cooperates with cellular retinoic acid-binding protein II, but also can activate PPARδ, which cooperates with FABP5. In cells that express a high FABP5/cellular retinoic acid-binding protein II ratio, RA preferentially activates PPARδ despite similar RA receptor and PPARδ expression levels, and the much lower affinity of the latter (Schug et al., 2007).

D. Cofactors

The PPARs require cofactors that modify and alter the chromatin structure to influence the transcriptional activity. These coregulators are called corepressors when they suppress and coactivators when they enhance transcription of target genes. In addition, coactivator-associated proteins also exist that directly interact with coactivators and not with the nuclear receptors. More than 200 nuclear receptor coregulators (coactivators, corepressors, and coactivator-associated proteins) have been identified thus far. The extent to which a given cofactor regulates a specific nuclear receptor remains unclear (Feige and Auwerx, 2007; Yu and Reddy, 2007). One of the best described cofactors in this respect is the transcriptional coactivator PPARγ coactivator 1α (PGC1α) (Lin et al., 2005). PGC1α binds to and coactivates most members of the nuclear receptor family, including PPARδ. Overexpression of PGC1α in skeletal muscle (Lin et al., 2002) leads to effects on muscle metabolism similar to those of overexpression of an activated form of PPARδ (Wang et al., 2004) (see discussion on fiber types in section III.A). The precise interaction between PPARδ and PGC1α remains to be clarified. PGC1α has been shown to synergistically coactivate PPARδ target genes in a PPARδ-ligand-dependent manner (Kleiner et al., 2009). Activation of PPARδ in skeletal muscle reportedly leads to increased PGC1α protein (Hancock et al., 2008). The interaction between PGC1α and PPARδ is further modulated by the transcriptional regulator Twist-1 in adipose cells (Pan et al., 2009), but whether this is also the case in skeletal muscle remains to be determined.

Silencing mediator for retinoic acid and thyroid hormone receptor (SMRT) and the nuclear receptor corepressor are corepressors that interact with the PPARs in the absence of ligands (DiRenzo et al., 1997; Zamir et al., 1997). PPARδ is the only PPAR that associates with these corepressors when bound to DNA (Krogsdam et al., 2002). It has been shown that PPARδ can repress PPARα- and PPARγ-activated transcription by interaction with SMRT, histone deacetylases, and SMRT and histone deacetylase-associated repressor proteins (Shi et al., 2002). Another ligand-dependent corepressor is RIP140, which interacts with many nuclear receptors including PPARs. RIP140 plays an important role in regulating metabolic processes in the myocytes, hepatocytes, and adipocytes (White et al., 2008). In skeletal muscle, reduction of RIP140 enhances expression of PPARδ-dependent genes involved in mitochondrial activity and fiber-type determination (Seth et al., 2007).

The corepressors possess or recruit histone deacetylases or other enzyme activities to keep a tight chromatin structure to repress gene transcription. When agonists bind to the receptors, coactivators are recruited. Coactivators are large proteins that contain one or more nuclear receptor boxes consisting of the conserved LXXLL (L, leucine; X, any amino acid) amphipathic α-helix consensus sequence that interacts with the AF-2 region in the PPARs. There are two different groups of coactivators: one group that possesses histone acetyltransferase or methyl transferase activities that remodel the chromatin structure and another group that enhances transcriptional activity by creating multiprotein complexes that form bridges between the nuclear receptors and the basal transcriptional machinery (Glass and Rosenfeld, 2000). Examples of the former group that interacts with PPARδ include members of steroid hormone receptor coactivator family and PGC1α (Wang et al., 2003; Lim et al., 2004; Yu and Reddy, 2007). The PPAR-binding protein belongs to the latter group of coactivator proteins that has been shown to bind to PPARδ (Lim et al., 2004).

Taken together, the in vivo regulation of PPARδ during different conditions probably depends on the complex interplay between expression levels of the three PPARs and RXR isotypes; affinity for a specific PPRE, ligand, and cofactor availability; and possibly the binding of other transcription factors in the vicinity of the PPRE.

E. Regulation of Peroxisome Proliferator-Activated Receptor δ by Phosphorylation

Phosphorylation has been reported to alter transcriptional activity of both PPARα and PPARγ (Burns and Vanden Heuvel, 2007). Insulin increases serine phosphorylation of PPARα (Shalev et al., 1996) and PPARγ (Zhang et al., 1996) via mitogen-activated protein kinase. Increased phosphorylation of PPARα has been reported in response to activators of protein kinase A

(Lazennec et al., 2000). Although similar phosphorylation sites are found in PPARδ, the functional role of these sites has not yet been investigated.

F. Regulation of Peroxisome Proliferator-Activated Receptor δ Expression in Skeletal Muscle

As mentioned in section II.A, PPARδ is the most abundant PPAR isoform in skeletal muscle (Braissant et al., 1996; Muoio et al., 2002; de Lange et al., 2004) and has a higher expression in oxidative type I muscle fibers compared with glycolytic type II muscle fibers (Wang et al., 2004). A number of different physiological and pathological factors have been reported to influence skeletal muscle PPARδ content (Table 1). Both short-term exercise (Watt et al., 2004; Mahoney et al., 2005) and endurance training (Russell et al., 2003; Fritz et al., 2006) lead to increased PPARδ expression in human and rodent skeletal muscle (Table 1). A short period of muscle unloading (mimicking disuse such as bed rest) was also associated with increased PPARδ mRNA content (Mazzatti et al., 2008). This increase was noted after 1 day of hind-limb unloading and had returned to control levels after 12 days, leading the authors to speculate that the increased expression of PPARδ after unloading represents an adaptive, stress-induced response to prevent further metabolic consequences (Mazzatti et al., 2008), which is not maintained after longer-term muscle unloading. Indeed, skeletal muscle PPARδ mRNA content is reduced in the skeletal muscle of subjects with a long-standing spinal cord injury (Krämer et al., 2006).

PPARδ also seems to be under nutritional control. Given the central role of PPARδ in controlling skeletal muscle lipid utilization, fasting, which results in a greater reliance on fatty acids, would be expected to increase PPARδ expression and/or activity. In line with this, a 6-, 24-, or 48-h starvation period results in a dramatic up-regulation of PPARδ mRNA in gastrocnemius muscle of mice (de Lange et al., 2006), which is restored to control level upon refeeding (Holst et al., 2003). In contrast, 12-h fasting in rats did not alter PPARδ mRNA expression in skeletal muscle (but led to reduced PPARδ expression in kidney and liver) (Escher et al., 2001). It is intriguing that down-regulation of human skeletal muscle PPARδ mRNA expression has been reported in healthy human subjects after a 48-h fast (Tsintzas et al., 2006), but data from shorter food deprivation times in humans are lacking. Thus, it seems likely that after food deprivation, there is a rapid but transient increase in skeletal muscle PPAR expression. This correlates with a rapid nuclear accumulations of PPARδ and the coactivator PGC1α after food deprivation (de Lange et al., 2006), which would subsequently lead to PPARδ-mediated changes in genes regulating fatty acid metabolism.

Exercise training and fasting both lead to increased free fatty acids, making elevated fatty acids an attractive physiological signal regulating skeletal muscle PPARδ content. However, endurance exercise performed either in the fasted state (when fatty acids are high) or after carbohydrate ingestion (avoiding an increase in fatty acids) resulted in similar increases in skeletal muscle PPARδ mRNA expression, suggesting that contraction per se is the more important regulator (Russell et al., 2005). Indeed, suppression of free fatty acids (using the antilipolytic drug nicotinic acid) actually increased mRNA expression of skeletal muscle PPARδ (Watt et al., 2004). Furthermore, skeletal muscle PPARδ mRNA expression is reduced in subjects with spinal cord injury (Krämer et al., 2006), a condition associated with elevated circulating free fatty acids. Incubation of cultured cells with different long-chain fatty acids, including palmitate, linoleate, and linolenate, have been reported to be without effect on PPARδ mRNA expression (Holst et al., 2003). A number of additional stimuli have also been reported to be without effect on PPARδ expression. These include isoproterenol, isobutyl methylxanthine, stable analogs of cyclic AMP, dexamethasone, cortisol, tri-iodothyronine, insulin in muscle cell cultures (Holst

TABLE 1

Factors regulating in vivo skeletal muscle PPARδ expression

Factor	Comments	Effect	System	Reference
Acute exercise bout	Cycling exercise	↑	Human vastus lateralis	Watt et al., 2004; Mahoney et al., 2005; Russell et al., 2005
Exercise training	3 and 6 weeks of exercise training	↑	Tibialis anterior, mouse	Luquet et al., 2003
	6 weeks of endurance training	↑	Human vastus lateralis	Russell et al., 2003
	4 months of moderate walking exercise	↑	Human vastus lateralis	Fritz et al., 2006
Inactivity	1-day muscle hind limb unloading	↑	Mouse soleus	Mazzatti et al., 2008
	12-day muscle hind limb unloading	↔	Mouse soleus	Mazzatti et al., 2008
Lipids	Reduction in circulating lipids using nicotinic acid	↑	Human vastus lateralis	Watt et al., 2004
Fasting	6-h fast	↑	Rat skeletal muscle	de Lange et al., 2006
	48-h fast	↔	Rat skeletal muscle	de Lange et al., 2006
	12-h fast	↔	Rat skeletal muscle	Escher et al., 2001
	24-h fast	↑	Mouse gastrocnemius muscle	Holst et al., 2003
	48-h fast	↓	Human vastus lateralis	Tsintzas et al., 2006
Age	Increasing age	↓	Human vastus lateralis	Nilsson et al., 2007
Pathology	Chronic obstructive pulmonary disease	↓	Human quadriceps femoris	Remels et al., 2007
	Spinal cord injury	↓	Human vastus lateralis	Krämer et al., 2006

↑, increase; ↓, decrease; ↔, no change.

et al., 2003), and in vivo insulin infusion during a 2-h hyperinsulinemic euglycemic clamp (Nilsson et al., 2007). Thus, the physiological signals regulating the effects of nutritional status, and muscle use, remain to be identified. To date, the majority of data regarding regulation of PPARδ expression has relied on determination of mRNA, and it is possible that a clearer understanding will emerge as better antibodies allow reliable assessment of PPARδ protein content and, more importantly, the activation status of PPARδ. Thus, it may be that presence of activating ligand is a more important physiological regulator than changes in total PPARδ content.

Although the data regarding the effect of fatty acids on PPARδ expression are conflicting, circulating fatty acids are important regulators of PPARδ activity. Again, the precise nature of this regulation remains unresolved. Recent data indicate that the fatty acid transporter CD36 may facilitate entry of PPARδ ligands (Nahlé et al., 2008). Because CD36 is itself a target gene of PPARδ (Table 2), this would lead to a positive feedback to amplify PPARδ effects in the presence of activating ligand (Fig. 3).

Skeletal muscle PPARδ expression has been reported to decline with age (Nilsson et al., 2007). In line with a physiological role for PPARδ in enhancing lipid utilization, increased central adiposity was negatively correlated to skeletal muscle PPARδ mRNA (Nilsson et al., 2007). Birth weight was found to be positively correlated to adult mRNA expression of skeletal muscle PPARδ (Nilsson et al., 2007). Taken together, these data suggest that skeletal muscle PPARδ plays an important role in the regulation of whole-body metabolism.

III. Regulation of Skeletal Muscle Metabolic Phenotype and Fiber Types

A. Skeletal Muscle Fiber Types

Skeletal muscle is classified into different fiber types that have different metabolic and ergogenic characteristics. Skeletal muscle has traditionally been classified by physical appearance (that is, red and white) in recognition of the fact that this correlated with contractile properties ("slow" or "fast," respectively) (Brooke and Kaiser, 1970; Spangenburg and Booth, 2003). The speed of muscle movement primarily depends on which isoform of myosin heavy chain (MHC) that is expressed in the muscle fiber (for review, see Harridge, 2007). In human skeletal muscle, there are three isoforms of MHC: MHC-I, MHC-IIa, and MHC-IIx (rodents express IIb), in order of increasing speed of contraction. Skeletal muscle is thus usually classifies as type (MHC) I "slow-red" and type IIa "fast red." So-called fast white muscles are categorized as IIx in humans and IIx and IIb in rodents (Spangenburg and Booth, 2003). These classifications are also coupled to the metabolic profile of the muscle fibers, with oxidative slow-twitch fibers containing more mitochondria than the fast-twitch glycolytic fibers (Schiaffino and Serrano, 2002; Spangenburg and Booth, 2003). In addition to increased mitochondrial content, insulin-stimulated glucose transport is also greater in slow-twitch muscle fibers than in fast-twitch glycolytic fibers, in part because of increased expression of glucose transporters and insulin signaling intermediates (Henriksen et al., 1990; Song et al., 1999; Daugaard et al., 2000). Furthermore, because whole-body insulin sensitivity is positively correlated with the proportion of slow-twitch oxidative fibers in humans (Lillioja et al., 1987), interest has focused on understanding the molecular regulation of muscle fiber types with the aim of using these targets to enhance insulin sensitivity.

B. Peroxisome Proliferator-Activated Receptor δ Is a Key Gene in the Regulation of Skeletal Muscle Fiber Types

The use of transgenic animals has given important insights into the molecular regulation of skeletal muscle fiber types. One of the first genes to be implicated as important for fiber-type regulation was PGC1α. Targeted muscle expression of PGC1α in mice resulted in a conversion of muscles normally rich in type II fibers to a slower oxidative type I muscle phenotype (Lin et al., 2002). In a similar manner, PPARδ was also shown to play a key role in the development of oxidative type I fibers. Transgenic mice with targeted skeletal muscle overexpression of either the wild type (Luquet et al., 2003) or an activated form (Wang et al., 2004) of the PPAR gene have an increased proportion of type I muscle. Furthermore, mice with reduced expression (null or heterozygous) of the RIP140 corepressor have increased formation of type I muscle fibers, whereas transgenic overexpression reduces type I muscle fibers (Seth et al., 2007). Thus, increased expression of PPARδ or its coactivator PGC1α, or the reduction of the RIP140 corepressor, enhances formation of type I fibers, suggesting a key role for alterations in PPARδ activity in the regulation of muscle fiber type. Indeed, mice in which PPARδ has been selectively ablated from muscle have fewer type I muscle fibers (Schuler et al., 2006). These PPARδ-ablated mice also have reduced skeletal muscle expression of PGC1α, suggesting that PPARδ may regulate at least the basal expression of one of its own important cofactors (Schuler et al., 2006).

