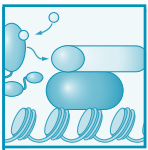


PHYSIOLOGICAL FUNCTIONS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR β

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Neels JG, Grimaldi PA. Physiological Functions of Peroxisome Proliferator-Activated Receptor β . *Physiol Rev* 94: 795–858, 2014; doi:10.1152/physrev.00027.2013.—The peroxisome proliferator-activated receptors, PPAR α , PPAR β , and PPAR γ , are a family of transcription factors activated by a diversity of molecules including fatty acids and fatty acid metabolites. PPARs regulate the transcription of a large variety of genes implicated in metabolism, inflammation, proliferation, and differentiation in different cell types. These transcriptional regulations involve both direct transactivation and interaction with other transcriptional regulatory pathways. The functions of PPAR α and PPAR γ have been extensively documented mainly because these isoforms are activated by molecules clinically used as hypolipidemic and antidiabetic compounds. The physiological functions of PPAR β remained for a while less investigated, but the finding that specific synthetic agonists exert beneficial actions in obese subjects uplifted the studies aimed to elucidate the roles of this PPAR isoform. Intensive work based on pharmacological and genetic approaches and on the use of both in vitro and in vivo models has considerably improved our knowledge on the physiological roles of PPAR β in various cell types. This review will summarize the accumulated evidence for the implication of PPAR β in the regulation of development, metabolism, and inflammation in several tissues, including skeletal muscle, heart, skin, and intestine. Some of these findings indicate that pharmacological activation of PPAR β could be envisioned as a therapeutic option for the correction of metabolic disorders and a variety of inflammatory conditions. However, other experimental data suggesting that activation of PPAR β could result in serious adverse effects, such as carcinogenesis and psoriasis, raise concerns about the clinical use of potent PPAR β agonists.

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I. INTRODUCTION

A. The Peroxisome Proliferator-Activated Receptor Subfamily

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. This superfamily, that comprises 48 members in human, includes endocrine receptors, such as steroid and thyroid hormone receptors, receptors activated by metabolites, such as PPARs and farnesoid X receptor, and orphan receptors which are constitutively activated or with unknown ligands. There are three different PPAR isoforms called α (NR1C1), β (NR1C2), and γ (NR1C3). The first PPAR, currently called PPAR α , was cloned from a mouse liver complementary

DNA library in 1990 by a group working on the mechanisms implicated in the promoting action of a variety of chemicals, such as hypolipidemic drugs or industrial plasticizers, on peroxisomal proliferation in rodent liver, hence the name of peroxisome proliferator-activated receptor (254). The identified protein presented a high degree of similarity with several members of the nuclear hormone receptor superfamily and displayed high expression levels in liver, kidney, heart, and brown adipose tissue. By using a transactivation assay, the authors demonstrated that PPAR α was activated by several hypolipidemic peroxisome proliferators, including fibrates, by phthalates, and also by saturated and unsaturated middle- and long-chain fatty acids (255).

Soon after its identification, it was demonstrated that PPAR α activates the transcription of the rat acyl CoA oxidase (ACO), the rate-limiting enzyme of peroxisomal fatty acid oxidation, and that this transcriptional induction involved the binding of PPAR α to the sequence TGACCTTT-GTCCT identified in the rat ACO promoter and termed peroxisome proliferator response element (PPRE) (597). Furthermore, the same group showed that the retinoid X receptor (RXR) was required for the binding of PPAR α to

the ACO PPRE and that activation of RXR by 9-*cis*-retinoic acid enhanced PPAR α action (255).

Two other PPAR isoforms called PPAR β (also called PPAR δ , NUC1, and FAAR) and PPAR γ were then found in *Xenopus laevis* (136), human (193, 508), and mouse (18, 91, 296, 682). The PPAR isoforms are encoded by separate genes located on different chromosomes, e.g., on chromosomes 22, 6, and 3 for the human isoforms α , β , and γ , respectively, and on chromosomes 15, 6, and 17 for the mouse isoforms α , β , and γ , respectively.

PPARs display a classical nuclear receptor organization in several functional domains. The NH₂ terminus region called A/B domain contains a ligand-independent transcriptional activation function (AF-1) (FIGURE 1A). Compared with other nuclear receptors, the activity of such AF-1 remains weak in PPAR α and γ isoforms and is almost insignificant in PPAR β . This lower functionality of AF-1 in PPAR β could be due to the shorter size of the A/B domain, e.g., 72 amino acids in mouse PPAR β protein versus more than 100 amino acids in the mouse α and γ isoforms. The central region or C domain is implicated in binding with PPRE via a two zinc-finger motif which is the hallmark of the nuclear receptors (FIGURE 1A). The DNA-binding region is highly conserved among the nuclear hormone receptors, and this characteristic has been used for the cloning of many nuclear receptors, including the PPARs, by low-stringency cross-hybridization screening of complementary DNA libraries with degenerated oligonucleotides covering this DNA sequence. The COOH-terminal region (D/E/F) contains the ligand-binding domain and is implicated in receptor heterodimerization with the obligatory transcriptional partner RXR (FIGURE 1A), which is another member of the nuclear hormone receptor superfamily (518), and interaction with coactivators (133, 134, 415) and corepressors (133). This region also contains a transcriptional activation function-2 (AF-2) motif that is required for ligand-dependent transcription activation.

Determination of the crystal structure of the ligand-binding domain (LBD) of the PPAR isoforms revealed that the three isoforms display a general structure already described for many other nuclear receptors. However, these studies also revealed some particularities in the PPAR LBD that appear larger and more hydrophobic than in other nuclear receptors, explaining the ability of PPARs to bind a very large variety of natural and synthetic lipophilic molecules (133, 605, 653) and some subtle differences within the LBD of PPAR isoforms that could be functionally important as determining isoform ligand selectivity (570, 654). Furthermore, these studies indicated that ligand binding stabilizes the COOH-terminal α helix of PPAR LBD in a conformation that favors interaction with coactivators and release of corepressor proteins, promoting transcriptional activity (FIGURE 1, B AND C) (272, 391, 685).

PPAR isoforms are expressed in a large variety of tissues and cell types. However, their expression levels are tissue dependent and modified by the physiological status in some tissues. PPAR α is expressed at high levels in tissues with elevated fatty acid catabolism such as liver, intestine, brown adipose tissue, and heart (255). Two forms of PPAR γ differing at their NH₂ terminus have been identified and display distinct expression patterns. PPAR γ 2 is almost exclusively found in white and brown adipocytes (590), while PPAR γ 1 is found in a larger variety of cell types and organs such as macrophages, vascular cells, gut, and brain (683). PPAR β mRNA displays a broad pattern of expression with higher mRNA amounts in intestine, heart, and liver than in brain and spleen (60, 269, 296).

The lack of specificity of commercially available PPAR β antibodies is a great limitation for the conclusions of several studies aimed to investigate the PPAR β expression at the protein level. By using quantitative Western blotting experiment and both positive and negative controls (in vitro translated PPAR β and tissues from PPAR β -deficient mice, respectively), Girroir et al. (186) provided the most compelling study on the expression patterns of PPAR β in mouse tissues. Quantitative Western blot analyses revealed that PPAR β expression is very high in small intestine and keratinocytes; high in liver, colon, kidney, and skin; and low in other tissues including brain, heart, lung, skeletal muscle, testis, spleen, and thymus. Further analyses showed that PPAR β protein is mostly found in nuclear fractions of these tissues and can be coimmunoprecipitated with RXR (186). However, it is important to note that the expression levels of both PPAR β mRNA and protein are different in the various cell types in a given tissue, as for instance higher expression levels in keratinocytes than in other skin cell types (186), higher expression levels in crypts than in upper part of the villi in small intestine and colon (389), or higher levels in oxidative than in glycolytic skeletal muscle fibers (631). Furthermore, expression levels of PPARs are subjected to physiological modifications in a tissue-dependent manner. For instance, during fasting, the PPAR β expression levels are reduced in liver (143) and increased in skeletal muscle (238).

It is now established that covalent modifications by phosphorylation, ubiquitination, or sumoylation are implicated in the regulation of PPAR α and PPAR γ functions, while information about such modifications for PPAR β are still limited. For instance, numerous studies have shown that PPAR α and PPAR γ are phosphorylated by various kinases, such as protein kinases A and C, mitogen-activated protein kinases, and AMP kinase (AMPK), and that these phosphorylations affect their activity at several steps including proteosomal degradation, ligand affinity, and DNA binding (80). Although it was reported that transcriptional activity of PPAR β is modulated by some signaling kinases, such as protein kinase A (207, 309, 319) and p38 mitogen-

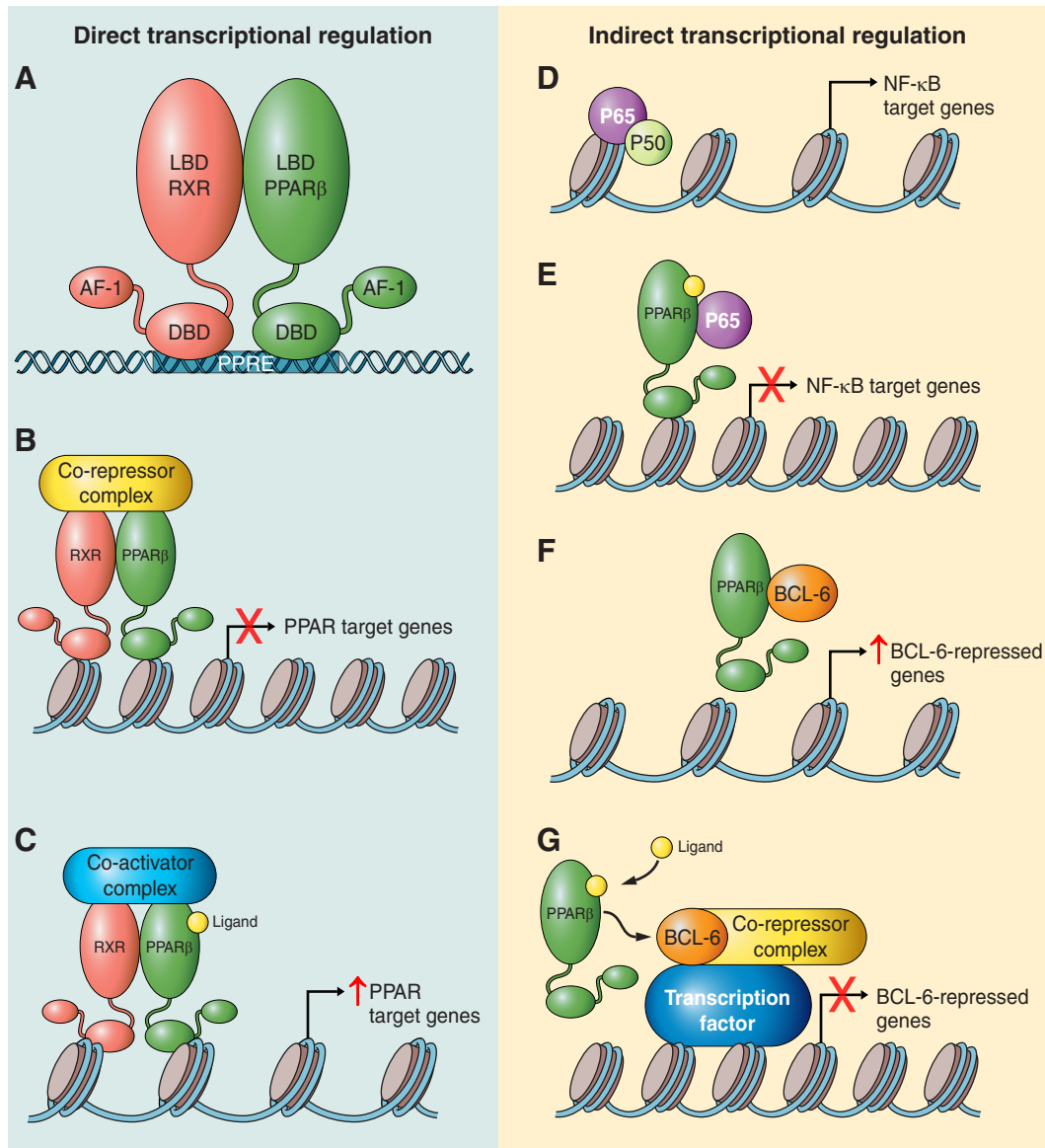


FIGURE 1. Molecular modes of action of PPAR β . Simplified scheme illustrating examples of direct and indirect transcriptional regulation by PPAR β . *A*: PPAR β can directly regulate transcription of target genes by forming a heterodimer with RXR and binding to PPRE sequences in the promoter- or transcribed-regions of target genes through DNA binding domains (DBD). Both nuclear receptors exhibit a similar organization in several functional domains. The NH₂-terminal region contains a ligand-independent transcriptional activation function (AF-1) domain, while the COOH-terminal region contains the ligand-binding domain (LBD). *B*: in the absence of ligand, the PPAR β /RXR heterodimer interacts with corepressors and other proteins, which results in recruitment of histone deacetylases (HDACs) and subsequent changes toward tight chromatin structure and transcription repression. *C*: the ligand binding-induced conformational change in PPAR β promotes a release of the corepressor complex and interaction with coactivators that directly or through recruitment of coactivator-associated proteins induces a chromatin structure remodeling by histone acetylation or methylation, stimulating transcription of PPAR β target genes. PPAR β can also indirectly regulate transcription. *D*: in the absence of ligand-bound PPAR β , the NF- κ B heterodimer consisting of P65 and P50 transactivates the transcription of its target genes. *E*: one of several ways by which PPAR β activation can indirectly regulate transcription of NF- κ B target genes is by directly interacting with P65 and thereby decreasing association of the NF- κ B dimer to its response element and inhibiting transcription of NF- κ B target genes. Another example by which PPAR β can indirectly regulate transcription is by interacting with the corepressor BCL-6. *F*: in this case, it is the inactive form of PPAR β that binds to BCL-6 and, as a result, BCL-6 is not available to repress the transcription of its target genes. *G*: activation of PPAR β leads to release of BCL-6, and the corepressor is able to perform its function and repress the transcription of target genes.

activated protein kinase (307), direct experimental data on the effect of phosphorylation on PPAR β transcriptional activity are still lacking. It has also been reported that the three PPAR isoforms are posttranslationally modified by ubiquitination, and these covalent modifications differently affect their transcriptional functions (622). Specifically, PPAR γ is rapidly ubiquitinated and degraded by the proteasome upon exposure to ligands (215). PPAR α is a short-lived protein, and ligand binding prevents its ubiquitination and its degradation by the proteasome; however, this protective effect of the ligand disappears after a few hours and the PPAR α protein is then rapidly degraded (55). PPAR β is also ubiquitinated in the absence of ligand and displays a short half-life, but when ligands are present, the PPAR β protein is protected from degradation by the proteasome by a specific inhibition of ubiquitination. Interestingly, this protection against degradation of both endogenous and ectopically expressed PPAR β protein is maintained as long as the ligand is present (181). In that respect, PPAR β displays a very singular feature as most members of the nuclear receptor family exhibit ligand-induced proteosomal degradation. This aspect could be important in physiological or pathological situations characterized by the production of high concentrations of natural PPAR β ligands or when synthetic ligands are chronically administered.

B. PPAR Agonists

The actual nature of endogenous PPAR ligands still remains a partially unsolved question. It is generally accepted that fatty acids, or more likely, fatty acid metabolites, are physiologically capable to bind and activate the three PPAR isoforms. Initial studies revealed that saturated and unsaturated long-chain fatty acids (LCFA) bind to PPAR α with almost similar affinity (K_d values ranging from 1 to 2 μ M) and less efficiently to PPAR β (K_d values from 3 to 10 μ M), while only unsaturated LCFA are able to bind to PPAR γ (163, 653). They also showed that metabolites of unsaturated LCFA interact more efficiently with PPARs and displayed strong isoform selectivity. For instance, 15-deoxy- Δ -12,14-PGJ₂ (15d-PGJ₂), a naturally occurring metabolite of prostaglandin D₂, is a potent and specific ligand/activator of PPAR γ (164, 297), while leukotriene B₄ and oleylethanolamide specifically bind and activate PPAR α (120, 171). Prostacyclin (PGI₂) has been described as a potent PPAR β agonist (214, 336), and several studies have proposed important regulatory roles for the PGI₂/PPAR β axis in various contexts, such as embryo hatching and implantation (278, 425) and vascular physiology (28, 283, 592). However, other authors provided experimental evidence arguing against an important physiological role of PGI₂ in PPAR β activation (152, 673). More recently, the arachidonic acid metabolite 15-hydroxyeicosatetraenoic acid (15-HETE) was shown to be a strong PPAR β agonist, while displaying less affinity for the other PPAR isoforms (104, 409). Lipoperoxidation products, such as 4-hy-

droxynonenal (4-HNE), 4-hydroperoxynonenal (104), and 4-hydroperoxynonenal hydroxydodeca-(2E,6Z)-dienal (4-HDDE) (473) also activate PPAR β .

It has been reported that all-*trans*-retinoic acid (ATRA), that binds to retinoic acid receptors (RAR) with very high affinity (K_d of 0.2 nM for human RAR γ) (566), is also a high-affinity ligand for PPAR β (K_d of 17 nM) but not for the other PPAR isoforms (K_d of 100–200 nM) (529) and efficiently activates PPAR β -mediated transcription (514, 529). However, these observations should be viewed with caution as they are not confirmed by two independent laboratories that concluded that ATRA does not bind to PPAR β and does not promote transcription of PPAR β target genes in several cell lines (63, 64, 476).

In intact cell models such as cells in culture, high concentrations of fatty acids and fatty acid derivatives are required to efficiently activate the PPARs arguing against the actual role of these lipidic molecules as physiological PPAR activators. However, the rapid metabolism of FA and eicosanoids could explain why high concentrations of these molecules are required to activate the PPAR pathways during long-term incubations. The findings that nonmetabolized fatty acid derivatives, such as 2-bromopalmitate (18) and thiol-substituted fatty acids (317), or stabilized eicosanoids, such as carbaprostacyclin (cPGI₂) (336), are more active than their native instable counterparts support this hypothesis.

As PPARs have a nuclear localization, the nucleoplasmic concentration of their ligands must be consistent with the affinity range of PPARs for these compounds. Some mechanisms allowing a nuclear delivery of PPAR ligands can be proposed, although remaining largely hypothetical or only partially established.

Based on the observations of active nuclear lipid metabolism in several tissues (reviewed in Refs. 149, 363), it can be proposed that FAs or other PPAR activators, such as eicosanoids, are produced directly in the nucleus. For instance, the enzymes required for the synthesis of PGI₂, e.g., phospholipase A₂, cyclooxygenase 2 (COX-2), and PGI synthase, display a perinuclear localization in uterine stromal cells, suggesting that the activation of PPAR β required for blastocyst implantation is related to a nuclear synthesis of its natural ligand. At present, however, the actual involvement of nuclear lipid metabolism in PPAR transcriptional activation remains to be firmly established.

Furthermore, a model in which PPAR ligands are transported from the cytosol to the nucleus by the fatty acid binding proteins (FABPs) and delivered to the PPARs is proposed by some authors. FABPs are members of the intracellular lipid binding proteins (ILBPs) family and have been implicated in cytoplasmic transport of lipophilic li-

gands, including FAs and FA metabolites, to intracellular compartments or enzymes within the cell. FABP isoforms differ in their expression profile and also in their affinity and specificity toward ligands. FABPs are widely expressed, and several tissues contain more than one FABP isoform. However, organs with high lipid-metabolizing capacity are characterized by a remarkable richness of one specific FABP isoform. For instance, FABP1, -3, and -4 are the predominant isoforms in liver, heart, and adipose tissue, respectively, and their amount can reach several percent of cytosolic protein (543).

FABP2 displays a high specificity for LCFAs, while other isoforms, such as FABP4 and -5, bind FA with high affinity and also eicosanoids and retinoids but with much weaker affinity. In contrast, FABP1 is able to bind multiple ligands including FA, FA metabolites, bile acids, heme, and several xenobiotics (543). It has been clearly established that FABPs play important and tissue-specific functions in the regulation of fatty acid metabolism, such as fatty acid catabolism in cardiac and skeletal muscles, lipid storage in adipose tissue, or lipid assimilation in intestine (561).

Several experimental observations argued in favor of an implication of FABPs in nuclear lipid signaling. It has been demonstrated that some of the FABP isoforms, i.e., FABP1 (62), FABP3 (61), FABP4, and FABP5 (223), are present at significant level in nuclei of various tissues and are directly involved in the nuclear import of FA and other hydrophobic molecules (244, 245, 374, 562). More recently, it was shown by different methods that some of the FABP isoforms interact in a discriminating manner with the various PPARs and by this mean promote a selective PPAR-induced transcriptional activation by specific delivery of the ligand. For instance, one study showed that FABP1 interacts with PPAR α (244), while another study demonstrated interaction with PPAR α and PPAR γ but not with PPAR β (648). FABP5 interacts specifically with PPAR β (580) while FABP4 interacts with PPAR γ (6). As these FABP isoforms display tissue-specific expression profiles, such a model for a functional selective cooperation between FABP and PPAR duos could explain, at least partly, why a ligand able to activate different PPARs, e.g., LCFA, exerts selective activating action on a specific PPAR isoform. Notwithstanding these very interesting and exciting observations, wide acknowledgement of this model requires further experimental work to explore and confirm its validity in other tissues and various physiological conditions and also to clarify some crucial points that remain controversial. For instance, publications from one group provided data showing that the binding of specific ligands induces subtle conformational changes in FABP4 and FABP5 promoting nuclear import and protein/protein interaction with PPAR γ and PPAR β , respectively (24, 183, 580). In contrast to these observations, data from another group revealed that direct ligand binding is not required for FABP4 nuclear import but only

increased nuclear FABP4 localization (6) and, also that interactions of FABP1 with PPAR α (648) and of FABP4 with PPAR γ (6) do not depend on the presence of ligands.

A model of ATRA-selective delivery by members of the ILBP family toward RAR or PPAR β was more recently proposed. Functional cooperation was previously described between two proteins with very high affinity for ATRA, namely, cellular retinoic acid-II (CRABP-II) (K_d in the 0.1 nM range)(131) and RARs (K_d in the 0.2 nM range) (566). In this model, CRABP-II translocates from cytoplasm to nucleus and through protein/protein interaction, delivers ATRA to RARs (78, 118). More recently, Noy and colleagues (514) provided data showing that ATRA also binds to FABP5 with high affinity (K_d of 35 nM) and that such a binding promotes FABP5 translocation to the nucleus where it interacts with PPAR β leading to enhancement of PPAR β transcriptional activation (514). Furthermore, these authors found that the ratio of FABP5 to CRABP-II in the cell determines the level of activation by ATRA of either RAR or PPAR β . Indeed, ATRA activates both RAR and PPAR β in cells containing high amounts of FABP5 and low or very low amounts of CRABP-II, such as HaCaT keratinocytes and particular mammary carcinoma cell lines (514, 515), adipocytes (46), and terminally differentiating P19 embryonic carcinoma cells (674), while when the expression level of CRABP-II is high, e.g., in particular mammary carcinoma cells lines (515), preadipocytes (46), or early differentiating P19 cells (674), ATRA exerts its transcriptional effects by activating RAR and not PPAR β . This model proposing a dual transcriptional control by ATRA, through activation of two nuclear receptors with large panels of target genes, could partly explain the pleiotropic actions of the hormone, including control of cell proliferation, morphogenesis, and metabolism. However, such a model is far from being generally accepted for several reasons.

First of all, two independent laboratories demonstrated that ATRA does not act as a PPAR β agonist even when used at pharmacological concentrations and in cells displaying high FABP5 to CRAB-II ratio, such as HaCaT cells (63, 64, 476) or COLO16 human cells (93). Indeed, it was shown that treatment of these cells with ATRA activates the RAR target gene expression but does not promote association of PPAR β with coactivators and PPAR β -mediated transcriptional activation (63, 64, 476). Furthermore, important divergences have been reported for the binding affinities of ATRA with both FABP5 and PPAR β . As the physiological concentrations of retinoids in serum and tissues are within the 1 to 10 nM range (113, 277, 398), it is clear that the affinity of retinoic acid for ILBPs and nuclear receptors must be in the same range of concentrations. For instance, these affinities are in the 0.1–0.2 nM window for the CRABP-II/RAR pair (131, 566). Noy and colleagues (276, 476) reported K_d values of 35 and 17 nM of ATRA for FABP5 and PPAR β , respectively. However, other authors

reported much weaker affinities of ATRA for both proteins, i.e., K_d within the 1 to 10 μM range (276, 476), that argues against a physiological relevance of an activation of the PPAR β transcriptional pathway by ATRA. Finally, it has been recently shown that in breast cancer cells, FABP5 is not translocated to the nucleus upon ATRA binding, but on the contrary, sequesters ATRA in the cytoplasm and thereby reduces its effects mediated by activation of the CRABP-II/RAR system (344).

A very large variety of PPAR synthetic activators have been described. However, only a restricted number of these molecules with agonistic activity on PPAR α and PPAR γ have been clinically used for treatment of metabolic disorders. For instance, fibrates, such as gemfibrozil, fenofibrate, or ciprofibrate, used in clinical practice for many years to improve blood lipid levels, exert a large part of their metabolic actions by a selective activation of PPAR α , while bezafibrate, which is a pan-PPAR activator, is playing additional beneficial effects including cardioprotective action (188). Briefly, fibrate activation of PPAR α regulates the expression of genes implicated in fatty acid catabolism, lipoprotein metabolism, and inflammatory responses in various tissues, including liver, heart, and vascular tissue (170).