It is important to keep in mind that fiber-type regulation in transgenic animals is a result of changed mRNA expression during actual muscle development. Whether similar processes are involved in fiber-type regulation in mature muscle remains to be determined. Although the PPARδ/PGC1α-dependent signals seem to play important roles in the induction/maintenance of slow oxidative type I fibers, other regulators have also been implicated. These include, for example, the phosphatase calcineurin (Chin et al., 1998; McCullagh et al., 2004). However, pharmacological inhibition of cal-

TABLE 2
Genes regulated by PPARδ in skeletal muscle

Gene	Effect	Comment	System	Reference
ABCA1	↑	Pharmacological activation	Cultured human muscle	Sprecher et al., 2007
ACADL	↑	Pharmacological activation	Rat muscle	Jucker et al., 2007
ACSL4	↑	Pharmacological activation	Rat muscle	Jucker et al., 2007
ADFP	↑	Pharmacological activation	C2C12 myotubes	Wang et al., 2003
Angiopoietin-like protein 4	↑	Pharmacological activation Long-chain fatty acids	Rat muscle Cultured human muscle C2C12 myotubes	Jucker et al., 2007; Staiger et al., 2009
COX II	↑	Constitutively active PPARδ	Mouse muscle	Tanaka et al., 2003; Wang et al., 2004
COX IV	↑	Constitutively active PPARd Pharmacological activation	Mouse muscle	Wang et al., 2004
m-CPT1	↑	Constitutively active PPARd Pharmacological activation	Mouse muscle Cultured primary mouse muscle Cultured human muscle C2C12 myotubes Rat muscle Human vastus lateralis (in vivo)	Muoio et al., 2002; Dressel et al., 2003; Tanaka et al., 2003; Wang et al., 2004; Jucker et al., 2007; Krämer et al., 2007; Sprecher et al., 2007; Narkar et al., 2008; Risérus et al., 2008; Kleiner et al., 2009
Cytochrome C	↑	Constitutively active PPARδ	Mouse muscle	Tanaka et al., 2003; Wang et al., 2004
FABP3	↑	Pharmacological activation Overexpression of PPARδ	Cultured human muscle Mouse muscle C2 C12 myotubes	Dressel et al., 2003; Luquet et al., 2003; Krämer et al., 2007; Seth et al., 2007
FAT/CD36	↑	Pharmacological activation Overexpression of PPARδ	C2C12 myotubes Cultured human muscle	Dressel et al., 2003; Holst et al., 2003; Sprecher et al., 2007
FoxO1	↑	Overexpression of PPARδ	C2C12 myotubes	Nahlé et al., 2008
H-FABP	↑	Pharmacological activation Overexpression of PPARδ	C2C12 myotubes	Holst et al., 2003
GLUT4/SLC2A4	↓	Pharmacological activation	Rat muscle	Jucker et al., 2007
IMPA2	↑	Pharmacological activation	Rat muscle	Jucker et al., 2007
LPL	↑	Pharmacological activation	C2C12 myotubes	Dressel et al., 2003
MAFbx	↑	Pharmacological activation	In vivo rat muscle	Constantin et al., 2007
Malonyl-CoA decarboxylase	↑	Pharmacological activation	Cultured human muscle	Muoio et al., 2002
MuRF1	↑	Pharmacological activation	In vivo rat muscle	Constantin et al., 2007
Myf5	↑	Pharmacological activation	In vivo mouse muscle	Gaudel et al., 2008
MyoD1	↑	Pharmacological activation	In vivo mouse muscle	Gaudel et al., 2008
Myoglobin	↑	Constitutively active PPARδ	In vivo mouse muscle	Tanaka et al., 2003; Wang et al., 2004
SCD1	↑	Pharmacological activation	C2C12 myotubes	Dressel et al., 2003
SCD2	↑	Pharmacological activation	C2C12 myotubes	Dressel et al., 2003
SREBP1c	↑	Pharmacological activation	C2C12 myotubes	Dressel et al., 2003
PECAM1	↑	Pharmacological activation	In vivo mouse muscle	Gaudel et al., 2008
PEPCK	↓	Pharmacological activation	Mouse muscle	Chen et al., 2008
PDK2	↑	Pharmacological activation	Cultured human muscle In vivo rat muscle	Abbot et al., 2005; Constantin et al., 2007
PDK4	↑	Pharmacological activation Overexpression	Cultured human muscle Mouse muscle C2C12 myotubes Rat muscle	Muoio et al., 2002; Dressel et al., 2003; Tanaka et al., 2003; Abbot et al., 2005; Constantin et al., 2007; Jucker et al., 2007; Krämer et al., 2007; Sprecher et al., 2007; Narkar et al., 2008; Kleiner et al., 2009
Troponin I	↑	Constitutively active PPARd Pharmacological activation	Mouse muscle	Tanaka et al., 2003; Wang et al., 2004
UCP2	↑	Constitutively active PPARd Pharmacological activation	Cultured human muscle Rat muscle Mouse muscle	Chevillotte et al., 2001; Wang et al., 2004; Jucker et al., 2007; Chen et al., 2008
UCP3	↑	Constitutively active PPARd Overexpression Pharmacological activation	Cultured human muscle Rat muscle C2C12 cells Mouse muscle	Son et al., 2001; Muoio et al., 2002; Wang et al., 2004; Jucker et al., 2007; Narkar et al., 2008; Kleiner et al., 2009
VEGF-A	↑	Pharmacological activation	In vivo mouse muscle	Gaudel et al., 2008

↑, increase; ↓, decrease; ↔, no change; ABCA1, ATP-binding cassette transporter protein-A1; ACADL, Acyl-CoA dehydrogenase long chain, ACSL4, acyl-CoA synthetase long-chain family member 4; ADFP, adipocyte differentiation-related protein; COX, cytochrome oxidase; m-CPT1, muscle carnitine palmitoyltransferase 1; IMPA2, inositol(*myo*)-1(or 4)-monophosphatase 2; FABP3, fatty acid binding protein 3; H-FABP, heart fatty acid binding protein; LPL, lipoprotein lipase; PEPCK, phosphoenolpyruvate carboxykinase; PDK4, pyruvate dehydrogenase kinase 4; SCD, stearoyl CoA desaturase; UCP, uncoupling protein; VEGF-A, vascular endothelial growth factor A.

cineurin by cyclosporin A results in impaired PPARδ-mediated induction of changes in myofiber metabolic phenotype (Gaudel et al., 2008), indicating a cross-talk between these different pathways. Finally, it is worth remembering that significant differences exist between rodent and human skeletal muscle with regard to fiber-type homogeneity/regulation and degree of skeletal muscle fiber-type transformation (Holloszy and Coyle, 1984; Delp and Duan, 1996). There is little evidence that switching between type II and type I muscle fibers actually happens in adult humans (Holloszy and Coyle, 1984; Delp and Duan, 1996; Harridge, 2007); thus, care

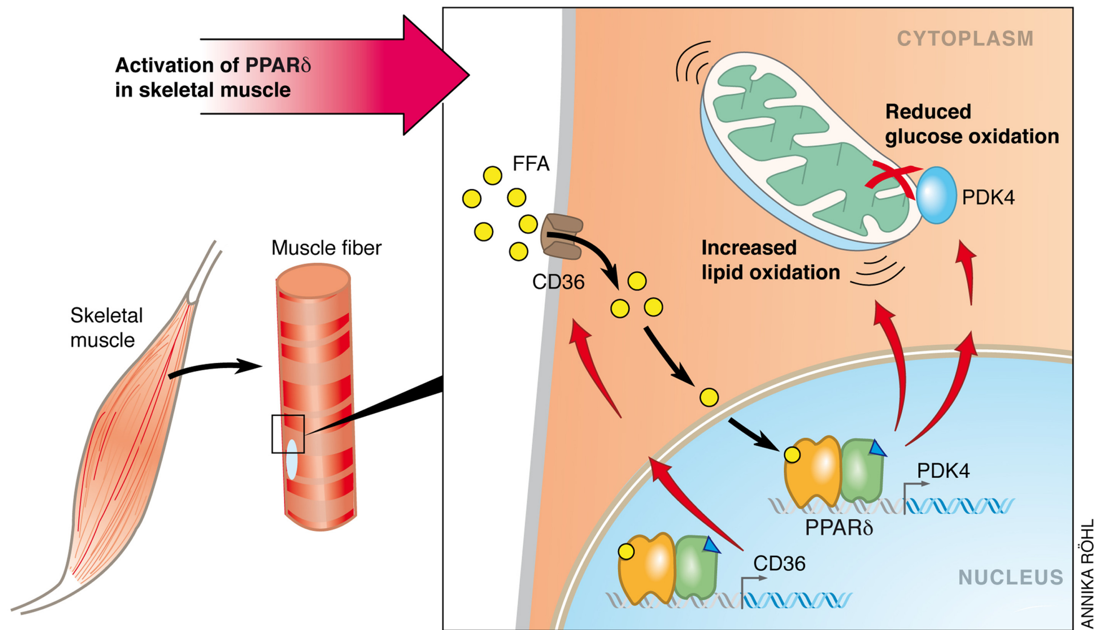

FIG. 3. PPARδ-mediated changes in gene expression lead to increased lipid oxidation: free fatty acids (FFA) enter skeletal muscle via the CD36 fatty acid transporter, for example, leading to activation of PPARδ-dependent genes. This includes PDK4, which reduces glucose oxidation, and several genes important for fatty acid oxidation. CD36 is itself also a PPARδ-dependent gene.

must be taken when translating results from transgenic animals to the human situation. However, even in human skeletal muscle, there is a higher expression of PPARδ and PGC1α in biopsies obtained from people with a high proportion of type I muscle fibers (such as elite cyclists), and a markedly reduced expression of PPARδ and PGC1α in skeletal muscle from subjects with spinal cord injuries in whom type I fibers are selectively lost (Krämer et al., 2006).

C. Peroxisome Proliferator-Activated Receptor δ and Regulation of Muscle Lipid Metabolism

1. Peroxisome Proliferator-Activated Receptor δ Enhances Expression of Genes Involved in Lipid Oxidation. Skeletal muscle is quantitatively the most dominant tissue with respect to lipid metabolism (Kiens, 2006; Houmard, 2008). In the fasted state, fatty acid oxidation is the foremost metabolic activity of skeletal muscle (Dagenais et al., 1976; Houmard, 2008). Thus, factors regulating skeletal muscle fatty acid oxidation will affect whole-body homeostasis. Plasma-free fatty acids enter the skeletal muscle cell either via diffusion through the plasma membrane or via receptor proteins in the plasma membrane, including CD36m, FABPpm, and FATP1. Once inside the cell, fatty acids are activated in the cytosol by reaction with CoA and ATP to form fatty acyl-CoA complexes, which may then enter the mitochondria for subsequent oxidation. The entry of long-chain fatty acyl-CoAs into the mitochondrion is facilitated by carnityl palmitoyl transferase, the activity of which is allosterically regulated by malonyl-CoA. For a more detailed review of these processes, see Kiens (2006). A number of key genes involved in fatty acid entry into the myocyte and subsequent oxidation have been shown to be target genes for PPARδ (see Table 2). Thus, one of the most direct measurable metabolic effects of PPARδ activation is increased fatty acid oxidation, which is evident both in cultured cell models in vitro (Muoio et al., 2002; Krämer et al., 2007; Sprecher et al., 2007; Kleiner et al., 2009), isolated skeletal muscle (Brunmair et al., 2006), and in vivo (Tanaka et al., 2003; Wang et al., 2003, 2004; Constantin et al., 2007; Jucker et al., 2007). The enhanced oxidation of lipids in skeletal muscle probably explains why PPARδ activation is particularly effective in protecting against the consequences of dietary lipid overload (Tanaka et al., 2003; Wang et al., 2003, 2004).

2. Peroxisome Proliferator-Activated Receptor δ Regulates Muscle Fuel Utilization. Increased PPARδ activation increases skeletal muscle lipid oxidation and regulates a number of genes involved in lipid oxidation. Key proteins in this respect are carnityl palmitoyl transferase, CD36, and pyruvate dehydrogenase kinase (PDK). PDK has four isozymes. PDK phosphorylates, resulting in the inactivation of the pyruvate dehydrogenase complex (PDC). This is the rate-limiting step in muscle carbohydrate oxidation. Increased PDK4 expression thus leads to PDC inhibition and reduced carbohydrate oxidation. Thus, PDC inhibition is a pivotal point that can alter fuel selection in skeletal muscle toward fat oxidation. Skeletal muscle contains two PDK isoforms, PDK2 and PDK4 (Holness et al., 2000). PDK4 has consistently been reported as a key target gene in response to PPARδ activation (Table 2). Recent functional analysis indicates that PDK2, PDK3, and PDK4 are primary PPARδ target genes in humans, with several PPRE rec-

ognition sequences in the promoters (Degenhardt et al., 2007). Exercise-induced PDC inhibition is much more potent in rats treated with the PPARδ agonist GW610742 (Constantin-Teodosiu et al., 2009), which probably depends on the PPARδ-driven enhanced PDK4 expression. In addition to enhanced expression of PDK, PPARδ activation concomitantly leads to increased expression of genes involved in uptake (such as CD36) and oxidation of fatty acids. Indeed, a direct functional interplay between PPARδ, CD36, and PDK4 has been proposed (Nahlé et al., 2008), such that CD36 mediates uptake of fatty acids required for activation of PPARδ, which in turn leads to increased expression of PDK4, and further increased expression of CD36. Thus, during fasting, when there are increased circulating fatty acids, this would lead to activation of PPARδ, which would alter metabolism to spare glucose and enhance lipid oxidation. Here, it is noteworthy that although fasting-mediated induction of PDK4 is unaltered in skeletal muscle from PPARα-null mice (Muoio et al., 2002), it is markedly blunted in skeletal muscle from PPARδ-null mice (Nahlé et al., 2008). This suggests that PPARδ is the primary isoform involved in regulating muscle fuel utilization in response to fasting.