Synthetic compounds with a very specific agonistic activity on PPAR γ , such as thiazolidinediones, have proven their efficacy to improve insulin sensitivity and blood lipids in type 2 diabetic patients and to control inflammatory re-

sponses. These actions implicate transcriptional regulation of genes implicated in differentiation, lipid and carbohydrate metabolism, and inflammation in several cell types, including adipocytes, macrophages, and vascular cells (591). Despite their efficacy in diabetic patients, the three marketed thiazolidinediones displayed a variety of adverse effects, such as hepatotoxicity (Troglitazone), risks of myocardial infarction (Rosiglitazone), and bladder cancer development (Pioglitazone), leading to their withdrawal or limitation of use in Europe and the United States (311). However, it must be noted that some of these deleterious side effects of thiazolidinediones remain controversial. For instance, while several studies reported a modest increase of bladder cancer incidence in diabetic patients after Pioglitazone administration (159, 331, 392, 600), other independent analyses showed that long-term use of thiazolidinediones is not significantly associated with increased risk of bladder cancer (142, 548, 634). Derivatives of phenoxyacetic acid, L-165041 (43), GW501516 and GW0742 (569), and MBX-8025 (41) are very potent and selective activators of PPAR β both in vitro and in vivo. EC_{50} values for these compounds when assessed with human recombinant PPAR β are ~ 1 nM for GW501516 and GW0742, 2 nM for MBX-8025, and 50 nM for L-165041, with 250- to 1,000-fold selectivity over the human PPAR α and PPAR γ isoforms (41, 43, 311) (FIGURE 2). Other specific and potent PPAR β synthetic agonists (350, 494) and antagonists (200, 530) have been described more recently, and all these compounds have been very useful tools for elucidating the bio-

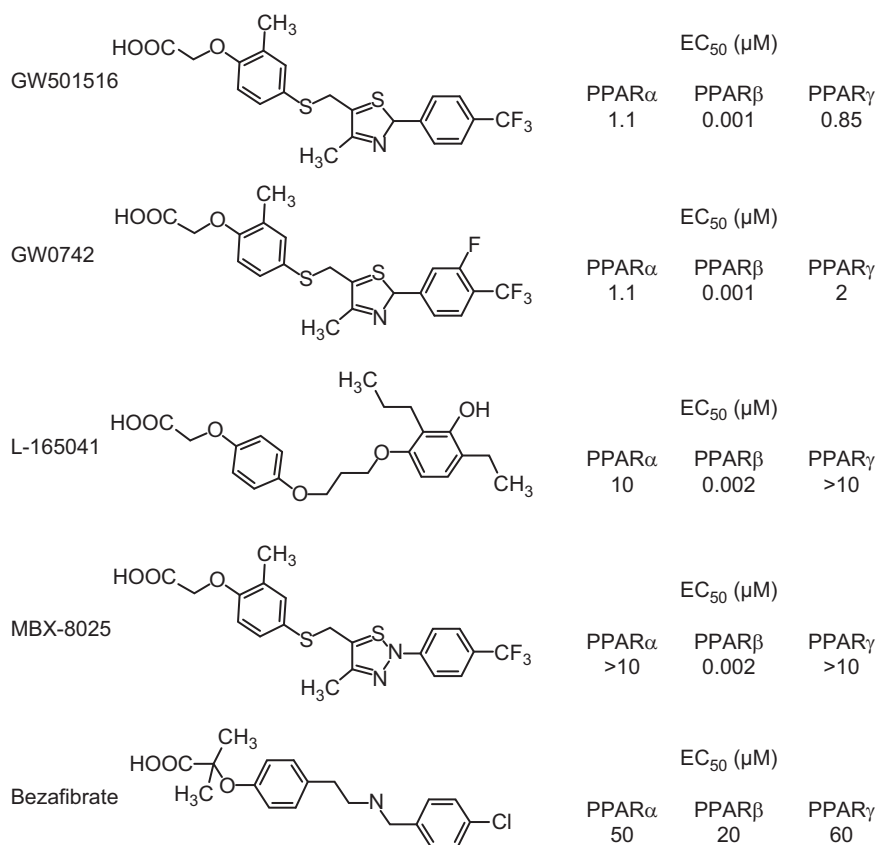


FIGURE 2. Chemical structure and human PPAR subtype selectivity of PPAR β synthetic agonists used in research and clinical trials. Activities on the different compounds are based on PPAR-GAL4 transactivation assay: Ref. 569 for GW501516 and GW0742, Ref. 642 for L-165041 and bezafibrate, and Ref. 101 for MBX-8025.

logical roles of PPAR β . Although PPAR β agonists are not yet in clinical use, human studies have been performed to test the efficacy of two compounds, GW501516 and MBX-8025, providing very encouraging findings for the treatment of metabolic disorders in dyslipidemic obese individuals. Administration of GW501516 for 2 wk to healthy sedentary subjects significantly decreased plasma triglyceride concentration, increased HDL-cholesterol concentrations, and enhanced *in vivo* lipid clearance (551), while in moderately obese subjects, the treatment lowered triglyceride, nonesterified fatty acids (NEFA), LDL-cholesterol, and insulin plasma fasting levels; improved insulin sensitivity; reduced liver fat content; and increased fatty acid oxidation (FAO) after a high-fat meal (477). More recently, it has been reported that treatment with MBX-8025 for 8 wk of dyslipidemic overweight patients results in reduction of plasma triglycerides, NEFA, apolipoprotein B-100, and LDL-cholesterol (41). In dyslipidemic, moderately obese patients, administration of either GW501516 (421) or MBX-8025 (101) for 6 and 8 wk, respectively, also exerts a potent beneficial action on lipoprotein profile by reducing the plasma concentrations of atherogenic particles.

Although no adverse effects were reported in these human studies, further investigations with larger groups of individuals and longer period of treatment are required to fully establish the safety of these PPAR β agonists.

C. Molecular Mechanisms of Transcriptional Regulation by PPAR β

1. Direct transcriptional regulation through binding to PPRE

PPARs exert part of their transcriptional regulating actions in the form of a heterodimer with RXRs, which binds to a specific DNA sequence called PPRE located in the promoter region or in the transcribed region of the target genes (**FIGURE 1A**). Even though some exceptions have been reported, the general scheme for such type of transcriptional regulation can be described as follows (153).

The PPRE consists of an imperfect direct repeat of the nuclear receptor consensus recognition sequence AGGTCA with one variable base spacing (direct repeat-1, DR-1) (426). Functional PPRES have been identified in a large number of genes involved in a variety of cellular functions, such as metabolic regulation, cell proliferation, cell differentiation, and inflammation.

Both PPARs/RXRs heterodimerization and DNA binding of the heterodimer are ligand independent, but ligand binding reduces the mobility of PPARs by increasing interactions with cofactors rather than DNA binding (154, 596). Activation of the PPAR/RXR heterodimer is induced by either PPAR ligands or RXR ligands (e.g., *9-cis*-retinoic

acid or synthetic ligands), whereas simultaneous presence of PPAR and RXR ligands leads to a synergistic induction of target genes (298).

As previously mentioned, ligand binding promotes a conformational change in the NH₂ terminus of PPAR that modifies the interaction of the nuclear receptor with cofactors, i.e., corepressors and coactivators that respectively reduce and enhance transcription of the target genes after establishment of large multiprotein complexes (**FIGURE 1, B AND C**).

In the absence of ligand, the PPAR β /RXR heterodimer interacts with corepressors and other proteins, which results in recruitment of histone deacetylases (HDACs) and subsequent changes toward tight chromatin structure and transcription repression (**FIGURE 1B**). The ligand binding-induced conformational change in the PPAR promotes a release of the corepressor complex and interaction with coactivators that directly or through recruitment of coactivator-associated proteins induces a chromatin structure remodeling by histone acetylation or methylation (**FIGURE 1C**) (483, 616). As for the other nuclear receptors, several corepressors and coactivators are known to play important roles in PPAR β -mediated gene transcription. For instance, it has been shown that unliganded PPAR β /RXR heterodimer is associated with silencing mediator for retinoic acid and thyroid hormone receptor (SMRT) or nuclear receptor corepressor (NCoR) when bound to PPRE sequences (309) and can, by this way, repress the transcriptional activity of the other PPAR isoforms (532). Another corepressor of a large number of nuclear receptors, the receptor interacting protein 140 (RIP140), represses the transcriptional activity of PPAR β in skeletal muscle and uterine cells (337, 524). The peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α) and steroid receptor coactivator-2 (SRC-2) are important coactivators for the PPAR β regulatory functions (337, 630). Although cofactors are not specific for PPARs, some of them display tissue-dependent differences in their expression level and are physiologically regulated in a tissue-dependent manner, adding a new step in the regulation of PPAR activity. For instance, and as it will be discussed in more detail in section III, both PGC1 α and PPAR β display a similar pattern of regulation in skeletal muscle, with upregulation during physical exercise and fasting, and a more abundant expression level in oxidative than in glycolytic fibers (195, 460).

PPAR β activation can have secondary effects on a large panel of genes that are not direct target genes of PPAR β , by directly regulating the transcription of other transcription factors, or of proteins that modulate the activity of a given transcription factor. For instance in myocytes, PPAR β activation increases the transcription and activity of forkhead box protein O1 (FoxO1) (406), a transcription factor implicated in many cellular functions, by direct PPRES-driven

transactivation mechanism. PPAR β also controls by a similar mechanism of action the expression of PGC1 (240), a co-activator of several transcription factors, and of calcineurin A (623), a phosphatase that activates the nuclear factor of activated T-cells (NFAT), which in turn regulates the transcription of several genes implicated in metabolism, differentiation, and immune functions. Similarly, PPAR β can directly regulate the transcription of the inhibitor- κ B α (I κ B α), an important inhibitor of the transcription factor nuclear factor κ B (NF- κ B) (81). More details of this and other mechanisms by which PPAR β can interact with the NF- κ B pathway is discussed in the next section.

2. Indirect transcriptional regulation by PPAR β

Besides a direct transactivation mechanism, and like the other members of the PPAR subfamily, PPAR β can affect transcription of a very large panel of genes by changing the activity of several transcription factors implicated in a variety of cellular functions including inflammation, differentiation, and metabolism (FIGURE 1, D-G). Such functional interferences between the PPAR β pathway and the activities of other transcription factors occur through protein/protein physical interaction between PPAR β and transcription factors within the nucleus, or modulation of signaling pathways affecting the activity of transcription factors. The physiological impact of these regulatory mechanisms will be discussed in more details in the following part of the review, and some examples of such PPAR β indirect transcriptional regulations are briefly presented in this section.

For instance, several studies have reported a potent inhibitory action of PPAR β activation on the NF- κ B pathway in various cell types and showed that PPAR β exerts its inhibitory effects on NF- κ B via multiple mechanisms depending on the cell type and biological condition. NF- κ B is a ubiquitously expressed transcription factor implicated in the regulation of various biological processes, including cell division, cell survival and apoptosis, innate immunology, and responses to inflammatory and metabolic stresses. NF- κ B consists of a heterodimer of two subunits, p65 and p50, in most cell types, which binds with the I κ B that sequesters the complex in the cytoplasm of nonstimulated cells. Exposition to various stimuli promotes phosphorylation of I κ B and its proteasomal degradation, allowing nuclear translocation of the p65/p50 heterodimer that transactivates the expression of several target genes (FIGURE 1D) (36, 203).

NF- κ B activation plays a central role in inflammatory responses related to several cardiac pathologies, and the pharmacological modulation of this pathway is of great potential interest to manage heart diseases. Initial work showed that pharmacological activation of either PPAR α or PPAR β reduces nuclear accumulation of p65 in human endothelial cells (479). More recent studies elucidated this phenomenon by the finding that in cardiomyocytes, PPAR β activa-

tion reduces I κ B protein degradation (128). In addition, as mentioned above, PPAR β activation upregulates I κ B α protein amount by a direct transactivation mechanism involving the binding of PPAR β /RXR heterodimer to a PPRE sequence in the I κ B α promoter (81). Furthermore, coimmunoprecipitation studies demonstrated that upon ligand activation, PPAR β physically interacts with the NF- κ B p65 subunit leading to a decreased association of the NF- κ B dimer to its responsive element on its target genes in cardiomyocytes (453) and microglial cells (510) (FIGURE 1E). A recent study demonstrated a new mechanism of repression of NF- κ B-dependent transactivation by pharmacological PPAR β activation in a human keratinocyte cell line, HaCaT (35). In these cells, PPAR β agonist treatment does not alter I κ B cellular content and p65 nuclear translocation, but reduces acetylation of the p65 subunit, which is important for the transcriptional activity of the NF- κ B heterodimer (464). This effect of PPAR β agonist is due to activation of AMPK that phosphorylates the transcriptional coactivator p300 decreasing its capacity to acetylate the p65 NF- κ B subunit (35).

Another way by which PPAR β can indirectly affect transcription is by binding to the corepressor B-cell lymphoma 6 (BCL-6) (320). In this case, it is the inactive form of PPAR β that binds to BCL-6 and, as a result, BCL-6 is not available to repress the transcription of its target genes (FIGURE 1F). Activation of PPAR β leads to release of BCL-6, and the corepressor is able to perform its function (FIGURE 1G). Finally, it has been clearly shown that PPAR β activation affects, by so far unexplored mechanisms, signaling pathways which control the activity of several transcription factors. For instance, in several cell type contexts, PPAR β activation results in activation of the phosphoinositide 3-kinase (PI3-K)/Akt pathway (123, 330, 482, 677) and inhibition of the mitogen-activated protein kinase-extracellular-signal-regulated kinase1/2 (MAPK-ERK1/2) (108, 387) leading to reduction of NF- κ B and signal transducer and activator of transcription 3 (STAT3) transcriptional activities (282, 482, 522, 523). However, it should be mentioned that PPAR β agonist treatment did not activate the Akt signaling pathway in several other studies (63, 64, 79).

Two studies combining genome-wide expression profiling for the identification of PPAR β -regulated genes and chromatin immunoprecipitation sequencing (ChIP-Seq) for PPAR β occupancy analysis on the targeted promoter sequences have recently illustrated the large variety of PPAR β regulated genes and were very informative on the multiplicity of the molecular mechanisms implicated in the transcriptional regulation by PPAR β . Human WPMY-1 myofibroblastic cells with normal or downregulated PPAR β expression and treatment with GW501516 were used by Adhikary et al. (5), while Khozoie et al. (286) used primary keratinocytes from either wild-type or PPAR β -deficient mice and GW0742 as pharmacological PPAR β activator. Genome-

wide expression profiling experiments showed that the number of PPAR β -regulated genes is very high, reaching ~4,300 in WPMY-1 cells and 612 in primary mouse keratinocytes and that the percentage of activated versus repressed genes by the PPAR β pathway is 65 versus 35% approximately in both studies. Both studies also revealed that the number of genes differentially regulated by PPAR β knockdown/deficiency is fourfold higher than the number of genes differentially regulated by treatment with exogenous ligand, suggesting that the presence of PPAR β protein, whether it is inactive or active (bound to endogenous ligand), is of major importance in PPAR β -regulated transcription in both cell types. Interestingly, in the two experimental models, only a small fraction of genes (12–15%) were both induced by PPAR β absence and activated by PPAR β agonists, effects that are in agreement with a mode of action involving direct transcriptional regulation (**FIGURE 1**), suggesting that the majority of PPAR β actions involve indirect transcriptional regulation.

In agreement with this, ChIP-Seq experiments revealed that, in primary keratinocytes, only 33% of the PPAR β -dependent regulated genes display PPAR β occupancy within 10 kb of the transcription starting site (TSS) on motifs that resembled the consensus PPRE sequence (286). However, this percentage is strongly increased in the class of genes activated or repressed by exogenous ligand, and it should also be kept in mind that in some cases PPRE binding sites have been located up to 140 kb from the TSS (5). Interestingly, binding sites for other transcription factors, such as activating transcription factor 4 (ATF4), cAMP response element binding protein (CREB), and E26 transformation-specific (ETS) were commonly associated near regions occupied by PPAR β , suggesting cooperation between PPAR β and other transcription factors (286).

Collectively, these data showed that in both human and mouse cells, PPAR β regulates the expression of a large number of genes by different mechanisms and that expression level of PPAR β , presence of agonists, cooperation with other transcription factors and with coregulators strongly influence the mode of action and transcriptional activity of the nuclear receptor.

In summary, PPAR β shares structural and functional characteristics with the other PPAR isoforms and other nuclear receptors. Like the other PPARs, PPAR β is activated by fatty acids, but particular fatty acid metabolites act as selective activators of this PPAR isoform, while discriminating interaction with specific cellular transporter of fatty acids provides a selective guiding of the activator to PPAR β . Moreover, ligand binding prevents ubiquitination-induced degradation of PPAR β , thereby contributing to the regulation of PPAR β protein levels. Despite a large pattern of tissue expression, PPAR β is more abundant in some tissues and cell types characterized by a high lipid catabolism, and

its abundance is physiologically regulated in a tissue-specific manner. PPAR β action is not only regulated by its level of expression and ligand availability, but also by the expression level of cofactors that form the co-repressor/-activator complexes that interact with PPAR β . Likewise, chromatin accessibility and number of available DNA binding sites also play a regulatory role. Like the other PPAR isoforms, PPAR β affects transcriptional expression of a large diversity of genes by several mechanisms of action through binding to specific responsive elements but also by modulating other regulatory transcriptional pathways. Taken together, the multiple levels and dynamic nature by which PPAR β action can be regulated, and how this can affect the expression levels of a very large panel of genes, explain the multiplicity of regulatory functions exerted by PPAR β on development, metabolism, and inflammation of several tissues and cell types.

II. PPAR β AND CELL PROLIFERATION, CELL DIFFERENTIATION, AND DEVELOPMENT

As previously indicated, PPAR β mRNA levels can be detected early on during embryogenesis and in a large variety of tissues and cell types in the adult (269, 296). Thus the multiplicity of phenotypes promoted by PPAR β gene disruption in the mouse was not surprising, but manifested the importance of this nuclear receptor in developmental regulations. Specifically, it was initially reported that, when compared with their control littermates, homozygous PPAR β -null mice display reduced body weight both during gestation and after birth (443) and defects in various tissues, including placenta, adipose tissue, skin, and intestine (27, 443).

A large number of publications demonstrated the implication of the PPAR β pathway in regulation of proliferation and differentiation of various cell types affecting development of several organs and revealed that activation of this signaling pathway can result in either reduction or enhancement of both cell proliferation and differentiation depending on the investigated cellular system.

A. Regulatory Functions of PPAR β in Placentogenesis

Lim et al. (336) showed that PPAR β expression is strongly induced in stromal cells surrounding the implanting blastocyst and, when activated by prostacyclin or synthetic agonist, increases both the rate and the quality of blastocyst implantation sites. Furthermore, germ line deletion of PPAR β exon 4, which encodes an essential part of the DNA binding domain, leads to placental defects and frequent embryonic lethality at day 10 of gestation (27). Interestingly enough, germ line deletion of PPAR β exon 8, the last

PPAR β exon, does not profoundly affect embryonic viability (443). Perhaps these discrepancies in phenotypes can be explained by differences in genetic backgrounds of the mice studied. In respect to the phenotype regarding embryonic lethality, it should be kept in mind that in the studies described in this review, which use the aforementioned and other knockout models of PPAR β , mice are studied that, in effect, have survived selection. By using both *in vivo* approaches and trophoblast cellular model, Nadra et al. (403) demonstrated that the PPAR β pathway is directly involved in the control of differentiation of trophoblast cells into giant cells. Indeed, the authors showed that a functional PPAR β pathway is required for normal placental giant cell layer formation *in vivo*. In addition, expression of specific markers of giant cells and morphological differentiation is massively increased by treatment of Rcho-1 trophoblast cells with a synthetic PPAR β agonist, while PPAR β silencing almost completely inhibited differentiation of Rcho-1 cells into giant cells. Further analysis revealed that the differentiating action of PPAR β on trophoblast cells involved activation of the PI3-K/Akt signaling pathway and modification of the expression of proteins, like inhibitor of MyoD family domain-containing protein (I-mfa) and inhibitor of DNA binding-2 (Id-2), known to affect the activity of transcription factors that play crucial roles in giant cell differentiation (403).

B. Regulatory Roles of PPAR β in Adipose Tissue Development

Genetic and pharmacological approaches definitely demonstrated that PPAR γ , which is maximally expressed in terminally differentiating preadipocytes, is a master gene of adipogenesis by controlling the expression of a large set of adipose-related genes and is at the crossroad of several adipogenic signaling pathways (75, 649). PPAR β is not directly implicated in the control of adipogenesis, but plays a role in the adaptive response of adipose tissue to dietary fatty acid content. It is known for a long time that adipose tissue development is controlled by the nutritional status, and this is illustrated by the high fat feeding-induced hypertrophic development of adipose tissue by increase in both number and size of adipocytes (151). *In vivo* studies have revealed that high-fat diet (HFD) (299) and especially diets containing saturated fatty acids (533) promote within days preadipose cell proliferation that precedes terminal differentiation. This adaptive response of adipose tissue to the dietary amount of fatty acids is physiologically important for increasing the storage capacity of energetic substrates when lipids are only occasionally available, but leads to obesity in situations characterized by chronic and excessive nutritional fatty acid supply.

It was shown that exposure of preadipose cells in culture to long-chain fatty acids (LCFA) also exerts adipogenic action by increasing both preadipocyte cell proliferation and ex-

pression of the terminal differentiation program. This adipogenic action of LCFA is limited to the preadipose state, as treatment of terminally differentiating cells is ineffective. Furthermore, since nonmetabolized fatty acids also exerted a potent adipogenic effect, it was proposed that the fatty acid *per se*, rather than a fatty acid metabolite, is the trigger for this adipogenic action (17).

Several experimental data showed that these actions of LCFA on preadipocyte proliferation and differentiation are mediated through activation of PPAR β , which is expressed during the early steps of adipose conversion (18). First, it was shown that forced expression of PPAR β confers to fibroblasts the ability to respond to LCFAs or PPAR β synthetic agonists by a resumption of cell proliferation after confluence and by a rapid transcriptional activation of genes implicated in fatty acid metabolism, such as FABP4 and acyl-CoA synthetase (ACS) and a delayed induction of PPAR γ mRNA (38, 207, 260). However, expression of a complete terminal differentiation program still requires treatment of these cells with natural or synthetic activators of PPAR γ (38, 207), demonstrating that PPAR β alone is not able to promote actual adipogenesis. The implication of PPAR β in the adipogenic action of LCFAs was also demonstrated by the finding that ectopic expression of a dominant negative PPAR β mutant in preadipose cell lines seriously impairs both LCFA-induced postconfluent cell proliferation and PPAR γ gene expression (39). Collectively, these data strongly suggest that PPAR β is an essential actor in the regulation by LCFAs of the first steps of adipocyte differentiation, *i.e.*, clonal expansion by proliferation of preadipose cells and increment of some adipose-related genes including PPAR γ , but that its activation does not promote actual terminal differentiation, which requires activation of PPAR γ by specific agonists.

Data coming from PPAR β -null animals have confirmed these observations obtained with cellular models. Specifically, it was reported that adult PPAR β -null mice exhibit a marked reduction in size of adipose stores, mainly due to a decreased number of adipocytes and display a reduced expression of PPAR γ mRNA in adipose tissue (27, 443). In line with these observations, preadipocytes derived from PPAR β -null mice fail to differentiate to adipocytes in standard differentiation medium (367). Moreover, it has also been reported that adipocyte-specific PPAR β deletion that occurs only during the last step of terminal differentiation does not affect adipose tissue development, demonstrating the lack of regulatory action of PPAR β in terminally differentiating adipocytes (27).

C. PPAR β in Skin Physiology and Pathologies

Epidermis is a stratified epithelium that is continuously regenerated. The basal layer of epidermis contains epidermal

stem cells, and their progeny are called transit amplifying cells, which undergo a few rounds of mitosis and then withdraw cell cycle to initiate terminal differentiation characterized by sequential expression of specific proteins and migration to form the upper epidermis layers as well as squamous and granular layers. The end of the process of keratinocyte differentiation is the formation of corneocytes, cells which have lost their nucleus and form the stratum corneum, the upper layer of epidermis consisting of a network of insoluble proteins and lipids. The processes of keratinocyte proliferation, differentiation, migration, and cell death are controlled by several signaling pathways, including c-Myc, transforming growth factor- α (TGF- α), Notch, CCAAT-enhancer-binding proteins (CEBPs), and PPARs (172, 304).

The three PPAR isoforms are expressed in mammalian skin but display a species-dependent expression pattern. In rodents, PPARs are expressed during fetal development and are undetectable in normal skin in adults (380, 381). However, it is important to note, as we noted above, that PPAR β was found to be highly expressed in keratinocytes in the skin (186). Interestingly, epidermal PPAR β expression is reactivated in adult mice upon stimulation of keratinocyte proliferation and differentiation by phorbol ester treatment or hair plucking, while PPAR α is only weakly increased and PPAR γ remains undetectable (381). In contrast, PPAR β remains highly expressed in basal and suprabasal adult human epidermis layers, while PPAR α and PPAR γ are confined to suprabasal layers (480, 638). Consistent with this localization in the epidermis layer containing the proliferative cell compartment and where keratinocytes are engaged in the differentiation process, numerous studies have demonstrated that PPAR β is implicated in the regulation of these steps of epidermis formation and plays important roles in skin physiology and diseases. Indeed, almost all the studies performed with cellular and animal models concluded that activation of the PPAR β pathway leads to cessation of cell proliferation and promotion of keratinocyte differentiation.