3. Peroxisome Proliferator-Activated Receptor δ and Mitochondrial Function. Evidence from transgenic mice with enhanced PPARδ function indicates that PPARδ may play a key role in the regulation of mitochondrial function (Luquet et al., 2003; Wang et al., 2004). Mammalian mitochondrial biogenesis is subject to complex physiological control (Scarpulla, 2008). Treatment with specific PPARδ agonists leads to increases of the expression of several genes involved in the pathway for fatty acid oxidation within the mitochondrial matrix that oxidizes fatty acids to acetyl-CoA (Table 2). Genes directly regulating mitochondrial biogenesis have not been reported to be classic PPARδ target genes (Scarpulla, 2008). The PPARδ coactivator PGC1α, however, is a master regulator of mitochondrial biogenesis (Wu et al., 1999; Handschin and Spiegelman, 2008). Although PGC1α mRNA expression is not changed after overexpression of PPARδ in transgenic mice (Luquet et al., 2003; Wang et al., 2004), transient overexpression of PPARδ in mouse skeletal muscle has been shown to result in increased PGC1α protein content (again without affecting PGC1α mRNA), concomitant with enhanced mitochondrial content (Hancock et al., 2008). Because of technical antibody-dependent challenges in correct quantification of PGC1α protein, many studies have relied on measuring PGC1α mRNA; thus, a PPARδ-dependent post-translational effect on PGC1α protein may have been missed. In support of a direct PPARδ-PGC1α interaction, in skeletal muscle cells established from mice lacking PGC1α, the ability of PPARδ activators to increase fatty acid oxidation was reduced (Kleiner et al., 2009). The maximal rates of ATP production in isolated mitochondria from soleus muscle was unchanged after administration of PPARδ agonist (GW610742) for 6 days to Wistar rats (Constantin et al., 2007). Taken together, current evidence suggests that PPARδ activation leads to increased mitochondrial numbers via PGC1α-dependent pathways but does not affect mitochondrial function per se. The precise nature of PPARδ-mediated increases in mitochondria numbers and biogenesis remains to be resolved.

4. Does Peroxisome Proliferator-Activated Receptor δ Activation Alter Skeletal Muscle Glucose Uptake? One of the key target genes of activated PPARδ is PDK4, the expression of which leads to reduced carbohydrate oxidation; thus, the expectation would be that activation of PPARδ reduces glucose oxidation. In line with this, in isolated rat skeletal muscle incubated in vitro, an short-term activation of PPARδ was without effect on glucose transport (Terada et al., 2006). The metabolic improvements noted in animal models (obese animal models or animals challenged with a high-fat diet; see section IV.A for a complete discussion) could be due to indirect effects on whole-body metabolism after resolution of excessive lipid deposition. There are reports, however, that activation of PPARδ may have direct effects that increase muscle glucose uptake. For example, we have reported that exposure of human skeletal muscle cells and C2C12 cells to a PPARδ agonist increased glucose uptake in a PPARδ-dependent manner (Krämer et al., 2005, 2007), which further depended on the presence of functional AMP-activated protein kinase (AMPK) on the cells. Furthermore, in an elegant in vivo study of tissue glucose uptake with use of positron emission tomography scanning, single-nucleotide polymorphisms (SNPs) of *PPARD* were linked to insulin sensitivity with respect to glucose uptake (Vänttinen et al., 2005). This was true for skeletal muscle glucose uptake but not for adipose tissue glucose uptake (Vänttinen et al., 2005). Further indirect evidence that PPARδ may directly enhance glucose metabolism comes from treatment studies in which administration of PPARδ agonists has been reported to reduce fasting insulin levels. However, further studies are warranted to directly determine the role of PPARδ on skeletal muscle glucose uptake.

5. Peroxisome Proliferator-Activated Receptor δ and Adenosine Monophosphate-Activated Protein Kinase. AMPK is an energy sensor that is activated when cell energy states are low (Long and Zierath, 2006). When activated, AMPK stimulates glucose uptake and lipid oxidation to produce energy while turning off energy-consuming processes. Muscle contraction has been shown to increase AMPK activity. It is noteworthy that AMPK is constitutively activated in muscles of transgenic mice harboring an activated form of PPARδ (Narkar et al., 2008). We have also noted an increase in AMPK activity in skeletal muscle cells exposed to pharmacological PPARδ activator (Krämer et al., 2005, 2007). Coimmunoprecipitation of PPARδ and the catalytic subunits of AMPK (α1 or α2) has been reported when PPARδ is

overexpressed (Narkar et al., 2008), suggesting a direct physical interaction between these two molecules. Although such an interaction has not yet been demonstrated with endogenous PPARδ, this suggests that there may be a cross-talk between AMPK and PPARδ-dependent signaling pathways, and it could explain how PPARδ activation leads to increased glucose uptake and metabolism.

D. Peroxisome Proliferator-Activated Receptor δ and Muscle Performance

The regulation of fiber types is complex, and some of this complexity derives from the difficulty in defining a fiber type. Indeed, the MHC classification system described in section III.A is just that: a way of grouping muscle fibers depending on the isoform of MHC expressed, but it conveniently also allows grouping into physiologically relevant subtypes. There is evidence that some fibers express more than one MHC isoform (Talmadge, 2000). With this caveat in mind, it remains relevant to consider that fiber-type composition has a direct influence on exercise performance, and there is also some evidence that exercise training may in turn influence fiber type. Indeed, some of the key factors implicated in the regulation of muscle fiber type are also known to be regulated by exercise training in mature muscle, including PPARδ and PGC1α.

Mouse models with muscle-specific PPARδ overexpression have increased endurance capacity (Luquet et al., 2003; Wang et al., 2004). Mice expressing active PPARδ in muscle were affectionately nicknamed "marathon mice" because they were able to run twice as far and for twice as long as their wild-type littermates (Wang et al., 2004). It is noteworthy that this enhanced running capacity is inherent in the PPARδ-overexpressing mice, and it is not due to altered behavior making them more physically active. Furthermore, in wild-type mice, 6 weeks of exercise training (a 45-min swim per day, 5 days per week) resulted in up-regulation of PPARδ protein in the tibialis anterior muscle (Luquet et al., 2003). Increased expression of PPARδ protein after exercise training has also been reported in human studies (Russell et al., 2003; Watt et al., 2004; Mahoney et al., 2005; Fritz et al., 2006).

A curious finding in this context is the report that administration of PPARδ agonist (GW610742) for 6 days to Wistar rats increased expression of the muscle-specific E3 ligases MAFbx and MuRF1 (Constantin et al., 2007). Up-regulation of MAFbx and MuRF1 has been linked to muscle catabolism (Lecker et al., 2004).

Nutritional status may influence the exercise effect on PPAR isoforms. As discussed in section II.F, fasting dramatically increases PPARδ mRNA expression in mice (Holst et al., 2003). Fasting is associated with increased circulating free fatty acids; however, nicotinic acid-mediated reduction in circulating free fatty acids increased PPARδ mRNA expression in human skeletal muscle (Watt et al., 2004). In the latter case, exercise in the presence of nicotinic acid was not able to further increase skeletal muscle PPARδ mRNA (Watt et al., 2004). Given the additional complexity of hormonal and nutrient regulation of these targets, dissecting exercise from nutritional effects on PPAR expression may be a challenge. Because PPARδ expression is not the only determinant of PPARδ activity, exercise-mediated effects on cofactors and on possible natural activating ligands may also contribute to the regulation of PPARδ-directed gene-regulatory events.

In addition to enhancing expression of genes required for lipid oxidation and myogenic markers, pharmacological activation of PPARδ in adult mice has recently been linked to a rapid and transient up-regulation of angiogenic markers (VEGF-A and PECAM-1) (Gaudel et al., 2008). In a mouse ischemic hind limb model, PPARδ agonist treatment resulted in improved vasculogenesis via regulation of endothelial progenitor cells, highlighting the potential for PPARδ agonism as a novel option for treatment of ischemic cardiovascular diseases (Han et al., 2008). Enhanced capillarization of skeletal muscle is a physiological response to endurance training. It is noteworthy that capillarization was more pronounced in animals treated with a PPARδ activator than in the muscles of PPARδ-overexpressing mice (animals expressing PPARδ specifically in skeletal muscle) (Piqueras et al., 2007). The reported angiogenic response thus may be limited to a subgroup of muscle fibers or may involve other cell types, such as endothelial cells.

E. Peroxisome Proliferator-Activated Receptor δ Effects in Cardiac Muscle

In parallel with the effects noted in skeletal muscle, PPARδ also has important effects on cardiac muscle. PPARδ mRNA is abundantly expressed in cardiomyocytes, where it regulates genes involved in fatty acid oxidation and lipid metabolism (Gilde et al., 2003). Cardiomyocyte-specific deletion of *Ppard* in mice results in cardiac dysfunction characterized by myocardial fat accumulation, cardiac hypertrophy, and finally heart failure. Furthermore, transgenic mice overexpressing PPARδ specifically in the heart are resistant to myocardial lipid accumulation on a high-fat diet and show no signs of cardiac dysfunction (Cheng et al., 2004). These PPARδ-overexpressing mice show increased cardiac glucose uptake and oxidation rates concomitant with increased *GLUT4* gene expression. Moreover, the expression of genes involved in fatty acid oxidation are increased in the heart of the cardiac-specific PPARδ-overexpressing mice; surprisingly, however, show no difference in fatty acid uptake or oxidation compared with wild-type control animals (Burkart et al., 2007). Thus, the relative protection from ischemia-reperfusion injury noted in these mice is probably due to an increased capacity for myocardial glucose utilization, which is a biological response to hypoxia (Opie and Sack, 2002)

IV. Peroxisome Proliferator-Activated Receptor δ and Metabolic Disease

A. Peroxisome Proliferator-Activated Receptor δ Agonists and Treatment of Metabolic Disease

Given the ability of PPARδ agonists to increase fatty acid catabolism, cholesterol efflux, and energy expenditure in muscle, interest has focused on therapeutic utility in the treatment of hyperlipidemia, atherosclerosis, and obesity. Diabetic dyslipidemia is characterized by high levels of triglyceride-rich, very-low-density lipoprotein particles and their cholesterol ester-rich remnant particles, low levels of high-density lipoprotein (HDL) cholesterol, and small dense low-density lipoproteins (Adiels et al., 2006). Our present knowledge regarding PPARδ in relation to metabolic diseases is based to a large extent on genetically modified animals and the use of high-affinity synthetic ligands for PPARδ, but it is also based on a few studies in humans and in vitro-based approaches.

Both the genetic leptin-resistant (*db/db*) and the leptin-deficient (*ob/ob*) mice are obese/diabetic animal models that have been investigated in relation to how PPARδ exerts its metabolic effects. One of the first studies using a synthetic PPARδ ligand in an obese and diabetic animal model was performed in *db/db* mice (Leibowitz et al., 2000). In these mice, treatment with the PPARδ agonist L-165041 improved the lipid profile by increasing the HDL cholesterol concentration, but the treatment had little or no effect on plasma glucose or triglyceride levels. Because the L-165041 is only a weak agonist of the murine PPARδ, other more potent PPARδ ligands were developed (Willson et al., 2000). Use of the potent and high-affinity synthetic PPARδ ligands in different animal models and in human studies showed that activation of PPARδ can promote reversal of metabolic abnormalities (Oliver et al., 2001; Jucker et al., 2007; Chen et al., 2008; Gaudel et al., 2008; Risérus et al., 2008; Kleiner et al., 2009). The diet-induced obesity that mice fed a high-fat diet develop could be prevented by treatment with GW501516 because of enhanced fatty acid utilization and energy expenditure (Tanaka et al., 2003). Although GW501516 treatment had no effects on blood glucose levels, the concentrations of plasma insulin decreased regardless of diet. Both glucose tolerance and insulin sensitivity were improved in these animals, and lipid accumulation in both skeletal muscle and liver were decreased. Leptin-deficient obese and diabetic *ob/ob* mice also showed improved glucose tolerance and reduced plasma insulin concentrations after treatment with GW501516 (Tanaka et al., 2003). Injection of monosodium L-glutamate results in the development of metabolic syndrome in mice. In this model, insulin resistance and dyslipidemia improved, and hyperleptinemia decreased after treatment with a specific PPARδ agonist (Chen et al., 2008). Spontaneously obese, insulin-resistant middle-aged rhesus monkeys treated with the PPARδ activator GW501516 displayed augmented serum HDL-cholesterol concentrations accompanied by decreased levels of small dense low-density lipoproteins, triglyceride, and insulin (Oliver et al., 2001). Furthermore, GW501516 treatment lowered the fasting plasma insulin without changing glucose levels. Many of the improvements in metabolic profiles noted in response to PPARδ agonists are mirrored in mice with transgenic overexpression of PPARδ specifically in skeletal muscle (Luquet et al., 2003; Wang et al., 2004), indicating that skeletal muscle may be a primary target organ. Effects on other tissues should not be ruled out, however. For example, activation of PPARδ in adipose tissue leads to improved lipid profiles, decreased lipid accumulation, and reduced adiposity. These transgenic mice are also resistant to obesity induced by a high-fat diet (Wang et al., 2003). The beneficial metabolic effects observed in these animals may also be due in part to a PPARδ-mediated alternative activation of adipocyte macrophages and hepatic Kupffer cells (Kang et al., 2008; Odegaard et al., 2008). It has been suggested that resident macrophages in adipose tissue and liver are important in controlling energy metabolism and insulin action by coordinating the classic (M1) and alternative (M2) programs of activation (Xu et al., 2003; Odegaard and Chawla, 2008). The M1-activated macrophages are proinflammatory and the M2-activated macrophages are anti-inflammatory. Stimulation with interferon γ and lipopolysaccharides activates M1 macrophages, whereas interleukins 4 and 13 activate M2 macrophages and PPARδ (Kang et al., 2008; Odegaard et al., 2008). PPARδ-deficient macrophages are unable to shift to the M2 phenotype, resulting in hepatic fat accumulation, decreased fatty acid β-oxidation, and increased insulin resistance in liver and skeletal muscle (Kang et al., 2008; Odegaard et al., 2008). Activation of PPARδ, which also has been shown to regulate transition from classic to alternative macrophage phenotypes, was not able to compensate for the loss of M2 activation in PPARδ-deficient macrophages (Kang et al., 2008). Recent data, however, indicate that, in human atherosclerotic plaques and primary human macrophages, mRNA expression of PPARδ does not correlate with mRNA expression of M2 markers (Bouhlel et al., 2009). Thus, there may be species differences regarding the effects of PPARδ in macrophages, underscoring again the idea that caution is warranted when drawing conclusions regarding human physiology based on murine observations.