For instance, treatment with specific PPAR β agonists inhibits cell proliferation of primary mouse keratinocytes (79), normal human epidermal keratinocytes (638), and various human keratinocyte cell lines, such as NCTC 2544 (364), N/TERT-1 (79), and HaCaT (63). This antiproliferative action of the chemical compounds involves PPAR β , as it is blunted in cells lacking the nuclear receptor (291, 364). The regulatory function of PPAR β on epidermal cell proliferation was also demonstrated *in vivo*. PPAR β -deficient mice show increased epidermal thickness due to increased cell proliferation in epidermal basal layer (358, 579) and display exacerbated epidermal hyperplasia in response of phorbol ester treatment (381, 443). Furthermore, phorbol ester-induced skin hyperplasia is prevented by topical application of GW0742 in wild-type mice, but not in PPAR β -deficient mice (48).

PPAR β genetic ablation does not result in important defects in mouse skin formation, indicating that PPAR β is not required for keratinocyte differentiation *in vivo* (358, 381, 443). Moreover, PPAR β deficiency does not totally impair increased expression of keratinocyte terminal differentiation markers, such as involucrin, transglutaminase I, and small proline-rich (SPR) proteins 1A and 2H, induced by topical application of phorbol ester to mouse skin (443, 579), or during the phorbol ester- or high Ca²⁺ concentration-induced differentiation of primary mouse keratinocytes (291). However, several studies from various laboratories have demonstrated that activation of the PPAR β pathway exerts a potent prodifferentiating action in keratinocytes.

For instance, treatment of normal human keratinocytes, mouse primary keratinocytes, and human keratinocyte cell lines with specific PPAR β agonists leads to increased transcriptional expression of several markers of keratinocyte differentiation, including involucrin, transglutaminase 1, SPR1A, and SPR2H (63, 79, 291, 509, 579, 638). Similar observations were made *in vivo* after topical administration of PPAR β agonists on mouse skin (291, 509). Interestingly, beside classical keratinocyte differentiation markers, PPAR β activation also induces both *in vitro* and *in vivo* the expression of proteins involved in lipid metabolism, such as fatty acid translocase (FAT/CD36), angiopoietin-like 4 (ANGPTL4), and perilipin 2 (also termed adipose differentiation-related protein, ADRP), and promotes triglyceride accumulation in keratinocytes (291, 509, 514, 638). Importantly, these transcriptional effects of PPAR β agonists are mediated through PPAR β as they are blunted or dramatically decreased by ablation of the nuclear receptor (48, 291, 358, 399, 579).

Consistent with these identified roles of PPAR β on keratinocyte proliferation and differentiation, perturbation of this regulatory pathway notably impacts skin physiology especially in situations of challenges. For instance, a role for PPAR β has been demonstrated in skin repair after injuries, such as disruption of permeability barrier function or skin wound healing.

The external layer of skin, the stratum corneum, which consists of corneocytes surrounded by an extracellular matrix of insoluble proteins and lipids, plays a crucial role in epidermal permeability barrier function, which regulates transepidermal water loss and protects against xenobiotic penetration and pathogen infections. When epidermal barrier is experimentally damaged by repeated administration of solvents or detergents or by mechanical stripping, it is reconstituted after a few days (156, 362). Schmutz et al. (509) showed that a pretreatment with PPAR β agonist notably accelerates epidermal permeability barrier repair after chemical or mechanical injury in adult mice and linked this action with positive effects of PPAR β pathway activation

on the expression of terminal differentiation markers such as filaggrin and loricrin. In addition, PPAR β -deficient mice display a significant delay in epidermal barrier function repair after skin injury compared with control littermates (358). Furthermore, a recent publication confirmed the involvement of the PPAR β pathway in permeability barrier development as PPAR β -deficient mouse embryos display a delayed maturation of the barrier function, while intra-amniotic administration of a PPAR β synthetic agonist accelerates stratum corneum formation and fetal epidermal barrier development in rat (266).

The implication of PPAR β in the process of reepithelialization of the wounded skin has also been well documented (383, 395, 578). The first evidence came with the finding that expression of PPAR α and PPAR β are reactivated in the wound boundaries of injured mouse skin with different time courses. PPAR β expression is dramatically increased very rapidly after skin injury and sustained at high level during the overall wound healing process, e.g., during the three successive phases of inflammation, proliferation, and maturation, while the expression of PPAR α occurs late and is only maintained during a short period of time corresponding to the inflammatory phase. Consistent with these different patterns of reactivation for PPAR α and PPAR β , the authors observed that in PPAR α -deficient mice, the process of wound healing is delayed only in the early phase, while deletion of one PPAR β allele results in delay in all phases of reepithelialization process and a differed final wound closure (381). Further work performed by the same group revealed that inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interferon- γ , released at the site of injury by both keratinocytes and inflammatory cells activate the stress-associated protein kinase pathway that, in turn, promotes the transcription of PPAR β gene via binding of the activator protein-1 (AP-1) transcription factor to its promoter and reactivation of PPAR β expression in the keratinocytes of the wound edges (579). High expression level of PPAR β promotes enhanced differentiation and migration of keratinocytes (381, 579) and increased survival of the keratinocytes both *in vitro* and *in vivo* (124, 579). It remains controversial whether PPAR β has an antiapoptotic role in keratinocytes or not. The group of Peters has published several publications that do not support an antiapoptotic role for PPAR β in keratinocytes (48, 63, 64, 79), while the groups of Wahli and collaborators claim the opposite (122, 124, 514, 579). Therefore, further independent studies are needed to clarify this issue.

Some observations strongly suggest that the PPAR β pathway is also involved in some skin pathologies, such as psoriasis and cancers. Psoriasis is a relatively common skin disorder characterized by hyperproliferation and disturbed differentiation of keratinocytes with inflammation and improper immune response (412, 593). An initial study suggested an overexpression of PPAR β in skin from psoriatic

patients (480). This observation was confirmed thereafter in other studies showing upregulation of PPAR β mRNA (4- to 10-fold increase) and protein (up to 4- to 5-fold increase) levels in psoriatic lesions when compared with normal epidermis (484, 485, 637). Moreover, PPAR β mRNA expression levels are strongly reduced after correction of the psoriatic phenotype (637). This PPAR β overexpression is probably a consequence of the chronic inflammation status of psoriatic epidermis, as PPAR β gene transcription is upregulated via activation of the stress-associated kinase cascade/AP-1 pathway by inflammatory cytokines (484, 579). In agreement with this hypothesis, treatments of psoriatic patients with methotrexate or psoralen plus UVA phototherapy, known to act primarily by decreasing inflammation and/or immune disorders, notably reduce the levels of PPAR β mRNA in psoriatic skin (141).

Furthermore, the PPAR β pathway appeared to be fully effective in psoriatic epidermis as evidenced by the strong upregulation of PPAR β target genes, such as FAT/CD36 and epidermal FABP, and it was proposed that lipoxygenase products, as 8-, 12-, and 15-HETE, that are accumulated in psoriatic epidermis, act as endogenous ligand to activate PPAR β (637).

Some studies suggest that the upregulation of PPAR β expression is not only a marker of psoriasis, but that uncontrolled activation of the PPAR β signaling pathway may be directly implicated in psoriasis pathogenesis. First, PPAR β was shown to control the transcription of the heparin-binding epidermal growth factor-like growth factor (HB-EGF) in human psoriatic epidermis (484), a factor known to play a central role in the keratinocyte hyperproliferation in psoriasis (670, 679). However, recent microarray and ChIP-seq data showed that HB-EGF is not a PPAR β target gene in keratinocytes (286). Second, PPAR β is overexpressed in T lymphocytes from psoriatic skin, and its activation stimulates proliferation and increases survival of T cells through the ERK1/2 signaling pathway, contributing to the maintenance of activated T cells in the lesional psoriatic epidermis (9). Third, Romanowska et al. (485) demonstrated that combined epidermal overexpression of PPAR β and treatment with synthetic PPAR β agonist for 2–3 wk promotes appearance of some psoriasis-like markers in mice, such as keratinocyte hyperproliferation, dendritic infiltration, and lymphocyte accumulation, while PPAR β overexpression alone or treatment of control mice with the PPAR β agonist do not induce these markers. In this model, the PPAR β transgene is specifically overexpressed in the sebaceous glands, and ligand-mediated activation of PPAR β in the sebaceous gland triggers sebocyte differentiation and delivery of sebum to the skin, containing lipoxygenase-derived bioactive lipids that can subsequently mediate a secondary induction of the PPAR β transgene in the epidermis (485). The proinflammatory effects observed in this model of PPAR β overexpression in the epidermis, that go against the

anti-inflammatory role that is attributed to PPAR β (discussed in detail in sect. IV), might be the consequence of the lipoxygenase-derived bioactive lipids present in the sebum that are very potent proinflammatory factors (448). Finally, transcriptomic analysis revealed a large, although not totally overlapping, similarity between actual psoriasis and PPAR β -induced psoriasis-like phenotype. Noteworthy, while interferon response genes are strongly induced in psoriasis, they are repressed in the skin disease induced by activation of PPAR β , in agreement with a PPAR β -induced anti-inflammatory response (485). Furthermore, in sharp contrast to psoriasis disease characterized by reduced epidermal terminal differentiation, mice overexpressing PPAR β treated with a PPAR β agonist display an augmentation of the number of terminally differentiated keratinocytes, leading to increased thickness of the upper epidermis layers and enhancement of expression levels of various genes of the keratinocyte terminal differentiation program (485), that is in agreement with previous studies showing a differentiating potential of PPAR β (121). Taken together, these observations are not without controversy, and further studies are needed to investigate in more detail whether strong activation of the PPAR β pathway could favor psoriasis disease occurrence. To date, no skin effects have been reported in the phase two trials for GW501516 and MBX8025 (101, 421). However, a particular caution may be given to such potential adverse effects of long-term PPAR β agonist administration especially in patients with epidermal inflammation or past history of psoriasis. Moreover, these observations also suggest that blocking the PPAR β pathway could have beneficial actions in psoriatic skin. Indeed, a recent publication reports that in keratinocyte-specific PPAR β overexpressing mice, topical administration of PPAR β specific antagonists reduces the psoriatic-like disease (200).

On the basis of the observation of both PPAR β and COX-2 overexpression in some epithelial cancers (257, 413), it has been proposed that the strong activation of the PPAR β pathway by COX-2-produced prostaglandins plays a

causal role in carcinogenesis. To date, a substantial amount of data argue against this hypothesis for the occurrence of chemically induced skin tumors and melanomas and, on the contrary, strongly suggest that PPAR β pathway activation could exert antitumorigenic action in skin (TABLE 1). As previously cited, PPAR β -null animals display exacerbated response to tumor promoters (381, 443), suggesting an antitumorigenic function for PPAR β in skin. Further studies showed that PPAR β deficiency leads to enhancement of the onset, size, and number of skin tumors induced by phorbol ester treatment when compared with control mice (290). Moreover, ligand activation of PPAR β by topical administration of GW0742 notably reduces chemically induced skin tumor formation and multiplicity in wild-type mice but not in PPAR β -deficient animals (48). The mechanisms by which the PPAR β pathway tempers chemically induced skin tumor development remain to be clarified. However, it has been shown that PPAR β negatively regulates the expression of proteins known to contribute to keratinocyte hyperproliferation and skin tumorigenesis, such as protein kinase C- α (PKC- α). PKC- α is activated by tumor promoters such as 12-O-tetradecanoylphorbol-13-acetate (TPA), and one of the mechanisms of desensitization of the PKC- α pathway is its ubiquitin-dependent proteasome degradation (329). Kim et al. (292) demonstrated greater TPA-induced accumulation of PKC- α protein and subsequent enhanced PKC- α signaling in skin from PPAR β -null animals compared with control mouse skin and showed that PKC- α accumulation is related to a reduced ubiquitin-dependent proteasome degradation of the protein in PPAR β -deficient animals. Indeed, they also demonstrated that PPAR β directly controls transcription of the ubiquitin C gene through binding to a PPRE and that TPA-induced ubiquitin C mRNA upregulation is almost totally blunted in PPAR β -deficient mouse skin leading to severe reduction in free intracellular ubiquitin levels (290). Thus, although it is not yet established that PPAR β activation upregulates ubiquitin C gene expression in skin, these data strongly suggest that the ubiquitin-dependent proteasome desensitization of PKC- α signaling during long-term treatment with tumor

Table 1. Role of PPAR β in skin cancer

Findings	Reference Nos.	Role in Cancer
PPAR β -null mice display exacerbated epidermal hyperplasia to tumor promoters.	358, 381, 443	-
PPAR β deficiency leads to enhancement of the onset, size, and number of skin tumors induced by phorbol ester treatment when compared with control mice.	290	-
Topical administration of GW0742 notably reduces chemically induced skin tumor formation and multiplicity in wild-type mice but not in PPAR β -deficient animals.	48	-
PPAR β promotes HRAS (Harvey rat sarcoma viral oncogene homolog)-induced senescence and chemically induced skin tumor suppression by potentiating ERK and repressing Akt signaling.	681	-
Src is activated by PPAR β in ultraviolet (UV) radiation-induced skin cancer, and this is accompanied by enhanced ERK signaling. In this model, fewer and smaller skin tumors were detected in PPAR β -deficient mice and a PPAR β antagonist prevented UV-dependent Src stimulation.	394	+

-, PPAR β plays an antitumorigenic role; +, PPAR β plays a pro-tumorigenic role.

promoters requires a functional PPAR β pathway. A recent study described that PPAR β promotes Harvey rat sarcoma viral oncogene homolog (HRAS)-induced senescence and chemically induced skin tumor suppression by potentiating ERK and repressing Akt signaling (681). However, another recent study found Src to be activated by PPAR β in UV radiation-induced skin cancer, and this was also accompanied by enhanced ERK signaling (394). The latter study detected fewer and smaller skin tumors in PPAR β -deficient mice, and a PPAR β antagonist prevented UV-dependent Src stimulation, suggesting that PPAR β promotes the development of UV-induced skin cancer in mice.