The currently available data regarding the impact of PPARδ activation on changes in body weight is ambiguous. Although GW501516 prevents weight gain in mice with diet-induced obesity and in *ob/ob* mice (Tanaka et al., 2003), this was not seen in *db/db* mice or ZUCKER *fa/fa* obese rats (Pelton, 2006). Other studies showed no effect on body weight during PPARδ agonist treatment (Oliver et al., 2001; Chen et al., 2008). PPARδ-deficient

mice show reduced adipose stores compared with wild-type animals (Peters et al., 2000; Tan et al., 2001; Barak et al., 2002), whereas mice carrying an adipose tissue-specific deletion of PPARδ showed no reduction in adiposity, showing that the adipose tissue responds to an exogenous stimulus, rather than to the receptor within the fat cell (Barak et al., 2002). However, *Ppard* knockout mice fed a high-fat diet showed increased adiposity, despite lower total body weight (Akiyama et al., 2004). Furthermore, *Ppard* knockout animals are glucose intolerant, have a decreased metabolic rate, and are not responsive to treatment with GW501516 (Tanaka et al., 2003; Luquet et al., 2004; Lee et al., 2006).

The positive influences on metabolic endpoints obtained in animal studies seem to hold up in the few human treatment studies published so far (Sprecher et al., 2007; Metabolex, 2008; Risérus et al., 2008; Christodoulides et al., 2009), the outcomes of which are summarized in Table 3. Young healthy subjects treated with GW501516 for 2 weeks reported no significant adverse effects, including liver and muscle responses. In this small group, the PPARδ agonist lowered plasma triglyceride and increased HDL concentrations (Sprecher et al., 2007). Treatment with the PPARδ agonist GW501516 for 2 weeks in healthy and moderately obese subjects led to reduction of plasma triglyceride, LDL cholesterol, and apolipoprotein B levels accompanied by decreased liver fat content and increased plasma fibroblast growth factor 21 levels (Risérus et al., 2008; Christodoulides et al., 2009). Despite the fact that the participants in these studies were healthy and glucose tolerant, there was a reduction in fasting glucose and improved insulin sensitivity. There is limited information regarding the effects of a novel PPARδ-targeting compound MBX-8025 (Metabolex, 2008); however, an 8-week trial reported reduced triglycerides, LDL, insulin, and glucose. It is noteworthy that there have been no reports of adverse reactions in any of the studies to date, and no increase of oxidative stress has been detected, probably because of increased fat oxidation in skeletal muscle (Risérus et al., 2008).

B. Single-Nucleotide Polymorphisms in Peroxisome Proliferator-Activated Receptor δ Have Been Linked to Altered Lipid Profiles

Over the past couple of years, there has been an increased focus on activation of PPARδ to unravel its function. Considerably less is known about the regulation of PPARδ expression per se and the physiological consequences of genetic variation within *PPARD*. Because PPARδ is an important regulator of genes involved in lipid and glucose metabolism, one might expect polymorphisms in *PPARD* to be associated with the metabolic syndrome, type 2 diabetes, obesity, and/or cardiovascular disease. Several association studies on the role of *PPARD* polymorphisms in relation to metabolic dysfunction and risk for diabetes and cardiovascular disease have been published (Skogsberg et al., 2003a,b; Shin et al., 2004; Gouni-Berthold et al., 2005; Vänttinen et al., 2005; Aberle et al., 2006a,b; Andrulionyte et al., 2006; Hu et al., 2006; Grarup et al., 2007; Hautala et al., 2007; Robitaille et al., 2007; Stefan et al., 2007; Lagou et al., 2008; Sáez et al., 2008; Thamer et al., 2008). More than 16 SNPs in *PPARD* have been analyzed thus far, and the majority of these relatively large association studies have investigated a polymorphism in exon 4, rs2016520, located 87 base pairs upstream of the translational start site. Figure 4 shows the three different haploblocks covering the *PPARD* locus obtained from public databases.

An initial study (Skogsberg et al., 2003a) that we conducted suggested that SNP rs2016520 in exon 4 was of functional relevance, influencing the binding of Sp-1

TABLE 3
Summary of reported effects of PPARδ activation in humans

When no arrow is indicated, data were as not reported.

	Sprecher et al., 2007	Risérus et al., 2008	Metabolex, 2008
Subjects			
Number	12	6	173
Description	Healthy male lean subjects	Healthy male obese subjects	Overweight or obese subjects with high cholesterol and triglycerides
Agonist	GW501516	GW501516	MBX-8025
Duration	2 weeks	2 weeks	8 weeks
Weight	ND	↓[a]	
Blood pressure	↔		
HDL	↑	↔	↑
LDL		↓	↓
Apo B		↓	
Fasting glucose		↓	↓
Fasting insulin		↓	↓
HOMA		↓	
Triglycerides	↓	↓	↓
Total cholesterol		↓	
Free fatty acids		↓	
Liver fat		↓	
FGF21		↑[a]	

↑, increase; ↓, decrease; ↔, no change.
[a] Reported in Christodoulides et al. (2009).

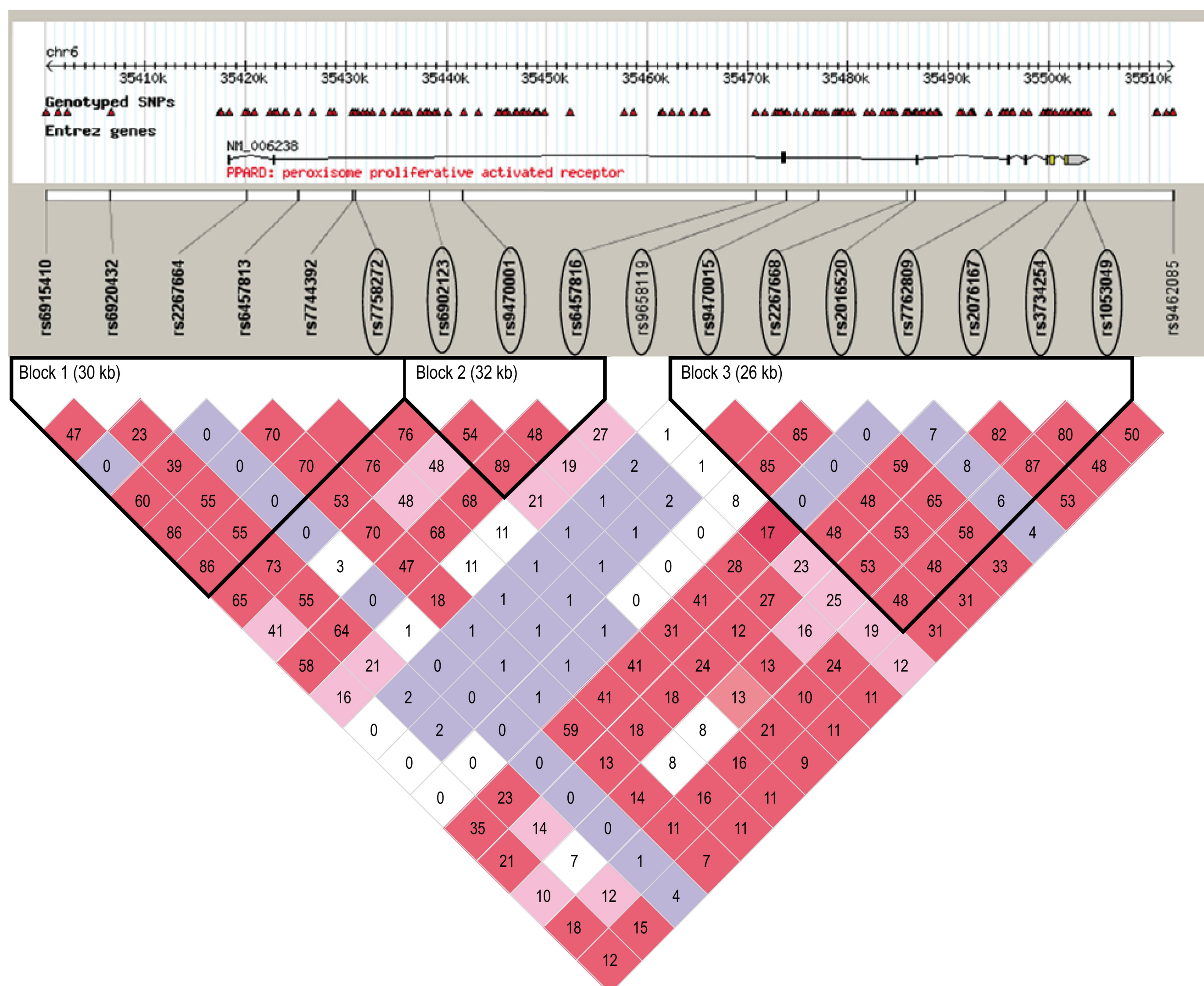

FIG. 4. Linkage disequilibrium (LD) estimates of genetic variants encompassing the *PPARD* gene. SNPs with minimum allele frequency ≥5% at a minimum of D′ > 0.8 covering the *PPARD* gene locus were selected from the HapMap CEU population (http://www.hapmap.org, release 22) using the Ensembl Genome Browser (http://www.ensembl.org). The position on chromosome 6, structure of the *PPARδ* gene, and the localization of included SNPs are shown above the LD values and haplotype blocks. Circled SNPs indicate genetic variants included in published association studies. Numbers in squares designate the degree of LD (R^2) between any two markers, and the LD estimates and haplotype blocks were made with the use of Haploview version 4.1 (http://www.broad.mit.edu/mpg/haploview).

and subsequent transcriptional activity. The minor C allele was associated with increased plasma LDL concentrations in 543 healthy middle-aged men (Skogsberg et al., 2003a). Considering the effect on plasma LDL concentrations, the effect on the incidence of myocardial infarction was assessed in the West of Scotland Coronary Prevention Study, consisting of men with hyperlipidemia and an increased risk of cardiovascular disease. Although subjects homozygous for the C allele showed only a tendency toward increased risk for coronary heart disease, and any major effect of the SNP in this respect could be excluded, an association between decreased HDL cholesterol concentrations in plasma and the minor C allele of the rs2016520 polymorphism was found (Skogsberg et al., 2003b). The impact of the rs2016520 polymorphism on HDL concentrations has been confirmed in a group of almost 1000 female patients with mixed hyperlipidemia (Aberle et al., 2006b). Relationships between the rs2016520 SNP and lipid levels and coronary lesions have also been investigated in the Lipoprotein and Coronary Atherosclerosis Study, consisting of 372 subjects that have had at least one coronary lesion. Significant associations between the minor C allele and increased plasma apolipoprotein B, total cholesterol, and triglyceride concentrations along with the maximum number of lesions were found (Chen et al., 2004). On the other hand, the rs2016520 in exon 4 showed no association with plasma lipid concentrations, body mass index (BMI), and atherosclerotic disease in a cohort consisting of 402 patients with type 2 diabetes

and 436 nondiabetic control subjects (Gouni-Berthold et al., 2005). Thus, taken together, no major influence of SNPs in *PPARD* on risk for coronary heart disease has been shown. This is in accordance with the data obtained from genome-wide association studies (GWAS), which have not identified *PPARD* as a risk gene for myocardial infarction.

A number of relationships between body fat and BMI-related phenotypes and polymorphisms in the *PPARD* have also been reported. An association of the minor C allele of the same rs2016520 polymorphism in exon 4 discussed in relation to lipoprotein regulation with a higher percentage of body fat in 376 nondiabetic Chinese subjects has been detected (Hu et al., 2006). In line with this finding is the report regarding a polymorphism located in exon 7 (rs2076167) that showed an odds ratio of 1.43 with respect to obesity in a case-control study comprising 725 obese subjects (BMI > 30) and 1228 non-obese control subjects (Sáez et al., 2008). Furthermore, a common haplotype including the major alleles of rs2016520 in exon 4 and rs1053049 in exon 9 has been shown to be associated with higher BMI in 249 nondiabetic control subjects from Korea (Shin et al., 2004). However, when all of these SNPs were tested in a large study comprising three cohorts consisting of 7495 white subjects, including 1416 subjects with type 2 diabetes, no associations of tag SNPs with either lipid concentrations or BMI were found (Grarup et al., 2007). Furthermore, a recent study in 2102 Greek children aged 1 to 6 years failed to detect any associations between the rs2016520 in exon 4 and adiposity measures (Lagou et al., 2008). The two latter studies are probably the only ones to date that have the statistical power to detect an association with obesity. It is noteworthy that none of the recent GWAS have identified the *PPARD* as an obesity gene.

The association between type 2 diabetes and polymorphisms in *PPARD* has also been investigated. A genetic variant in intron 2 (rs69021239) was associated with an increased risk of conversion from impaired glucose tolerance to type 2 diabetes in female subjects, but not male subjects, in the STOP-NIDDM trial consisting of 769 middle-aged subjects during a 5-year follow-up period. This risk was more pronounced in combination with SNPs of the *PPARGC1A* and *PPARG2* genes (Andrulionyte et al., 2006). On the other hand, Grarup et al. (2007) found no major effect of SNPs in *PPARD* on the risk for type 2 diabetes. Again, this is in line with the absence of finding the *PPARD* in GWAS for type 2 diabetes. Although the study by Grarup et al. (2007) did identify a haplotype containing minor alleles of rs2076169 (intron 5) and rs2076167 (exon 7) that were associated with increased insulin sensitivity, after correction for multiple hypothesis testing, the association was no longer statistically significant.

Because PPARδ is considered to act as a metabolic sensor, the influence of *PPARD* SNPs in relation to changes in diet have been investigated. There is considerable environmental influence on the impact of PPARδ-associated risks. Dietary fat intake has been shown to influence the relationship between the *PPARD* exon 4 SNP rs2016520 and the risk of having three or more components of the metabolic syndrome in 340 subjects (Robitaille et al., 2007). Individuals consuming less than 34.4% of energy from fat were protected against features of the metabolic syndrome, which is of interest considering the high binding affinity of long-chain fatty acids as potential ligands for PPARδ.

In summary, there is no clear evidence that genetic variation in the *PPARD* has a major effect on myocardial infarction, obesity, or type 2 diabetes; however, the observation that *PPARD* SNPs interact with nutrients, and possible response to physical activity, suggests that genetic variation in the *PPARD* may determine metabolic response to external factors, such as diet and exercise. These possible connections require further study.