Activation of the PPAR β pathway could exert beneficial actions against melanoma progression. It was initially shown that human melanocytes express the three PPAR isoforms and that ligand activation of either PPAR α or PPAR γ exert growth inhibitory action and increase melanocyte terminal differentiation, while treatment with bezafibrate, used as PPAR β agonist, was ineffective (279). More recent studies demonstrated the PPAR β expression in human melanoma cell lines, human normal melanocytes, and melanomas in vivo and reported a growth inhibitory action of specific PPAR β agonists on melanoma cells (185, 386). Various gain- and loss-of-function experiments directly implicated the transcription factor Wilms' tumor suppressor 1 (WT1) in the growth inhibitory effects of the PPAR β pathway in melanoma cells (386). Indeed, it was demonstrated that PPAR β binds to a PPRE present in the WT1 gene promoter and represses the transcription of the WT1 gene in melanoma cells and subsequently downregulates the expression of WT1 target genes, such as nestin and zyxin, previously shown to be required for malignant melanoma cell proliferation (624).

Collectively, and despite some conflicting findings, it can be concluded that PPAR β is implicated in regulatory mechanisms of skin physiology and in skin pathologies. Although dispensable for epidermal differentiation, PPAR β acts with other factors, including the other PPAR isoforms, as a positive regulator of the expression of keratinocyte terminal differentiation program resulting in enhancement of the barrier functions of the epidermis. In normal skin, PPAR β exerts antiproliferative action during the differentiation process of keratinocytes, and PPAR β activation efficiently reduces both tumor promoter-induced skin hyperplasia and melanoma cell proliferation. In addition, the PPAR β signaling pathway appears to be implicated in the control of the wound healing process. In response to inflammatory stimuli and through AP-1 stimulation, PPAR β is locally and strongly overexpressed in injured skin and acts as a key regulator of keratinocyte proliferation, survival, and differentiation during reepithelialization of the wounded skin. Finally, PPAR β is also strongly overexpressed in psoriatic lesions, probably in response to local inflammation, and there is controversial experimental evidence suggesting that

its activation by lipidic ligands produced in situ plays a causal role in the development and/or the progression of psoriasis.

D. PPAR β in Intestine Physiology and Pathologies

Several publications reported high expression levels of PPAR β mRNA and protein in small and large intestines from various species including human and rodents (1, 60, 71, 186, 229, 247, 389), suggesting important roles for this nuclear receptor in intestine development and/or physiology. In reality, the knowledge on the regulatory roles of PPAR β in intestinal functions remains quite limited, while there are a considerable number of publications reporting highly controversial data with evidence for either pro- or antitumorigenic activity of PPAR β in intestine and particularly in colon.

1. Regulatory functions of PPAR β in intestinal physiology

In situ hybridization experiments revealed that in adult mouse small intestine, PPAR β is expressed in the entire intestinal epithelium with a stronger expression level at the bottom of the crypts than in the upper part of the intestinal villi that mainly contains the differentiated enterocytes (613). Consistently, the PPAR β pathway exerts regulatory roles in the specific functions of various cell types of intestinal epithelium, namely, Paneth cells, enteroendocrine cells, and enterocytes.

Varnat et al. (613) demonstrated an important regulatory function of the PPAR β pathway in Paneth cell differentiation. These authors showed a decreased number of differentiated Paneth cells in duodenal epithelium of PPAR β -deficient mice with a reduced expression of Paneth cell markers, such as lysozyme protein and α -defensin, and consequently a diminished bactericidal activity in the small intestine. Conversely, treatment of control mice with a PPAR β -specific agonist results after 12 days in increased Paneth cell number and augmented expression of the specific Paneth cell markers. The PPAR β pathway notably impacts the functions of Paneth cells in enteric innate immunity as its activation leads to an increment in bactericidal activity in small intestine, whereas disruption of the pathway results in the opposite phenotype and profound changes in the composition of intestinal microbiota in PPAR β -deficient mice compared with control littermates. Further investigations revealed that the effects of PPAR β on Paneth cell differentiation implicate a reduced activity of hedgehog signaling, which is one of the main signaling pathways controlling intestinal epithelium development (7), through a negative control of Indian hedgehog gene transcription (613).

PPAR β is also implicated in the regulation of lipid metabolism in enterocytes. For instance, it has been demonstrated that PPAR β plays a central role in the adaptive response of lipid metabolism in the mouse small intestine to changes in the lipid content of the diet by controlling the transcription of the FABP1 gene by a PPRE-driven transactivation mechanism (455). Furthermore, PPAR β controls the expression of intestinal proteins implicated in cholesterol trafficking in enterocytes, and these regulations could explain at least partly the improving actions of PPAR β agonists on lipoprotein profile in both primates and human (41, 101, 420, 477). Two independent groups reported that pharmacological activation of PPAR β resulted in a 2- to 2.5-fold increase in fecal neutral cholesterol excretion in mouse but did not affect hepatobiliary cholesterol secretion (72, 607). Although not totally elucidated, this effect of PPAR β activation appeared to be mainly related to modifications in the intestinal cholesterol trafficking. First, PPAR β pharmacological activation reduces the intestinal cholesterol reabsorption efficiency in mice without modifications in total fat absorption (72, 607). Examination of the effects of PPAR β agonists on intestinal gene expression did not reveal modifications in expression levels of proteins implicated in cholesterol metabolism, such as ATP-binding cassette a1, g5 and g8, but showed a notable downregulation (40–50% decrease) of the Niemann-Pick C1 Like 1 (NPC1L1) mRNA level (72, 607). NPC1L1 plays a critical role in intestinal cholesterol reabsorption and is directly involved in the effects of ezetimibe, a drug that inhibits cholesterol absorption (14). The similarity of the effects of either PPAR β agonist administration or ezetimibe treatment on intestinal cholesterol absorption strongly suggests that the PPAR β -induced reduction in cholesterol absorption is related to the downregulation of the intestinal NPC1L1 expression. In addition to this reduced intestinal cholesterol absorption, it has been shown that PPAR β activation increases fecal cholesterol excretion by stimulating the transintestinal cholesterol efflux (TICE) which is a major pathway for cholesterol excretion in mouse (608). Vrnin et al. (620) showed that 2 wk of PPAR β agonist administration stimulates TICE rate by about twofold and that this effect coincides with upregulation of intestinal ras-related protein 9 (Rab9) and lysosome membrane protein II (LIMP2), two proteins linked to intracellular trafficking of cholesterol (620). Further data are clearly required to fully understand the molecular mechanisms implicated in these effects of PPAR β pathway activation on fecal cholesterol excretion. However, the already available observations are of great interest given the role of reverse cholesterol transport in atherosclerosis. Moreover, as fatty acid-enriched diets reproduce the effects of PPAR β agonists on both intestinal NPC1L1 gene expression (16, 285) and TICE (609) in rodents, it can be proposed that high concentrations of fatty acids in intestinal lumen are acting as natural activators of PPAR β in regulation of fecal cholesterol excretion. This hypothesis must be validated by more direct experimental evidence based on the use of

PPAR β -deficient transgenic models or specific PPAR β antagonists to exclude implication of other fatty acid-activated transcription factors such as PPAR α that also exerts inhibitory action on intestinal cholesterol absorption by downregulating NPC1L1 expression in mice (606).

Lastly, a recent publication described a regulatory role for PPAR β in another cell type of the intestinal epithelium, the enteroendocrine L cells. Enteroendocrine L cells of the small and large intestine produce glucagon-like peptides (GLP), GLP-1 and GLP-2, by alternative cleavages of proglucagon. GLP-1 is released by enteroendocrine L cells in response to nutrient absorption, and the main actions of GLP-1 are to stimulate the glucose-induced insulin secretion in pancreatic beta-cells, to inhibit glucagon secretion by pancreatic alpha-cells, and to decrease appetite and food intake by affecting the hypothalamic-pituitary function and by delaying gastric emptying (180, 239). Daoudi et al. (110) clearly established a role for PPAR β in the control of GLP-1 production by L cells. In this publication, the authors showed that exposure of mouse and human L cell lines or ex vivo human jejunum to PPAR β agonists increases expression of proglucagon mRNA and promotes GLP-1 release. Moreover, administration of PPAR β agonists enhances intestinal proglucagon mRNA expression level by two- to threefold in wild-type mice, but not in PPAR β -deficient mice. Furthermore, a recent study demonstrated that PPAR β activation stimulated GLP-1 receptor expression in pancreatic β cells, thereby protecting these cells from palmitate-induced apoptosis, and enhanced glucose-stimulated insulin secretion (668). Finally, pharmacological activation of PPAR β for 2–3 wk activates intestinal GLP-1 release restoring pancreatic insulin secretion in response to glucose in the obese diabetic *ob/ob* mouse model. These observations strongly suggest that the PPAR β -promoted GLP-1 secretion could be of therapeutic interest for diabetic patients as various strategies aimed to activate the GLP-1 pathway have become well-established treatments for type 2 diabetes (411).

2. PPAR β in intestinal cancers

In recent years, the role of PPAR β in intestinal cancer has attracted intense research efforts providing a large amount of experimental data. However, as conflicting results have been reported, it is still difficult to conclude whether PPAR β exerts either protumorigenic or antitumorigenic functions in intestinal epithelium. In this section we focus only on the main findings on this issue, and the reader will find more complete description and discussion of the highly controversial results in several recently published reviews of the abundant literature on this field of research (440–442, 657).

He et al. (221) reported the first evidence for a deregulated PPAR β expression in colorectal cancer (CRC) cells showing that, like other genes implicated in CRC development in-

cluding the protooncogenes cyclin D1 (587) and c-Myc (222), PPAR β is a direct target of the β -catenin/Tcf-4 (Tcf-4) transcriptional pathway and consequently is upregulated by adenomatous polyposis coli (APC) deficiency. The β -catenin/Tcf4 pathway plays a crucial role in the control of intestinal cell proliferation and differentiation. In the normal situation, nuclear concentration of β -catenin is maintained low by its interaction with a cytoplasmic complex with axin and APC that promotes phosphorylation by glycogen synthase 3-beta (GSK3- β), ubiquitination, and degradation of β -catenin by the proteasome. Invalidating mutations on APC or mutations that prevent β -catenin degradation lead to strong nuclear accumulation of β -catenin and as a consequence overactivation of the β -catenin/Tcf-4 transcriptional pathway resulting in uncontrolled intestinal cell proliferation and CRC. In humans, the majority of familial and sporadic CRC are linked to APC mutations (535). Consistently, He et al. showed that PPAR β mRNA is upregulated in colorectal carcinomas from four patients versus paired normal colon tissue, a finding confirmed in another study with six patients (197, 221). Overexpression of PPAR β mRNA was also described in an experimental models of CRC, i.e., azoxymethane (AOM)-induced colon tumors in rats (197), while Shao et al. (527) showed that PPAR β expression is upregulated by oncogenic Ras in rat intestinal epithelial cells.

There are several experimental data arguing against a direct control of PPAR β gene expression by the β -catenin/Tcf-4 transcriptional pathway as initially proposed (221). For instance, in Apc^{min/+} mice, an animal model for familial adenomatous polyposis carrying an inactivating mutation of APC and spontaneously developing intestinal adenomas (563), independent laboratories reported that PPAR β expression levels are similar or reduced in adenomas when compared with normal intestinal mucosa, while well-known β -catenin/tcf4 target genes, such as cyclin D1, exhibited strong overexpression (92, 161, 162, 361, 389, 422, 468). Furthermore, the use of a mouse transgenic model for conditional ablation of APC gene showed that loss of APC in adult animals promotes β -catenin nuclear accumulation and upregulation of c-Myc mRNA expression within days in intestinal mucosa, while PPAR β mRNA and protein expression levels are reduced (468). Conversely, conditional ablation of β -catenin in the intestinal epithelium of adult mice notably reduced expression levels of the β -catenin/Tcf4 target genes cyclin D1 and c-Myc but did not affect PPAR β expression (160).