C. Single-Nucleotide Polymorphisms in Peroxisome Proliferator-Activated Receptor δ in Relation to Skeletal Muscle Function and Physical Performance

Based on the roles that PPARδ plays in muscle fiber composition and mitochondrial oxidative pathways involving fatty acid oxidation and oxidative phosphorylation, several genetic association studies have been performed in relation to function of the skeletal muscle. The relationship between *PPARD* SNPs and glucose uptake was investigated in 129 healthy individuals by use of the hyperinsulinemic-euglycemic clamp technique combined with fluorine-18-labeled fluorodeoxyglucose and positron emission tomography. Three SNPs of *PPARD* and a haplogenotype of these variants were significantly associated with increased insulin-stimulated whole-body and skeletal muscle glucose uptake but not with subcutaneous adipose tissue glucose uptake (Vänttinen et al., 2005).

The impact of the polymorphisms rs2016520, in exon 4, and rs2076167, in exon 7, has been investigated in response to regular exercise in sedentary healthy black ($n = 264$) and white subjects ($n = 477$) (Hautala et al., 2007). After 20 weeks of endurance training, black subjects homozygous for the minor C allele of rs2016520 showed a significantly lower training-induced increase in maximal oxygen consumption and maximal power output compared with carriers of the major T allele. A similar trend was also observed in white subjects. Endurance training depends on the capacity of skeletal muscle fat oxidative capacity, and any constitutive or induced reduction in PPARδ function or expression might impair the ability to adequately up-regulate fat oxidation in skeletal muscle. In addition, both polymorphisms were associated with plasma HDL concentrations that were influenced by endurance training (Hautala et al., 2007).

How genetic variants of *PPARD* influence changes in aerobic physical fitness, insulin sensitivity, and body composition have been studied in persons with an increased risk for type 2 diabetes who participated in a 9-month exercise and dietary lifestyle intervention program. The minor alleles of three SNPs rs6902123 (intron 2), rs2267668 (intron 3), and rs1053049 (exon 9) have been shown to be associated with reduced response to the lifestyle intervention resulting in a smaller increase in relative muscle volume, and a reduced decrease in adipose tissue mass and ectopic fat storage in liver (Thamer et al., 2008). Carriers of the minor G allele of rs2267668 had a smaller increase in individual anaerobic threshold, a precise measurement of aerobic physical fitness, compared with homozygous carriers of the major A allele. Moreover, individuals carrying the minor C allele of the rs1053049 had a smaller reduction in fasting insulin levels compared with subjects homozygous for the major T allele (Thamer et al., 2008). A separate analysis of this cohort detected an additive effect of the rs2267668 (exon 3) and the Gly423Ser polymorphism in the *PPARGC1A*, resulting in an even smaller increase in the individual anaerobic threshold and insulin sensitivity (Stefan et al., 2007). Analyses of skeletal muscle mitochondrial activity in cultured myotubes obtained from healthy young subjects showed that carriers of the minor G allele of rs2267668 had lower mitochondrial function compared with subjects homozygous for the major A allele (Stefan et al., 2007). Overall, these studies suggest that *PPARD* SNPs might be of importance in predicting the effectiveness of lifestyle interventions and energy utilization in skeletal muscle, but most studies to date are rather small and need to be replicated.

D. Is Skeletal Muscle Peroxisome Proliferator-Activated Receptor Expression Altered in Metabolic Disease?

We have reported recently that skeletal muscle protein expression of PPARδ increased significantly after physical exercise in patients with type 2 diabetes after a 4-month low-intensity exercise program (Fritz et al., 2006). It is noteworthy that an increase in skeletal muscle protein expression of PPARδ was associated with improvements in several clinical parameters; PPARδ expression was unchanged in subjects who did not improve their clinical profile after exercise. Increased skeletal muscle PPARδ mRNA expression has been noted in healthy, glucose-tolerant subjects undergoing biliopancreatic diversion (enhancing insulin sensitivity and glucose oxidation); however, in subjects with type 2 diabetes, there was a blunted increase in glucose oxidation and no increase in skeletal muscle PPARδ mRNA expression after biliopancreatic diversion (Hernández-Alvarez et al., 2009). Taken together with results indicating that polymorphisms in the *PPARD* may affect exercise response, this suggests that PPARδ may be one key factor coordinating exercise-mediated changes in metabolism. These data also suggest a direct implication of PPARδ in the muscle remodeling that occurs during endurance training and possibly in the beneficial effects of exercise on metabolic syndrome.

V. Concluding Thoughts

A. What Will Be the Therapeutic Impact of Peroxisome Proliferator-Activated Receptor δ Agonists?

Drugs directed against PPARα (fibrates) and PPARγ (thiazolidinediones) have proven to be efficacious therapy against hyperlipidemia and type 2 diabetes/insulin resistance, respectively. In this review, we have focused on the effects of PPARδ in skeletal muscle. As suggested in Fig. 5, physiological activation of PPARδ occurs when there is an increased need for skeletal muscle lipid utilization, leading to a number of adaptations that have a positive impact in insulin resistance. PPARδ differs from PPARα and PPARγ in that it has a wider tissue-specific expression pattern and it has direct effects on skeletal muscle metabolism. Because the effects of PPARδ have been studied less intensively than those of PPARα and PPARγ, less is also known regarding safety issues. In a genetically modified animal model, intestinal tumorigenesis, but not colon carcinogenesis, was increased in response to GW501516 (Gupta et al., 2004). On the other hand, mice lacking PPARδ have an increased predisposition to intestinal tumors (Reed et al., 2004); other reports suggest that ligand activation of PPARδ is without effect (Hollingshead et al., 2007) or, in fact, inhibits growth of human cancer cell lines (Bility et al., 2008; Borland et al., 2008) and colon carcinogenesis in mice (Marin et al., 2006).

PPARδ is a key regulator of skeletal muscle lipid oxidation, and, as outlined in section III, activation of PPARδ should have many potential beneficial effects in the context of metabolic disease. PPARδ-mediated effects in tissues other than skeletal muscle have also highlighted the possible utility of activators of PPARδ for treatment of dyslipidemia and atherosclerosis (Takahashi et al., 2007; Billin, 2008; Reilly and Lee, 2008). Considering that diabetic patients have decreased cardiac glucose utilization and an increase in myocardial fatty acid uptake and oxidation, PPARδ agonists might be useful therapeutic agents in treating lipotoxic cardiomyopathy.

Although genetic data link *PPARD* polymorphisms to enhanced glucose metabolism in skeletal muscle (Vänttinen et al., 2005), and clinical correlative evidence between PPARδ activation and improved whole-body glucose metabolism (Fritz et al., 2006; Stefan et al., 2007), there is also evidence that PPARδ agonism (induced by GW610742X administration in rats), inhibits carbohydrate oxidation during contraction by blunting PDC activation (Constantin-Teodosiu et al., 2009). Thus, it is possible that pharmacological activation of PPARδ with

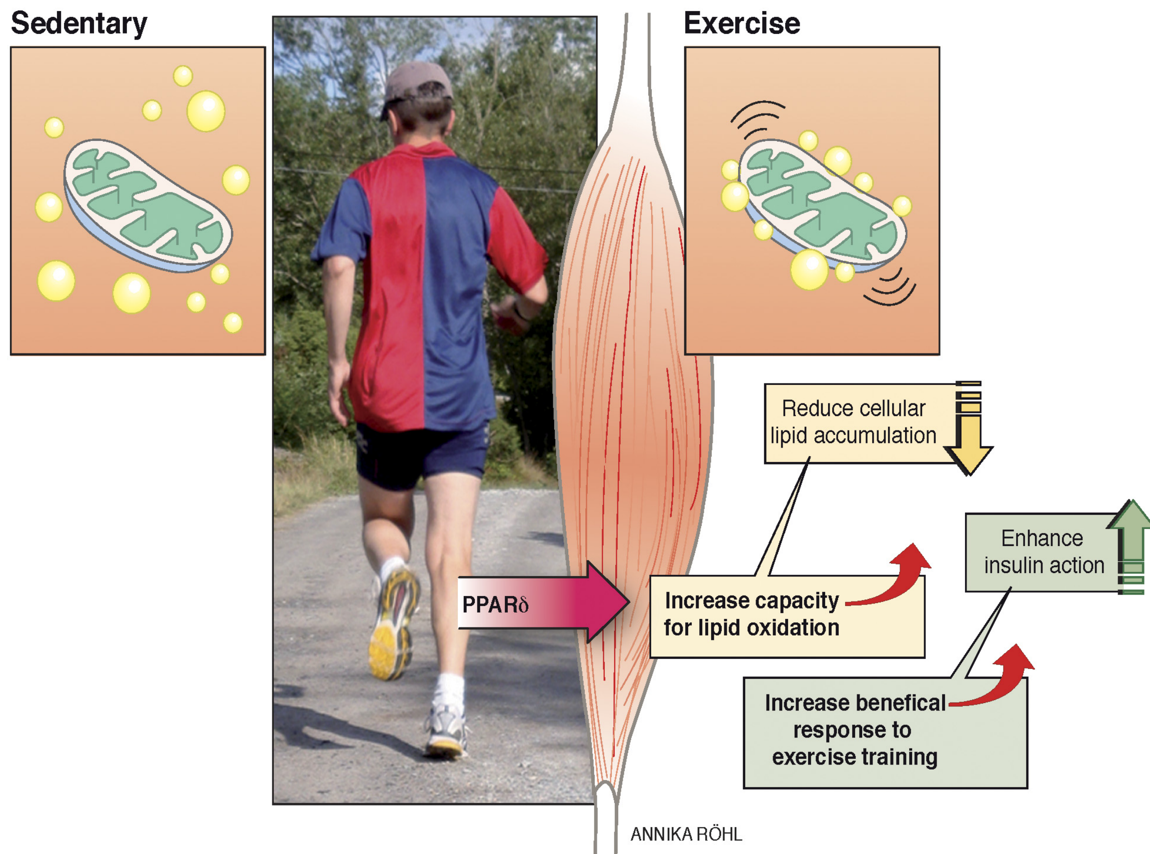

FIG. 5. Outline of skeletal muscle responses to activation of PPARδ. The ability to up-regulate PPARδ activity and subsequent changes in gene transcription may be a key step in exercise-mediated metabolic improvements.

agonist and ligands and the results obtained after physiological intervention such as training will be different. Indeed, from a skeletal muscle perspective, a key question remains whether the increased lipid oxidation will mediate long-term metabolic benefits, particularly when a sedentary lifestyle is maintained. In line with this, a recent report has proposed that obesity results in an excessive fatty acid load on mitochondria, causing accumulation of incompletely oxidized intermediates, including acylcarnitine esters, while decreasing levels of metabolites of the tricarboxylic acid cycle (Koves et al., 2008). Mice with targeted deletion of either malonyl-CoA decarboxylase 1 (Koves et al., 2008) or PDK4 (Jeoung and Harris, 2008) are protected against diet-induced insulin resistance. In both these scenarios, skeletal muscle lipid oxidation is suppressed, and utilization of glucose is increased (Bouzakri et al., 2008; Jeoung and Harris, 2008), which is the inverse of what is known in the response to activation of PPARδ. The limited information available from pharmacological activation of PPARδ in humans, however, has indicated increased lipid oxidation and enhanced insulin sensitivity (Karpe and Ehrenborg, 2009). On the other hand, it remains to be seen whether the PPARδ-mediated increase in skeletal muscle lipid oxidation would confer metabolic benefits that are sustainable in the context of a sedentary, low-energy lifestyle. The outcome of longer-term clinical trials are eagerly awaited.

B. Will Peroxisome Proliferator-Activated Receptor δ Agonists Be "Exercise" Pills?

With all the evidence linking activation, or total skeletal muscle content of PPARδ, to muscle performance, it is interesting to speculate whether pharmacological activators would enhance physical performance. Indeed, many less reputable Internet pages promise enhanced muscle growth and performance by use of PPARδ activators. Recent evidence may actually prove that some of these claims are correct, at least in part. Administration of GW0742 to adult mice resulted in increased myofiber numbers and increased oxidative capacity (Gaudel et al., 2008). Likewise, administration of the GW501516 to sedentary mice for 4 weeks increased skeletal muscle expression of a number of important oxidative genes (Narkar et al., 2008). In the latter case, however, drug administration did not alter the muscle fiber type or enhance the endurance capacity of the mice. However, when GW501516 was administered to mice that were undergoing an exercise training program, then the PPARδ agonist increased exercise-induced improvements in endurance (Narkar et al., 2008). If these results translate to the human situation, activation of PPARδ might boost the effect of exercise that is per-

formed. This has implications beyond exercise performance. As discussed in section IV.C, there is emerging evidence that the ability of exercise to affect metabolic health may vary within the general population; some people may be more "exercise resistant." This opens up the possibility that pharmacological activation of PPARδ may boost the efficacy of exercise training in subjects that seem to be relatively unresponsive to exercise-mediated effects on metabolism. Thus, although pharmacological activation of PPARδ may indeed potentiate the daily training benefits induced by exercise, both for the amateur and elite athlete, it will not supersede the need to actually perform the exercise.

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REFERENCES

Abbot EL, McCormack JG, Reynet C, Hassall DG, Buchan KW, and Yeaman SJ (2005) Diverging regulation of pyruvate dehydrogenase kinase isoform gene expression in cultured human muscle cells. *FEBS J* **272:**3004–3014.

Abbott BD (2009) Review of the expression of peroxisome proliferators-activated receptors alpha (PPARalpha), beta (PPARbeta), and gamma (PPARgamma) in rodent and human development. *Reprod Toxicol* **75:**72–77.

Aberle J, Hopfer I, Beil FU, and Seedorf U (2006a) Association of peroxisome proliferator- activated receptor delta +294T//C with body mass index and interaction with peroxisome proliferator-activated receptor alpha L162V. *Int J Obes (Lond)* **30:**1709–1713.

Aberle J, Hopfer I, Beil FU, and Seedorf U (2006b) Association of the T+294C polymorphism in PPAR delta with low HDL cholesterol and coronary heart disease risk in women. *Int J Med Sci* **3:**108–111.

Adiels M, Olofsson SO, Taskinen MR, and Borén J (2006) Diabetic dyslipidaemia. *Curr Opin Lipidol* **17:**238–246.

Akiyama TE, Lambert G, Nicol CJ, Matsusue K, Peters JM, Brewer HB Jr, and Gonzalez FJ (2004) Peroxisome proliferator-activated receptor beta/delta regulates very low density lipoprotein production and catabolism in mice on a Western diet. *J Biol Chem* **279:**20874–20881.

Andrulionyte L, Peltola P, Chiasson JL, Laakso M, and STOP-NIDDM Study Group (2006) Single nucleotide polymorphisms of PPARD 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* **55:**2148–2152.

Auboeuf D, Rieusset J, Fajas L, Vallier P, Frering V, Riou JP, Staels B, Auwerx J, Laville M, and Vidal H (1997) Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-alpha in humans: no alteration in adipose tissue of obese and NIDDM patients. *Diabetes* **46:**1319–1327.

Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, Boland R, and Evans RM (2002) Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. *Proc Natl Acad Sci U S A* **99:**303–308.

Barish GD, Narkar VA, and Evans RM (2006) PPAR delta: a dagger in the heart of the metabolic syndrome. *J Clin Invest* **116:**590–597.

Baron AD, Brechtel G, Wallace P, and Edelman SV (1988) Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol* **255:** E769–E774.

Bility MT, Devlin-Durante MK, Blazanin N, Glick AB, Ward JM, Kang BH, Kennett MJ, Gonzalez FJ, and Peters JM (2008) Ligand activation of peroxisome proliferator-activated receptor beta/delta (PPAR beta/delta) inhibits chemically induced skin tumorigenesis. *Carcinogenesis* **29:**2406–2414.

Billin AN (2008) PPAR-beta/delta agonists for type 2 diabetes and dyslipidemia: an adopted orphan still looking for a home. *Expert Opin Investig Drugs* **17:**1465–1471.

Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, and Mangelsdorf DJ (2006) Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* **126:**789–799.

Borland MG, Foreman JE, Girroir EE, Zolfaghari R, Sharma AK, Amin S, Gonzalez FJ, Ross AC, and Peters JM (2008) Ligand activation of peroxisome proliferator-activated receptor-beta/delta inhibits cell proliferation in human HaCaT keratinocytes. *Mol Pharmacol* **74:**1429–1442.

Bouhlel MA, Brozek J, Derudas B, Zawadzki C, Jude B, Staels B, and Chinetti-Gbaguidi G (2009) Unlike PPARgamma, PPARalpha or PPARbeta/delta activation does not promote human monocyte differentiation toward alternative macrophages. *Biochem Biophys Res Commun* **386:**459–462.

Bouzakri K, Austin R, Rune A, Lassman ME, Garcia-Roves PM, Berger JP, Krook A, Chibalin AV, Zhang BB, and Zierath JR (2008) Malonyl coenzymeA decarboxylase regulates lipid and glucose metabolism in human skeletal muscle. *Diabetes* **57:** 1508–1516.

Bouzakri K, Koistinen HA, and Zierath JR (2005) Molecular mechanisms of skeletal muscle insulin resistance in type 2 diabetes. *Curr Diabetes Rev* **1:**167–174.

Braissant O, Foufelle F, Scotto C, Dauça M, and Wahli W (1996) Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. *Endocrinology* **137:** 354–366.

Brooke MH and Kaiser KK (1970) Muscle fiber types: how many and what kind? *Arch Neurol* **23:**369–379.

Brunmair B, Staniek K, Dörig J, Szöcs Z, Stadlbauer K, Marian V, Gras F, Anderwald C, Nohl H, Waldhäusl W, et al. (2006) Activation of PPAR-delta in isolated rat skeletal muscle switches fuel preference from glucose to fatty acids. *Diabetologia* **49:**2713–2722.

Burkart EM, Sambandam N, Han X, Gross RW, Courtois M, Gierasch CM, Shoghi K, Welch MJ, and Kelly DP (2007) Nuclear receptors PPARbeta/delta and PPARalpha direct distinct metabolic regulatory programs in the mouse heart. *J Clin Invest* **117:**3930–3939.

Burns KA and Vanden Heuvel JP (2007) Modulation of PPAR activity via phosphorylation. *Biochim Biophys Acta* **1771:**952–960.

Chen S, Tsybouleva N, Ballantyne CM, Gotto AM Jr, and Marian AJ (2004) Effects of PPARalpha, gamma and delta haplotypes on plasma levels of lipids, severity and progression of coronary atherosclerosis and response to statin therapy in the lipoprotein coronary atherosclerosis study. *Pharmacogenetics* **14:**61–71.

Chen W, Wang LL, Liu HY, Long L, and Li S (2008) Peroxisome proliferator-activated receptor delta-agonist, GW501516, ameliorates insulin resistance, improves dyslipidaemia in monosodium L-glutamate metabolic syndrome mice. *Basic Clin Pharmacol Toxicol* **103:**240–246.

Cheng L, Ding G, Qin Q, Huang Y, Lewis W, He N, Evans RM, Schneider MD, Brako FA, Xiao Y, et al. (2004) Cardiomyocyte-restricted peroxisome proliferator-activated receptor-delta deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. *Nat Med* **10:**1245–1250.

Chevillotte E, Rieusset J, Roques M, Desage M, and Vidal H (2001) The regulation of uncoupling protein-2 gene expression by omega-6 polyunsaturated fatty acids in human skeletal muscle cells involves multiple pathways, including the nuclear receptor peroxisome proliferator-activated receptor beta. *J Biol Chem* **276:**10853–10860.

Chew CH, Samian MR, Najimudin N, and Tengku-Muhammad TS (2003) Molecular characterisation of six alternatively spliced variants and a novel promoter in human peroxisome proliferator-activated receptor alpha. *Biochem Biophys Res Commun* **305:**235–243.

Chin ER, Olson EN, Richardson JA, Yang Q, Humphries C, Shelton JM, Wu H, Zhu W, Bassel-Duby R, and Williams RS (1998) A calcineurin-dependent transcriptional pathway controls skeletal muscle fiber type. *Genes Dev* **12:**2499–2509.

Christodoulides C, Dyson P, Sprecher D, Tsintzas K, and Karpe F (2009) Circulating FGF21 is induced by PPAR agonists but not ketosis in Man. *J Clin Endocrinol Metab* doi: jc.2009-0111v1.

Cimini A, Bernardo A, Cifone MG, Di Marzio L, Di Loreto S, Cifone G, and Di Muzio L (2003) TNFalpha downregulates PPARdelta expression in oligodendrocyte progenitor cells: implications for demyelinating diseases. *Glia* **41:**3–14.

Clausen T (1986) Regulation of active Na^+-K^+ transport in skeletal muscle. *Physiol Rev* **66:**542–580.

Constantin-Teodosiu D, Baker DJ, Constantin D, and Greenhaff PL (2009) PPARdelta agonism inhibits skeletal muscle PDC activity, mitochondrial ATP production and force generation during prolonged contraction. *J Physiol* **587:**231–239.

Constantin D, Constantin-Teodosiu D, Layfield R, Tsintzas K, Bennett AJ, and Greenhaff PL (2007) PPARdelta agonism induces a change in fuel metabolism and activation of an atrophy programme, but does not impair mitochondrial function in rat skeletal muscle. *J Physiol* **583:**381–390.

Cronet P, Petersen JF, Folmer R, Blomberg N, Sjöblom K, Karlsson U, Lindstedt EL, and Bamberg K (2001) Structure of the PPARalpha and -gamma ligand binding domain in complex with AZ 242; ligand selectivity and agonist activation in the PPAR family. *Structure* **9:**699–706.

Dagenais GR, Tancredi RG, and Zierler KL (1976) Free fatty acid oxidation by forearm muscle at rest, and evidence for an intramuscular lipid pool in the human forearm. *J Clin Invest* **58:**421–431.

Daugaard JR, Nielsen JN, Kristiansen S, Andersen JL, Hargreaves M, and Richter EA (2000) Fiber type-specific expression of GLUT4 in human skeletal muscle: influence of exercise training. *Diabetes* **49:**1092–1095.

de Lange P, Farina P, Moreno M, Ragni M, Lombardi A, Silvestri E, Burrone L, Lanni A, and Goglia F (2006) Sequential changes in the signal transduction responses of skeletal muscle following food deprivation. *FASEB J* **20:**2579–2581.

de Lange P, Ragni M, Silvestri E, Moreno M, Schiavo L, Lombardi A, Farina P, Feola A, Goglia F, and Lanni A (2004) Combined cDNA array/RT-PCR analysis of gene expression profile in rat gastrocnemius muscle: relation to its adaptive function in energy metabolism during fasting. *FASEB J* **18:**350–352.

DeFronzo RA (1988) Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* **37:**667–687.

DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, and Felber JP (1981) The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* **30:**1000–1007.

Degenhardt T, Saramäki A, Malinen M, Rieck M, Väisänen S, Huotari A, Herzig KH, Müller R, and Carlberg C (2007) Three members of the human pyruvate dehydrogenase kinase gene family are direct targets of the peroxisome proliferator-activated receptor beta/delta. *J Mol Biol* **372:**341–355.

Delp MD and Duan C (1996) Composition and size of type I, IIA, IID/X, and IIB fibers and citrate synthase activity of rat muscle. *J Appl Physiol* **80:**261–270.

Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, and Wahli W (1996) The PPARalpha-leukotriene B4 pathway to inflammation control. *Nature* **384:**39–43.

DiRenzo J, Söderstrom M, Kurokawa R, Ogliastro MH, Ricote M, Ingrey S, Hörlein A, Rosenfeld MG, and Glass CK (1997) Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors. *Mol Cell Biol* **17:**2166–2176.

Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevrivy DJ, and Leid M (1997) p300 functions as a coactivator for the peroxisome proliferator-activated receptor alpha. *J Biol Chem* **272:**33435–33443.

Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevrivy DJ, and Leid M (1999) Identification of nuclear receptor corepressor as a peroxisome proliferator-activated receptor alpha interacting protein. *J Biol Chem* **274:**15901–15907.

Dressel U, Allen TL, Pippal JB, Rohde PR, Lau P, and Muscat GE (2003) The peroxisome proliferator-activated receptor beta/delta agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. *Mol Endocrinol* **17:**2477–2493.

Escher P, Braissant O, Basu-Modak S, Michalik L, Wahli W, and Desvergne B (2001) Rat PPARs: quantitative analysis in adult rat tissues and regulation in fasting and refeeding. *Endocrinology* **142:**4195–4202.

Fajas L, Auboeuf D, Raspé E, Schoonjans K, Lefebvre AM, Saladin R, Najib J, Laville M, Fruchart JC, Deeb S, et al. (1997) The organization, promoter analysis, and expression of the human PPARgamma gene. *J Biol Chem* **272:**18779–18789.

Feige JN and Auwerx J (2007) Transcriptional coregulators in the control of energy homeostasis. *Trends Cell Biol* **17:**292–301.

Feige JN, Gelman L, Tudor C, Engelborghs Y, Wahli W, and Desvergne B (2005) Fluorescence imaging reveals the nuclear behavior of peroxisome proliferator-activated receptor/retinoid X receptor heterodimers in the absence and presence of ligand. *J Biol Chem* **280:**17880–17890.

Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, and Evans RM (1995) 15-Deoxy-delta 12,14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. *Cell* **83:**803–812.

Fritz T, Krämer DK, Karlsson HK, Galuska D, Engfeldt P, Zierath JR, and Krook A (2006) Low-intensity exercise increases skeletal muscle protein expression of PPARdelta and UCP3 in type 2 diabetic patients. *Diabetes Metab Res Rev* **2:**492–498.

Fruchart JC, Duriez P, and Staels B (1999) Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. *Curr Opin Lipidol* **10:**245–257.

Gaudel C, Schwartz C, Giordano C, Abumrad NA, and Grimaldi PA (2008) Pharmacological activation of PPARbeta promotes rapid and calcineurin-dependent fiber remodeling and angiogenesis in mouse skeletal muscle. *Am J Physiol Endocrinol Metab* **295:**E297–E304.

Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, et al. (2006) Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial [published erratum appears in *Lancet* **368:**1770, 2006]. *Lancet* **368:**1096–1105.

Gervois P, Fruchart JC, and Staels B (2007) Drug Insight: mechanisms of action and therapeutic applications for agonists of peroxisome proliferator-activated receptors. *Nat Clin Pract Endocrinol Metab* **3:**145–156.

Gervois P, Torra IP, Chinetti G, Grötzinger T, Dubois G, Fruchart JC, Fruchart-Najib J, Leitersdorf E, and Staels B (1999) A truncated human peroxisome proliferator-activated receptor alpha splice variant with dominant negative activity. *Mol Endocrinol* **13:**1535–1549.

Gilde AJ, van der Lee KA, Willemsen PH, Chinetti G, van der Leij FR, van der Vusse GJ, Staels B, and van Bilsen M (2003) Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. *Circ Res* **92:**518–524.

Gillilan RE, Ayers SD, and Noy N (2007) Structural basis for activation of fatty acid-binding protein 4. *J Mol Biol* **372:**1246–1260.

Glass CK and Rosenfeld MG (2000) The coregulator exchange in transcriptional functions of nuclear receptors. *Genes Dev* **14:**121–141.

Gouni-Berthold I, Giannakidou E, Faust M, Berthold HK, and Krone W (2005) The peroxisome proliferator-activated receptor delta +294T/C polymorphism in relation to lipoprotein metabolism in patients with diabetes mellitus type 2 and in non-diabetic controls. *Atherosclerosis* **183:**336–341.

Grarup N, Albrechtsen A, Ek J, Borch-Johnsen K, Jørgensen T, Schmitz O, Hansen T, and Pedersen O (2007) Variation in the peroxisome proliferator-activated receptor delta gene in relation to common metabolic traits in 7,495 middle-aged white people. *Diabetologia* **50:**1201–1208.

Guardiola-Diaz HM, Rehnmark S, Usuda N, Albrektsen T, Feltkamp D, Gustafsson JA, and Alexson SE (1999) Rat peroxisome proliferator-activated receptors and brown adipose tissue function during cold acclimatization. *J Biol Chem* **274:** 23368–23377.

Gupta RA, Wang D, Katkuri S, Wang H, Dey SK, and DuBois RN (2004) Activation of nuclear hormone receptor peroxisome proliferator-activated receptor-delta accelerates intestinal adenoma growth. *Nat Med* **10:**245–247.

Han JK, Lee HS, Yang HM, Hur J, Jun SI, Kim JY, Cho CH, Koh GY, Peters JM, Park KW, et al. (2008) Peroxisome proliferator-activated receptor-delta agonist enhances vasculogenesis by regulating endothelial progenitor cells through genomic and nongenomic activations of the phosphatidylinositol 3-kinase/Akt pathway. *Circulation* **118:**1021–1033.

Hancock CR, Han DH, Chen M, Terada S, Yasuda T, Wright DC, and Holloszy JO (2008) High-fat diets cause insulin resistance despite an increase in muscle mitochondria. *Proc Natl Acad Sci U S A* **105:**7815–7820.