In sharp contrast to the initial studies showing an overexpression of PPAR β in a very limited numbers of human intestinal tumor samples, more recent studies analyzing larger numbers of patients, the amounts of PPAR β mRNA and PPAR β protein in CRC samples, and paired adjacent nontumoral tissues provided more mitigated results. Delage et al. (116) reported a very modest (18%) higher PPAR β

mRNA expression level in a collection of 20 CRC samples when compared with normal tissue, while in the same study, the authors found a more robust overexpression of COX-2 mRNA (850%), a well-known marker of intestinal cancer, in tumoral samples (641). No statistical differences were noted in PPAR β mRNA levels from tumoral versus adjacent control tissue in three studies with, respectively, 17, 33, and 86 patients with colon or rectal cancer (161, 663). One study showed a reduced PPAR β mRNA expression in precancerous cells when compared with normal tissues for 10 patients with familial adenomatous polyposis (389). In some of these studies, it was noted that the range of values is very large and especially for the tumoral group, suggesting high variability among samples. This is exemplified in the study by Feilchenfeldt et al. (155) that compared PPAR β mRNA expression levels in tumor samples versus control tissue in a population of 17 CRC patients and showed no change for 12 patients, increased expression for 4 patients, and decreased expression for 1 patient (155). Finally, several genome-wide expression profiling analyses did not reveal overexpression of PPAR β mRNA in CRC samples when compared with normal tissues (241, 271, 416, 489, 542).

Globally, data coming from immunoblotting quantification of PPAR β protein expression confirmed the main conclusions made for PPAR β mRNA quantification with a very diverse expression level of PPAR β among CRCs. A first study showed that the amounts of PPAR β protein are very diverse among CRC samples (573). Another study revealed a significant lower expression of PPAR β protein in colonic adenocarcinomas than paired normal tissue for 19 patients, while, and as expected, cyclin D1 protein abundance displayed an opposite feature. Furthermore, in the same study, no significant change in PPAR β protein expression was observed for 14 rectal cancers when compared with control tissue (161), whereas another study showed that PPAR β protein was overexpressed by sevenfold in primary rectal when compared with normal rectal mucosa, although the number of analyzed samples was not clearly stated (661). Furthermore, proteomic analyses revealed that PPAR β protein amounts are lower in human colon tumoral samples than in control tissues (44, 601, 602).

Several reports based on the use of both transgenic and pharmacological approaches have raised the fundamental question of a causal role of PPAR β in intestinal tumorigenesis (summarized in **TABLE 2**). Park et al. (428) reported that PPAR β gene disruption in the human CRC cell line HTC116 only slightly reduces the growth rate of the cells in vitro, but decreases their ability to promote tumor formation when injected into nude mice, with a twofold reduction in tumor frequency and a considerable reduction in the tumor size, suggesting that PPAR β is important for CRC tumorigenesis mainly by its crucial role for in vivo growth of tumoral cells. However, in a more recent study, Yang et

Table 2. Role of PPAR β in intestinal cancer

Findings	Reference Nos.	Role in Cancer
<i>Mouse studies</i>		
PPARβ deficiency		
PPAR β gene disruption in the human CRC cell line HTC116 only slightly reduces the growth rate of the cells in vitro, but decreases their ability to promote tumor formation when injected into nude mice.	428	+
PPAR β knock-down in human colon carcinoma cells KM12C stimulates their growth both in vitro and in vivo in nude mice.	662	-
PPAR β gene disruption by deletion of exon 4 in the APC ^{min/+} genetic background does not significantly affect both the number and the mean size of intestinal polyps but reduces the number of largest polyps in the small intestine.	27	=
PPAR β gene disruption by deletion of exon 8 in the APC ^{min/+} genetic background does not significantly affect both the number and the mean size of polyps in the colon but did lead to an increase in the average number and size of small intestinal polyps ($n = 10-11$ per group).	361	=/-
PPAR β gene disruption by deletion of exon 8 in the APC ^{min/+} genetic background enhances the number of colon polyps in both male and female mice and number of small intestine polyps in female but not in male mice ($n = 15-26$ per group).	212	-
PPAR β gene disruption by deletion of exon 8 in the APC ^{min/+} genetic background enhances the number of colon polyps in female but not in male mice, while polyp numbers in the small intestine do not differ. The size of small intestine polyps is increased in both male and female mice ($n = 6-12$ per group).	468	-
PPAR β -deficient (exon 8) mice displayed an increase in the number of polyps following treatment with azoxymethane (AOM) compared with wild-type control mice.	212, 230, 361	-
PPAR β deficiency by deleting exons 4 and part of 5 resulted in a reduction in the number of polyps in small intestine and colon with a more marked reduction in the number of the largest polyps in APC ^{min/+} mice.	628	+
Mice with an intestinal-specific PPAR β disruption by exon 4 deletion display a very marked resistance to AOM-induced colonic tumorigenesis.	686	+
Mice with an intestinal-specific disruption of PPAR β by deletion of exon 4 did not exhibit any change in colonic tumor formation when treated with AOM and DSS.	393	=
PPARβ activation		
Treatment of adult APC ^{min/+} for 6 wk with GW501516 led to a twofold increase in the total number of polyps and to enlargement of polyps in the small intestine, but did not change the number of colonic polyps.	198	+
Treatment of adult APC ^{min/+} for 7 wk with GW501516 increased the number of polyps in both small intestine and colon.	628	+
In the AOM-induced model of colonic tumorigenesis, long-term treatment (22 wk) with a high dose of GW0742 decreased tumor incidence by approximately twofold, while treatment with lower doses was not effective.	230, 361	-
No effects on both number and size of polyps in small intestine and colon were observed after a 6-wk treatment of APC ^{min/+} mice with GW0742.	361	=
<i>Human studies</i>		
No correlation between expression of PPAR β and Ki-67 and no correlation between expression level of PPAR β and clinicopathological parameters of CRC.	573	=
Overexpression of both PPAR β and COX-2 in CRCs was associated with upregulation of the angiogenic factor VEGF-A and increased tumor microvessel density and decreased survival rate after resection of primary colon tumors, whereas no association was established between the other phenotypes of PPAR β and COX-2 expression in CRCs and angiogenic parameters.	671, 672	+
High PPAR β expression in primary cancers exerts a protective action against transition toward more aggressive phenotypes. No relationships were established between the level of PPAR β expression and COX-2 expression or apoptosis. Examination of the relationship between PPAR β expression level in primary cancers and patient survival over a 15-yr follow-up period supported the role of PPAR β as a tumor suppressor in CRC.	661	-
Patients who have higher tumor expression of PPAR β display improved overall postsurgery survival than patients with low PPAR β tumor expression.	253	-

-, PPAR β plays an antitumorigenic role; +, PPAR β plays a protumorigenic role; =, no significant role for PPAR β demonstrated in tumorigenesis.

al. (662) demonstrated that PPAR β knockdown in human colon carcinoma cells KM12C stimulates their growth both in vitro and in vivo into nude mice, suggesting an antitumorogenic function for the nuclear receptor.

To explore the implication of the nuclear receptor in intestinal tumorigenesis, several laboratories have investigated the impact of either global or intestine-specific genetic disruption of PPAR β in genetically induced (APC^{min/+} mouse model), or chemically induced (AOM-treated mice) models of intestinal carcinogenesis. These experimental approaches provided conflicting results. Barak et al. (27) showed with a very limited number of animals that germline PPAR β gene disruption by deletion of exon 4 in the APC^{min/+} genetic background does not significantly affect both the number and the mean size of intestinal polyps but reduces the number of largest polyps in the small intestine, suggesting that PPAR β is dispensable for colorectal polyp formation in APC^{min/+} mice. This contrasts with data obtained with PPAR β -deficient mice generated by deletion of exon 8. Harman et al. (212) reported that such a PPAR β germline genetic disruption significantly enhances the number of polyps in colons of both females and males in APC^{min/+} mice (by 6- and 3-fold, respectively), while the number of polyps is less affected in the small intestine of females (~2-fold) and not significantly changed in the small intestine of males. Interestingly, APC^{min/+}/PPAR β -deficient mice displayed earlier mortality than APC^{min/+} control mice (212), but this was not confirmed in a later study (468). Moreover, PPAR β deficiency resulted in an enhanced number of colon polyps upon AOM treatment compared with wild-type control mice (212, 230, 361). Collectively, these data suggest that a functional PPAR β pathway exerts protective action in both genetic and chemical mouse models of intestinal tumorigenesis. However, another study performed with PPAR β null mice generated by deletion of exon 4 and part of exon 5 led to the opposite conclusion. Indeed, PPAR β deficiency by deleting exon 4 and part of exon 5 resulted in a reduction in the number of polyps in small intestine (3-fold) and colon (2-fold) with a more marked reduction in the number of the largest polyps in both male and female APC^{min/+} mice (628).

To further elucidate the role of PPAR β in intestinal tumorigenesis, animal models for an intestinal epithelium-specific disruption of PPAR β gene were generated by deleting exon 4 (393, 686). Zuo et al. (686) reported that mice with an intestinal-specific PPAR β disruption by exon 4 deletion display a very marked resistance to AOM-induced colonic tumorigenesis, with reduction of tumor incidence of 33-fold in heterozygous PPAR β ^{+/-} mice and 65-fold in homozygous PPAR β -deficient mice. In contrast, mice with an intestinal-specific disruption of PPAR β by deletion of exon 4 did not exhibit any change in colonic tumor formation when treated with AOM and sodium dextran sulfate (DSS), suggesting that intestinal PPAR β expression is dispensable for

colonic tumorigenesis (393). Interestingly, chronic inflammation induced by DSS was notably increased in PPAR β -deficient animals, indicating that intestinal PPAR β exerts anti-inflammatory action in gut (393).

Pharmacological approaches aimed to explore pro- or anti-tumorogenic potential of synthetic PPAR β agonists also provided mixed results. Treatment of adult APC^{min/+} for 6 wk with GW501516 led to a twofold increase in the total number of polyps and to enlargement of polyps in the small intestine, but did not change the number of colonic polyps (198). Another study with a similar experimental protocol concluded that pharmacological activation of PPAR β increased the number of polyps in both small intestine (2-fold increase) and colon (3- to 4-fold increase) with particular augmentation of large tumor number (628). In contrast, no effects on both number and size of polyps in small intestine and colon were observed after a 6-wk treatment of APC^{min/+} mice with GW0742, another potent and specific PPAR β agonist (361). In the AOM-induced model of colonic tumorigenesis, long-term treatment (22 wk) with a high dose of GW0742 decreased tumor incidence by approximately twofold (361), while treatment with lower doses was not effective (230, 361).

Given the large disparities in the results obtained with animal models, no clear picture emerges about the role of PPAR β and of its pharmacological activation on intestinal tumorigenesis. The reasons for these disparities remain uncertain, although several explanations could be proposed. For instance, for some authors, the inconsistent or contradictory results obtained with PPAR β -deficient mouse models, i.e., targeted deletion of either exon 4/5 or exon 8, could be the consequence of the synthesis of a truncated protein remaining at least partly functional in animals with a targeted deletion of exon 8 in PPAR β gene (628, 686). This hypothesis appears incorrect as no immunoreactive protein (with normal or low molecular weight) can be detected by Western blotting analysis with an antibody raised against the NH₂-terminal PPAR β peptide in small intestine and colon of mice carrying PPAR β gene disruption by deletion of exon 8 (212). A more plausible explanation for these disparities among the diverse studies is the variability in the genetic backgrounds of the animal models used. For instance, some of the studies have been performed with PPAR β -deficient animals on a mixed genetic background (27, 628), while other studies were performed with PPAR β -deficient mice on a pure C57BL/6 genetic background (212, 361). Such differences in genetic background are especially important when these animals are crossed with APC^{min/+} mice as it has been clearly demonstrated that the genetic background strongly influences the penetrance of the Min phenotype due to strain-specific impact of loci, called modifiers of the Min phenotype (Mom), that strongly modify the severity of Min phenotype (132, 369). Indeed, APC^{min/+} mice on the C57BL/6J background develop more intestinal

tumors than APC^{min/+} mice on mixed genetic backgrounds. Other differences in animal housing conditions that might influence other pathways involved in intestinal tumorigenesis, such as inflammatory status or COX-2 enzymatic pathway, could also explain the disparities among the diverse studies with animal models.

To date, three studies performed by different laboratories have examined the relationships between PPAR β expression level in intestinal tumors and morphological or clinical characteristics of human CRCs, by using immunohistochemical (IHC) analyses coupled or not with quantitative measurements of PPAR β protein abundances in CRC samples and in normal intestinal mucosa.