Handschin C and Spiegelman BM (2008) The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature* **454:**463–469.

Harridge SD (2007) Plasticity of human skeletal muscle: gene expression to in vivo function. *Exp Physiol* **92:**783–797.

Hautala AJ, Leon AS, Skinner JS, Rao DC, Bouchard C, and Rankinen T (2007) Peroxisome proliferator-activated receptor-delta polymorphisms are associated with physical performance and plasma lipids: the HERITAGE Family Study. *Am J Physiol Heart Circ Physiol* **292:**H2498–H2505.

Hawley JA and Holloszy JO (2009) Exercise: it's the real thing! *Nutr Rev* **67:**172–178.

Hawley JA and Zierath JR (2004) Integration of metabolic and mitogenic signal transduction in skeletal muscle. *Exerc Sport Sci Rev* **32:**4–8.

Henriksen EJ, Bourey RE, Rodnick KJ, Koranyi L, Permutt MA, and Holloszy JO (1990) Glucose transporter protein content and glucose transport capacity in rat skeletal muscles. *Am J Physiol* **259:**E593–E598.

Hernández-Alvarez MI, Chiellini C, Manco M, Naon D, Liesa M, Palacín M, Mingrone G, and Zorzano A (2009) Genes involved in mitochondrial biogenesis/function are induced in response to bilio-pancreatic diversion in morbidly obese individuals with normal glucose tolerance but not in type 2 diabetic patients. *Diabetologia* **52:**1618–1627.

Hollingshead HE, Killins RL, Borland MG, Girroir EE, Billin AN, Willson TM, Sharma AK, Amin S, Gonzalez FJ, and Peters JM (2007) Peroxisome proliferator-activated receptor-beta/delta (PPARbeta/delta) ligands do not potentiate growth of human cancer cell lines. *Carcinogenesis* **28:**2641–2649.

Holloszy JO and Booth FW (1976) Biochemical adaptations to endurance exercise in muscle. *Annu Rev Physiol* **38:**273–291.

Holloszy JO and Coyle EF (1984) Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol* **56:**831–838.

Holness MJ, Kraus A, Harris RA, and Sugden MC (2000) Targeted upregulation of pyruvate dehydrogenase kinase (PDK)-4 in slow-twitch skeletal muscle underlies the stable modification of the regulatory characteristics of PDK induced by high-fat feeding. *Diabetes* **49:**775–781.

Holst D, Luquet S, Nogueira V, Kristiansen K, Leverve X, and Grimaldi PA (2003) Nutritional regulation and role of peroxisome proliferator-activated receptor delta in fatty acid catabolism in skeletal muscle. *Biochim Biophys Acta* **1633:**43–50.

Houmard JA (2008) Intramuscular lipid oxidation and obesity. *Am J Physiol Regul Integr Comp Physiol* **294:**R1111–R1116.

Hu C, Jia W, Fang Q, Zhang R, Wang C, Lu J, and Xiang K (2006) Peroxisome proliferator-activated receptor (PPAR) delta genetic polymorphism and its association with insulin resistance index and fasting plasma glucose concentrations in Chinese subjects. *Diabet Med* **23:**1307–1312.

Jeoung NH and Harris RA (2008) Pyruvate dehydrogenase kinase-4 deficiency lowers blood glucose and improves glucose tolerance in diet-induced obese mice. *Am J Physiol Endocrinol Metab* **295:**E46–E54.

Jucker BM, Yang D, Casey WM, Olzinski AR, Williams C, Lenhard SC, Legos JJ, Hawk CT, Sarkar SK, and Newsholme SJ (2007) Selective PPARdelta agonist treatment increases skeletal muscle lipid metabolism without altering mitochondrial energy coupling: an in vivo magnetic resonance spectroscopy study. *Am J Physiol Endocrinol Metab* **293:**E1256–E1264.

Juel C (1996) Lactate/proton co-transport in skeletal muscle: regulation and importance for pH homeostasis. *Acta Physiol Scand* **156:**369–374.

Juge-Aubry C, Pernin A, Favez T, Burger AG, Wahli W, Meier CA, and Desvergne B (1997) DNA binding properties of peroxisome proliferator-activated receptor subtypes on various natural peroxisome proliferator response elements. importance of the 5′-flanking region. *J Biol Chem* **272:**25252–25259.

Kang K, Reilly SM, Karabacak V, Gangl MR, Fitzgerald K, Hatano B, and Lee CH (2008) Adipocyte-derived Th2 cytokines and myeloid PPARdelta regulate macrophage polarization and insulin sensitivity. *Cell Metab* **7:**485–495.

Karpe F and Ehrenborg EE (2009) PPARdelta in humans: genetic and pharmacological evidence for a significant metabolic function. *Curr Opin Lipidol* **20:**333–336.

Kiens B (2006) Skeletal muscle lipid metabolism in exercise and insulin resistance. *Physiol Rev* **86:**205–243.

Kim HI and Ahn YH (2004) Role of peroxisome proliferator-activated receptor-gamma in the glucose-sensing apparatus of liver and beta-cells. *Diabetes* **53 (Suppl 1):**S60–S65.

Kim HJ, Woo IS, Kang ES, Eun SY, Kim HJ, Lee JH, Chang KC, Kim JH, and Seo HG (2006) Identification of a truncated alternative splicing variant of human PPARgamma1 that exhibits dominant negative activity. *Biochem Biophys Res Commun* **347:**698–706.

Kleiner S, Nguyen-Tran V, Baré O, Huang X, Spiegelman B, and Wu Z (2009) PPARδ agonism activates fatty acid oxidation via PGC-1α but does not increase mitochondrial gene expression and function. *J Biol Chem* 284:18624–18633.

Kliewer SA, Lenhard JM, Willson TM, Patel I, Morris DC, and Lehmann JM (1995) A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. *Cell* **83:**813–819.

Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, et al. (1997) Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. *Proc Natl Acad Sci U S A* **94:**4318–4323.

Kliewer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature* **358:**771–774.

Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, Bain J, Stevens R, Dyck JR, Newgard CB, et al. (2008) Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab* **7:**45–56.

Krämer DK, Ahlsén M, Norrbom J, Jansson E, Hjeltnes N, Gustafsson T, and Krook A (2006) Human skeletal muscle fibre type variations correlate with PPARalpha, PPARdelta and PGC-1alfa mRNA [published erratum appears in *Acta Physiol* (*Oxf*) **189:**101, 2007]. *Acta Physiol* (*Oxf*) **188:**207–216.

Krämer DK, Al-Khalili L, Guigas B, Leng Y, Garcia-Roves PM, and Krook A (2007) Role of AMP kinase and PPARdelta in the regulation of lipid and glucose metabolism in human skeletal muscle. *J Biol Chem* **282:**19313–19320.

Krämer DK, Al-Khalili L, Perrini S, Skogsberg J, Wretenberg P, Kannisto K, Wallberg-Henriksson H, Ehrenborg E, Zierath JR, and Krook A (2005) Direct activation of glucose transport in primary human myotubes after activation of peroxisome proliferator-activated receptor delta. *Diabetes* **54:**1157–1163.

Krogsdam AM, Nielsen CA, Neve S, Holst D, Helledie T, Thomsen B, Bendixen C, Mandrup S, and Kristiansen K (2002) Nuclear receptor corepressor-dependent

repression of peroxisome-proliferator-activated receptor delta-mediated transactivation. *Biochem J* **363:**157–165.
Lagou V, Scott RA, Manios Y, Chen TL, Wang G, Grammatikaki E, Kortsalioudaki C, Liarigkovinos T, Moschonis G, Roma-Giannikou E, et al. (2008) Impact of peroxisome proliferator-activated receptors gamma and delta on adiposity in toddlers and preschoolers in the GENESIS Study. *Obesity* (*Silver Spring*) **16:**913–918.
Lazennec G, Canaple L, Saugy D, and Wahli W (2000) Activation of peroxisome proliferator-activated receptors (PPARs) by their ligands and protein kinase A activators. *Mol Endocrinol* **14:**1962–1975.
Lecker SH, Jagoe RT, Gilbert A, Gomes M, Baracos V, Bailey J, Price SR, Mitch WE, and Goldberg AL (2004) Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *FASEB J* **18:**39–51.
Lee CH, Olson P, Hevener A, Mehl I, Chong LW, Olefsky JM, Gonzalez FJ, Ham J, Kang H, Peters JM, et al. (2006) PPARdelta regulates glucose metabolism and insulin sensitivity. *Proc Natl Acad Sci U S A* **103:**3444–3449.
Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, and Kliewer SA (1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* **270:**12953–12956.
Lehrke M and Lazar MA (2005) The many faces of PPARgamma. *Cell* **123:**993–999.
Leibowitz MD, Fiévet C, Hennuyer N, Peinado-Onsurbe J, Duez H, Bergera J, Cullinan CA, Sparrow CP, Baffic J, Berger GD, et al. (2000) Activation of PPARdelta alters lipid metabolism in *db/db* mice. *FEBS Lett* **473:**333–336.
Levy J (1999) Abnormal cell calcium homeostasis in type 2 diabetes mellitus: a new look on old disease. *Endocrine* **10:**1–6.
Lillioja S, Young AA, Culter CL, Ivy JL, Abbott WG, Zawadzki JK, Yki-Järvinen H, Christin L, Secomb TW, and Bogardus C (1987) Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. *J Clin Invest* **80:**415–424.
Lim HJ, Moon I, and Han K (2004) Transcriptional cofactors exhibit differential preference toward peroxisome proliferator-activated receptors alpha and delta in uterine cells. *Endocrinology* **145:**2886–2895.
Lin J, Handschin C, and Spiegelman BM (2005) Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab* **1:**361–370.
Lin J, Wu H, Tarr PT, Zhang CY, Wu Z, Boss O, Michael LF, Puigserver P, Isotani E, Olson EN, et al. (2002) Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature* **418:**797–801.
Lin Q, Ruuska SE, Shaw NS, Dong D, and Noy N (1999) Ligand selectivity of the peroxisome proliferator-activated receptor alpha. *Biochemistry* **38:**185–190.
Long YC and Zierath JR (2006) AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest* **116:**1776–1783.
Lundell K, Thulin P, Hamsten A, and Ehrenborg E (2007) Alternative splicing of human peroxisome proliferator-activated receptor delta (PPAR delta): effects on translation efficiency and trans-activation ability. *BMC Mol Biol* **8:**70.
Luquet S, Lopez-Soriano J, Holst D, Fredenrich A, Melki J, Rassoulzadegan M, and Grimaldi PA (2003) Peroxisome proliferator-activated receptor delta controls muscle development and oxidative capability. *FASEB J* **17:**2299–2301.
Luquet S, Lopez-Soriano J, Holst D, Gaudel C, Jehl-Pietri C, Fredenrich A, and Grimaldi PA (2004) Roles of peroxisome proliferator-activated receptor delta (PPARdelta) in the control of fatty acid catabolism. A new target for the treatment of metabolic syndrome. *Biochimie* **86:**833–837.
Mahoney DJ, Parise G, Melov S, Safdar A, and Tarnopolsky MA (2005) Analysis of global mRNA expression in human skeletal muscle during recovery from endurance exercise. *FASEB J* **19:**1498–1500.
Marin HE, Peraza MA, Billin AN, Willson TM, Ward JM, Kennett MJ, Gonzalez FJ, and Peters JM (2006) Ligand activation of peroxisome proliferator-activated receptor beta inhibits colon carcinogenesis. *Cancer Res* **66:**4394–4401.
Mayerson AB, Hundal RS, Dufour S, Lebon V, Befroy D, Cline GW, Enocksson S, Inzucchi SE, Shulman GI, and Petersen KF (2002) The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* **51:**797–802.
Mazzatti DJ, Smith MA, Oita RC, Lim FL, White AJ, and Reid MB (2008) Muscle unloading-induced metabolic remodeling is associated with acute alterations in PPARdelta and UCP-3 expression. *Physiol Genomics* **34:**149–161.
McCullagh KJ, Calabria E, Pallafacchina G, Ciciliot S, Serrano AL, Argentini C, Kalhovde JM, Lømo T, and Schiaffino S (2004) NFAT is a nerve activity sensor in skeletal muscle and controls activity-dependent myosin switching. *Proc Natl Acad Sci U S A* **101:**10590–10595.
Metabolex (2008) Metabolex announces positive results from phase 2 clinical trial of MBX-8025. Metabolex, Inc., Hayward, CA. Available at: http://www.metabolex.com/news/nov182008.html
Miyamoto T, Kakizawa T, Ichikawa K, Nishio S, Takeda T, Suzuki S, Kaneko A, Kumagai M, Mori J, Yamashita K, et al. (2001) The role of hinge domain in heterodimerization and specific DNA recognition by nuclear receptors. *Mol Cell Endocrinol* **181:**229–238.
Muoio DM, MacLean PS, Lang DB, Li S, Houmard JA, Way JM, Winegar DA, Corton JC, Dohm GL, and Kraus WE (2002) Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) alpha knock-out mice. Evidence for compensatory regulation by PPAR delta. *J Biol Chem* **277:**26089–26097.
Nagy L, Tontonoz P, Alvarez JG, Chen H, and Evans RM (1998) Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. *Cell* **93:**229–240.
Nahlé Z, Hsieh M, Pietka T, Coburn CT, Grimaldi PA, Zhang MQ, Das D, and Abumrad NA (2008) CD36-dependent regulation of muscle FoxO1 and PDK4 in the PPAR delta/beta-mediated adaptation to metabolic stress. *J Biol Chem* **283:**14317–14326.
Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H, et al. (2008) AMPK and PPARdelta agonists are exercise mimetics. *Cell* **134:**405–415.
Nilsson E, Poulsen P, Sjögren M, Ling C, Ridderstråle M, Groop L, and Vaag A (2007) Regulation of skeletal muscle PPAR delta mRNA expression in twins. *J Physiol* **584:**1011–1017.
Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, and Milburn MV (1998) Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. *Nature* **395:**137–143.
Nuclear Receptors Nomenclature Committee (1999) A unified nomenclature system for the nuclear receptor superfamily (Letter). Cell **97:**161–163.
Odegaard JI and Chawla A (2008) Mechanisms of macrophage activation in obesity-induced insulin resistance. *Nat Clin Pract Endocrinol Metab* **4:**619–626.
Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, Vats D, Morel CR, Goforth MH, Subramanian V, Mukundan L, Ferrante AW, and Chawla A (2008) Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. *Cell Metab* **7:**496–507.
Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznaidman ML, Lambert MH, et al. (2001) A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci U S A* **98:**5306–5311.
Opie LH and Sack MN (2002) Metabolic plasticity and the promotion of cardiac protection in ischemia and ischemic preconditioning. *J Mol Cell Cardiol* **34:**1077–1089.
Palmer CN, Hsu MH, Griffin KJ, Raucy JL, and Johnson EF (1998) Peroxisome proliferator activated receptor-alpha expression in human liver. *Mol Pharmacol* **53:**14–22.
Pan D, Fujimoto M, Lopes A, and Wang YX (2009) Twist-1 is a PPARdelta-inducible, negative-feedback regulator of PGC1alpha in brown fat metabolism. *Cell* **137:**73–86.
Pelton P (2006) GW-501516 GlaxoSmithKline/Ligand. *Curr Opin Investig Drugs* **7:**360–370.
Peters JM, Lee SS, Li W, Ward JM, Gavrilova O, Everett C, Reitman ML, Hudson LD, and Gonzalez FJ (2000) Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor beta(delta). *Mol Cell Biol* **20:**5119–5128.
Piqueras L, Reynolds AR, Hodivala-Dilke KM, Alfranca A, Redondo JM, Hatae T, Tanabe T, Warner TD, and Bishop-Bailey D (2007) Activation of PPARbeta/delta induces endothelial cell proliferation and angiogenesis. *Arterioscler Thromb Vasc Biol* **27:**63–69.
Reed KR, Sansom OJ, Hayes AJ, Gescher AJ, Winton DJ, Peters JM, and Clarke AR (2004) PPARdelta status and Apc-mediated tumourigenesis in the mouse intestine. *Oncogene* **23:**8992–8996.
Reilly SM and Lee CH (2008) PPAR delta as a therapeutic target in metabolic disease. *FEBS letters* **582:**26–31.
Remels AH, Schrauwen P, Broekhuizen R, Willems J, Kersten S, Gosker HR, and Schols AM (2007) Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. *Eur Respir J* **30:**245–252.
Rennie MJ (2007) Exercise- and nutrient-controlled mechanisms involved in maintenance of the musculoskeletal mass. *Biochem Soc Trans* **35:**1302–1305.
Rennie MJ, Wackerhage H, Spangenburg EE, and Booth FW (2004) Control of the size of the human muscle mass. *Annu Rev Physiol* **66:**799–828.
Risérus U, Sprecher D, Johnson T, Olson E, Hirschberg S, Liu A, Fang Z, Hegde P, Richards D, Sarov-Blat L, et al. (2008) 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* **57:**332–339.
Robitaille J, Gaudet D, Pérusse L, and Vohl MC (2007) Features of the metabolic syndrome are modulated by an interaction between the peroxisome proliferator-activated receptor-delta -87T>C polymorphism and dietary fat in French-Canadians. *Int J Obes* (*Lond*) **31:**411–417.
Russell AP, Feilchenfeldt J, Schreiber S, Praz M, Crettenand A, Gobelet C, Meier CA, Bell DR, Kralli A, Giacobino JP, et al. (2003) Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle. *Diabetes* **52:**2874–2881.
Russell AP, Hesselink MK, Lo SK, and Schrauwen P (2005) Regulation of metabolic transcriptional co-activators and transcription factors with acute exercise. *FASEB J* **19:**986–988.
Sabatino L, Casamassimi A, Peluso G, Barone MV, Capaccio D, Migliore C, Bonelli P, Pedicini A, Febbraro A, Ciccodicola A, et al. (2005) A novel peroxisome proliferator-activated receptor gamma isoform with dominant negative activity generated by alternative splicing. *J Biol Chem* **280:**26517–26525.
Sáez ME, Grilo A, Morón FJ, Manzano L, Martínez-Larrad MT, González-Pérez A, Serrano-Hernando J, Ruiz A, Ramírez-Lorca R, and Serrano-Ríos M (2008) Interaction between Calpain 5, Peroxisome proliferator-activated receptor-gamma and Peroxisome proliferator-activated receptor-delta genes: a polygenic approach to obesity. *Cardiovasc Diabetol* **7:**23.
Saluja I, Granneman JG, and Skoff RP (2001) PPAR delta agonists stimulate oligodendrocyte differentiation in tissue culture. *Glia* **33:**191–204.
Scarpulla RC (2008) Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol Rev* **88:**611–638.
Schiaffino S and Serrano A (2002) Calcineurin signaling and neural control of skeletal muscle fiber type and size. *Trends Pharmacol Sci* **23:**569–575.
Schug TT, Berry DC, Shaw NS, Travis SN, and Noy N (2007) Opposing effects of retinoic acid on cell growth result from alternate activation of two different nuclear receptors. *Cell* **129:**723–733.
Schuler M, Ali F, Chambon C, Duteil D, Bornert JM, Tardivel A, Desvergne B, Wahli W, Chambon P, and Metzger D (2006) PGC1 alpha expression is controlled in skeletal muscles by PPAR beta, whose ablation results in fiber-type switching, obesity, and type 2 diabetes. *Cell Metab* **4:**407–414.
Schulman IG, Shao G, and Heyman RA (1998) Transactivation by retinoid X receptor-peroxisome proliferator-activated receptor gamma (PPARgamma) het-

erodimers: intermolecular synergy requires only the PPARgamma hormone-dependent activation function. *Mol Cell Biol* **18:**3483–3494.

Seth A, Steel JH, Nichol D, Pocock V, Kumaran MK, Fritah A, Mobberley M, Ryder TA, Rowlerson A, Scott J, et al. (2007) The transcriptional corepressor RIP140 regulates oxidative metabolism in skeletal muscle. *Cell Metab* **6:**236–245.

Shalev A, Siegrist-Kaiser CA, Yen PM, Wahli W, Burger AG, Chin WW, and Meier CA (1996) The peroxisome proliferator-activated receptor alpha is a phosphoprotein: regulation by insulin. *Endocrinology* **137:**4499–4502.

Sher T, Yi HF, McBride OW, and Gonzalez FJ (1993) cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor. *Biochemistry* **32:**5598–5604.

Shi Y, Hon M, and Evans RM (2002) The peroxisome proliferator-activated receptor delta, an integrator of transcriptional repression and nuclear receptor signaling. *Proc Natl Acad Sci U S A* **99:**2613–2618.

Shin HD, Park BL, Kim LH, Jung HS, Cho YM, Moon MK, Park YJ, Lee HK, and Park KS (2004) Genetic polymorphisms in peroxisome proliferator-activated receptor delta associated with obesity. *Diabetes* **53:**847–851.

Sinacore DR and Gulve EA (1993) The role of skeletal muscle in glucose transport, glucose homeostasis, and insulin resistance: implications for physical therapy. *Phys Ther* **73:**878–891.

Skogsberg J, Kannisto K, Cassel TN, Hamsten A, Eriksson P, and Ehrenborg E (2003a) Evidence that peroxisome proliferator-activated receptor delta influences cholesterol metabolism in men. *Arterioscler Thromb Vasc Biol* **23:**637–643.

Skogsberg J, Kannisto K, Roshani L, Gagne E, Hamsten A, Larsson C, and Ehrenborg E (2000) Characterization of the human peroxisome proliferator activated receptor delta gene and its expression. *Int J Mol Med* **6:**73–81.

Skogsberg J, McMahon AD, Karpe F, Hamsten A, Packard CJ, Ehrenborg E, and West of Scotland Coronary Prevention Study (2003b) Peroxisome proliferator activated receptor delta genotype in relation to cardiovascular risk factors and risk of coronary heart disease in hypercholesterolaemic men. *J Intern Med* **254:**597–604.

Son C, Hosoda K, Matsuda J, Fujikura J, Yonemitsu S, Iwakura H, Masuzaki H, Ogawa Y, Hayashi T, Itoh H, et al. (2001) Up-regulation of uncoupling protein 3 gene expression by fatty acids and agonists for PPARs in L6 myotubes. *Endocrinology* **142:**4189–4194.

Song XM, Ryder JW, Kawano Y, Chibalin AV, Krook A, and Zierath JR (1999) Muscle fiber type specificity in insulin signal transduction. *Am J Physiol* **277:**R1690–R1696.

Spangenburg EE and Booth FW (2003) Molecular regulation of individual skeletal muscle fibre types. *Acta Physiol Scand* **178:**413–424.

Sprecher DL, Massien C, Pearce G, Billin AN, Perlstein I, Willson TM, Hassall DG, Ancellin N, Patterson SD, Lobe DC, et al. (2007) Triglyceride:high-density lipoprotein cholesterol effects in healthy subjects administered a peroxisome proliferator activated receptor delta agonist. *Arterioscler Thromb Vasc Biol* **27:**359–365.

Staiger H, Haas C, Machann J, Werner R, Weisser M, Schick F, Machicao F, Stefan N, Fritsche A, and Häring HU (2009) Muscle-derived angiopoietin-like protein 4 is induced by fatty acids via peroxisome proliferator-activated receptor (PPAR)-delta and is of metabolic relevance in humans. *Diabetes* **58:**579–589.

Stefan N, Thamer C, Staiger H, Machicao F, Machann J, Schick F, Venter C, Niess A, Laakso M, Fritsche A, et al. (2007) Genetic variations in PPARD and PPARGC1A determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle intervention. *J Clin Endocrinol Metab* **92:**1827–1833.

Takahashi S, Tanaka T, and Sakai J (2007) New therapeutic target for metabolic syndrome: PPARdelta. *Endocr J* **54:**347–357.

Talmadge RJ (2000) Myosin heavy chain isoform expression following reduced neuromuscular activity: potential regulatory mechanisms. *Muscle Nerve* **23:**661–679.

Tan NS, Michalik L, Desvergne B, and Wahli W (2004) Peroxisome proliferator-activated receptor-beta as a target for wound healing drugs. *Expert Opin Ther Targets* **8:**39–48.

Tan NS, Michalik L, Noy N, Yasmin R, Pacot C, Heim M, Flühmann B, Desvergne B, and Wahli W (2001) Critical roles of PPAR beta/delta in keratinocyte response to inflammation. *Genes Dev* **15:**3263–3277.

Tan NS, Shaw NS, Vinckenbosch N, Liu P, Yasmin R, Desvergne B, Wahli W, and Noy N (2002) Selective cooperation between fatty acid binding proteins and peroxisome proliferator-activated receptors in regulating transcription. *Mol Cell Biol* **22:**5114–5127.

Tanaka T, Yamamoto J, Iwasaki S, Asaba H, Hamura H, Ikeda Y, Watanabe M, Magoori K, Ioka RX, Tachibana K, et al. (2003) Activation of peroxisome proliferator-activated receptor delta induces fatty acid beta-oxidation in skeletal muscle and attenuates metabolic syndrome. *Proc Natl Acad Sci U S A* **100:**15924–15929.

Terada S, Wicke S, Holloszy JO, and Han DH (2006) PPARdelta activator GW-501516 has no acute effect on glucose transport in skeletal muscle. *Am J Physiol Endocrinol Metab* **290:**E607–E611.

Thamer C, Machann J, Stefan N, Schäfer SA, Machicao F, Staiger H, Laakso M, Böttcher M, Claussen C, Schick F, et al. (2008) Variations in PPARD determine the change in body composition during lifestyle intervention: a whole-body magnetic resonance study. *J Clin Endocrinol Metab* **93:**1497–1500.

Tomaru T, Satoh T, Yoshino S, Ishizuka T, Hashimoto K, Monden T, Yamada M, and Mori M (2006) Isolation and characterization of a transcriptional cofactor and its novel isoform that bind the deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-gamma. *Endocrinology* **147:**377–388.

Tontonoz P, Hu E, Graves RA, Budavari AI, and Spiegelman BM (1994) mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev* **8:**1224–1234.

Tsintzas K, Jewell K, Kamran M, Laithwaite D, Boonsong T, Littlewood J, Macdonald I, and Bennett A (2006) Differential regulation of metabolic genes in skeletal muscle during starvation and refeeding in humans. *J Physiol* **575:**291–303.

Uppenberg J, Svensson C, Jaki M, Bertilsson G, Jendeberg L, and Berkenstam A (1998) Crystal structure of the ligand binding domain of the human nuclear receptor PPARgamma. *J Biol Chem* **273:**31108–31112.

Vänttinen M, Nuutila P, Kuulasmaa T, Pihlajamäki J, Hällsten K, Virtanen KA, Lautamäki R, Peltoniemi P, Takala T, Viljanen AP, et al. (2005) Single nucleotide polymorphisms in the peroxisome proliferator-activated receptor delta gene are associated with skeletal muscle glucose uptake. *Diabetes* **54:**3587–3591.

Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, and Evans RM (2003) Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell* **113:**159–170.

Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, Bayuga-Ocampo CR, Ham J, Kang H, and Evans RM (2004) Regulation of muscle fiber type and running endurance by PPARdelta. *PLoS Biol* **2:**e294.

Watt MJ, Southgate RJ, Holmes AG, and Febbraio MA (2004) Suppression of plasma free fatty acids upregulates peroxisome proliferator-activated receptor (PPAR) alpha and delta and PPAR coactivator 1alpha in human skeletal muscle, but not lipid regulatory genes. *J Mol Endocrinol* **33:**533–544.

White R, Morganstein D, Christian M, Seth A, Herzog B, and Parker MG (2008) Role of RIP140 in metabolic tissues: connections to disease. *FEBS Lett* **582:**39–45.

Willson TM, Brown PJ, Sternbach DD, and Henke BR (2000) The PPARs: from orphan receptors to drug discovery. *J Med Chem* **43:**527–550.

Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, Troy A, Cinti S, Lowell B, Scarpulla RC, et al. (1999) Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **98:**115–124.

Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, et al. (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* **112:**1821–1830.

Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, et al. (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell* **3:**397–403.

Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Kliewer SA, Gampe RT Jr, McKee DD, et al. (2001) Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. *Proc Natl Acad Sci U S A* **98:**13919–13924.

Yu K, Bayona W, Kallen CB, Harding HP, Ravera CP, McMahon G, Brown M, and Lazar MA (1995) Differential activation of peroxisome proliferator-activated receptors by eicosanoids. *J Biol Chem* **270:**23975–23983.

Yu S and Reddy JK (2007) Transcription coactivators for peroxisome proliferator-activated receptors. *Biochim Biophys Acta* **1771:**936–951.

Zamir I, Zhang J, and Lazar MA (1997) Stoichiometric and steric principles governing repression by nuclear hormone receptors. *Genes Dev* **11:**835–846.

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