An unexpected observation of these IHC analyses is that the PPAR β antibodies reveal a signal predominantly located in the cytoplasm of tumoral cells with little expression in nuclei, while the protein is more abundant in nuclei than in cytoplasm in normal mucosa (573, 661, 671). Further analyses, as Western blot comparing nuclear extracts with cytoplasmic fractions, are needed to confirm that the detected cytoplasmic signal corresponds to the PPAR β protein. However, confirmation of such a differential cellular location of PPAR β between normal and tumoral intestinal mucosa would raise the question of the functionality and the role of cytoplasmic PPAR β in CRC development. In addition, all these studies also revealed a great disparity of the PPAR β protein levels among CRCs with high expression level of cytoplasmic PPAR β protein in approximately half of the tumors and low expression PPAR β protein amounts in the other half (573, 661, 671).

In contrast, these IHC studies differ in the relationship between expression level of PPAR β and clinicopathological characteristics of the tumors. Takayama et al. (573) reported that cells expressing high amounts of cytoplasmic PPAR β often exhibit features of highly malignant morphology with loss of cellular polarity and large nucleus, while low-expressing cytoplasmic PPAR β cancer cells display more normal morphology, but the authors did not find significant correlation between the cytoplasmic expression of PPAR β and Ki-67, a cell proliferation marker. Moreover, no significant correlation was found between expression level of PPAR β and clinicopathological parameters of CRC in this report (573). Yoshinaga et al. (671) investigated by IHC analysis the expression of PPAR β and COX-2 in CRC samples from 52 patients with diverse clinical characteristics and matched normal adjacent tissues. This study allowed a distinction between CRC with overexpression of PPAR β alone (8 patients), COX-2 alone (16 patients), both PPAR β and COX-2 (17 patients), and normal expression of PPAR β and COX-2 (11 patients) and revealed that the overexpression of both PPAR β and COX-2 in CRCs was associated with upregulation of the angiogenic factor VEGF-A and increased tumor microvessel density, whereas

no association was established between the other phenotypes of PPAR β and COX-2 expression in CRCs and angiogenic parameters (671). More recently, the same group reported that expression of both PPAR β and COX-2 in CRCs is associated with liver metastasis and with decreased survival rate of the patients after resection of primary colon tumors (672). This study suggesting that overexpression of both PPAR β and COX-2 in cancer cells is associated with poor prognosis is of interest but not totally conclusive as it is based on a quite limited number of patients per group and, more importantly, this study is only based on IHC determination of PPAR β overexpression without any accurate certification of the specificity of the antibody used. This is a great limitation of the research as it is known that several commercially available PPAR β antibodies display a large degree of nonspecific immunoreactivity and react not only with PPAR β protein but also cross-react with several other proteins (186). To date, the more convincing analysis on the association between PPAR β expression level and human CRC development was reported by Yang et al. (661). Importantly, this study included a large number of well-characterized resected CRCs with examination of several biological and clinical parameters, and the PPAR β expression level was determined by both quantitative immunoblotting and IHC analyses. This study showed that primary cancers with high expression of PPAR β when compared with those with low expression exhibited higher frequency of stage 1 (40 vs. 10%), lower frequency of stages 2–4, and lower frequency of lymph node metastases. High PPAR β expression in primary cancers was related to low expression of the proliferation marker Ki-67 and to better differentiation index, while no relationships were established between the level of PPAR β expression and COX-2 expression or apoptosis. All these observations suggested that high expression level in primary cancers exerts a protective action against transition toward more aggressive phenotypes. Examination of the relationship between PPAR β expression level in primary cancers and patient survival over a 15-yr follow-up period supported the role of PPAR β as a tumor suppressor in CRC. Indeed, the authors showed that high expression level of PPAR β in primary cancers was significantly related to an impressive increase (3- to 4-fold) of postoperative survival in patients for a period of observation of 15 yr (661). Noteworthy, nearly similar observations showing that patients who have higher tumor expression of PPAR β display improved overall post-surgery survival than patients with low PPAR β tumor expression were previously reported by Ishizuka et al. (253) in a study carried out with a smaller number of patients (26 CRC cases) and within a shorter period of observation (32 mo postsurgery).

Collectively, the substantial amount of data provided by these studies clearly shows that dysregulation of PPAR β expression is not a general feature of CRCs, but remains insufficient to establish the role of PPAR β signaling in pre-

venting or promoting colonic tumorigenesis as illustrated by the opposite conclusions of recently published reviews on this issue (440, 444, 657).

For some authors, several data support the idea that activation of the PPAR β pathway is protective against intestinal tumorigenesis by acting at various steps. First, the activation of the PPAR β pathway leads to augmented expression of colonocyte differentiation markers both *in vivo* (230, 361) and in CRC cells (161), while knockdown of PPAR β in CRC cells results in increased cell proliferation (664), reduction of terminal differentiation, and exacerbation of several malignant phenotypes (660). Second, PPAR β activation could also reduce intestinal tumorigenesis by reduction of inflammation that has been described as an important factor in initiation, progression, and metastasis of colon tumorigenesis (586, 603). As it will be presented in a next section, PPAR β exerts anti-inflammatory action by multiple mechanisms in various tissues including intestine (37, 232, 393). Third, as previously discussed, PPAR β activation results in enhancement of the protective functions of Paneth cells and thereby could reduce infection-induced intestinal inflammation (423). Finally, pharmacological PPAR β activation could also prevent colon carcinogenesis by reduction of insulin resistance, obesity, and lipid disorders that have been associated with high risk of CRC (30, 144, 424, 595).

For other authors, several data support the idea that activation of the PPAR β pathway could have procarcinogenic action in intestinal mucosa through anti-apoptotic and angiogenic effects, and various signaling pathways have been proposed for these actions of PPAR β . For instance, some studies have suggested a positive feedback loop between COX-2 and PPAR β in which on the one hand PPAR β activates COX-2 expression in CRC cells (312), cholangiocarcinoma cells (656), and human lung carcinoma cells (182) and, on the other hand, PGE₂, the main metabolite of COX-2 in CRC cells, enhances the transcriptional activity of PPAR β through the PI3K/Akt pathway (628, 629). However, another group did not confirm such a PPAR β -promoted upregulation of COX-2 in hepatocellular and CRC cell lines and did not observe enhancement of COX-2 expression in intestinal polyps from APC^{min/+} mice or AOM-treated mice after administration of a synthetic PPAR β agonist (230, 231). In addition, the finding that PPAR β overexpression in human CRC is not always associated with COX-2 upregulation does not support such a model (661, 671).

Another mechanism proposed to explain the protumorigenic action of PPAR β in CRC cells is a functional antagonism between PPAR β and PPAR γ (687), leading to suppression of the anti-apoptotic effect of PPAR γ related to downregulation of survivin and caspase-3 (627).

A link between the 15-lipoxygenase-1 (15-LOX-1) enzymatic pathway and its primary product, the oxidative metabolite of linoleic acid 13-*S*-hydroxyoctadecadienoic acid (13-*S*-HODE) and dysregulated PPAR β expression in CRC cells was also proposed to explain the beneficial action of NSAIDs on colon tumorigenesis. It has been reported that downregulation of 15-LOX-1 and decrease in 13-*S*-HODE production that take place early in CRCs is linked to reduced apoptosis, enhanced angiogenesis, and increased tumorigenesis and that NSAIDs exert part of their antitumorigenic action by transcriptional upregulation of 15-LOX-1 (251). Shureiqi et al. (534) showed that both 15-LOX-1 forced expression and treatment with 13-*S*-HODE downregulate PPAR β expression and activity in CRC cells and that functional 15-LOX-1 enzymatic pathway is required for the NSAID-promoted PPAR β downregulation, NSAID-induced cell apoptosis, and NSAID-promoted inhibition of tumor formation in a nude mouse xenograft model with CRC cells. It must be noted that other studies did not confirm such an implication of the PPAR β pathway in the anticarcinogenic action of NSAIDs and indeed showed that NSAIDs have no effect on PPAR β expression in normal colon tissue and colon tumors from APC^{min/+} mice, that both NSAIDs and PPAR β agonist attenuated proliferation of colon cancer cells and that the NSAID-promoted antitumorigenic effect in AOM-induced model of colonic tumorigenesis is still occurring in PPAR β -deficient mice (161, 162, 230).

Further studies are clearly required to establish a clear picture on the actual role of PPAR β in CRC initiation and progression. To date, data on the effects of specific PPAR β agonist on human CRC development are lacking as the studies performed with administration of specific PPAR β agonists GW501516 or MBX-8025 are not informative due to the short duration of treatment. However, it is interesting to note that a preventive effect of bezafibrate, a pan-PPAR ligand (439), on the development of colon cancer has been reported for patients who received the compound for up to 6 yr (583). Indeed, this study showed that administration of bezafibrate at a dose known to fully activate both PPAR β and PPAR α (642) to patients with coronary heart disease (1,506 patients in the bezafibrate group versus 1,505 patients in the placebo group) exerts a protective effect on colon cancer development (8 cases in the bezafibrate group versus 17 cases in the placebo group after 6 yr of treatment). Although it is not possible to attribute this preventive effect to the sole activation of PPAR β , such an observation does not favor the hypothesis of a protumorigenic potential of activation of this transcription factor.

In summary, PPAR β exerts regulatory functions in several cell types of intestinal epithelium, i.e., enterocytes, Paneth cells, enterochrine L cells, and colonocytes. In these cell types, PPAR β activation results in enhancement of their specific and diverse physiological functions such as absorp-

tion of lipids, cholesterol excretion, secretion of proteins involved in enteric innate immunity, or secretion of intestinal hormones. Collectively, these effects of PPAR β should be considered as beneficial in the context of metabolic disorders and could explain, at least partly, the improvement of several metabolic parameters, such as lipoprotein profile or insulin sensitivity, promoted by PPAR β agonist administration to obese rodents or to moderately obese patients.

E. PPAR β in Endothelial Cell Physiology

The three PPAR isoforms are expressed in endothelial cells (53, 652), and it has been shown that, while activation of PPAR α and PPAR γ exert antiproliferative effect in endothelial cells and antiangiogenic actions both in vitro and in vivo, PPAR β activation displays opposite effects at least in physiological conditions (51, 396).

Indeed, it was reported that the specific PPAR β agonist GW501516 exerts dose-dependent positive effects on the expression of VEGF-A and its receptor VEGF-R1, and increases proliferation rate in human umbilical vein endothelial cell (HUVEC) cultures (559). Moreover, PPAR β activation also induces an actual VEGF-dependent angiogenic response as demonstrated in various in vitro and in vivo models of endothelial tube formation in a process that requires PPAR β as forced expression of a PPAR β dominant negative form impairs such a process (450). As it will be discussed in more details in a following section, transgenic or pharmacological activation of the PPAR β signaling pathway promotes upregulation of VEGF-A expression and angiogenesis in skeletal muscle and heart leading to an enhancement of capillary density (178, 623).

There are also some data that do not support a potential angiogenic role for PPAR β . A recent publication described an anti-angiogenic effect of GW501516 and L-165041 PPAR β agonists on HUVECs by a potent repressive action on VEGFR2 expression (377). However, such effects observed only at very high doses of agonists appeared to be PPAR β -independent as they were not affected by PPAR β silencing and therefore could be related to the lack of specificity of these agonists when used at very high concentrations (429). It was also reported that ligand activation of PPAR β exerts suppressive effects on cathepsin B expression and activity in HUVEC by a process that requires functional PPAR β pathway and implicates a posttranslational mode of action (471). Although it has been shown that cathepsin downregulation is associated with reduced VEGF expression (357) and inhibition of angiogenesis (458), the authors did not provide direct evidence that PPAR β -promoted cathepsin B downregulation actually reduces VEGF expression and angiogenesis in HUVECs (471). Moreover, Yang et al. (662) reported that treatment of the human colon cell line KM12C with a PPAR β agonist reduces VEGF expression, while PPAR β knockdown has the opposite effect.

Interestingly, the work from Muller-Brusselback et al. (399) revealed a more complex role of the PPAR β pathway in regulation of endothelial cell proliferation and angiogenesis. The use of a tumor xenograft model and a Matrigel plug assay in control and PPAR $\beta^{-/-}$ mice showed that PPAR β deficiency resulted in uncontrolled proliferation of endothelial cells and reduction of microvessel maturation and tumor vascularization while retroviral transduction of PPAR β in deficient cells restores arrest of cell proliferation and microvessel maturation. These observations suggest that complete abolition of PPAR β signaling leads to deregulation of angiogenesis resulting in appearance of hyperplastic undifferentiated microvascular structures and that PPAR β plays a crucial role in growth arrest and subsequent differentiation of endothelial cells. Further analysis identified the cell cycle inhibitor p57KIP2 as a PPAR β target gene and suggested that p57KIP2 is directly involved in PPAR β -dependent inhibition of cell proliferation (399).

How PPAR β regulates VEGF-A gene expression remains unclear. A PPRE consensus element was identified in the VEGF promoter and implicated in the repressive effect of PPAR γ on transcriptional activity of VEGF gene in endometrial cells (434). However, another study concluded that the PPAR-driven activation of VEGF gene expression in bladder cancer cells is an indirect mechanism requiring de novo protein synthesis and involving the MAPK pathway (150). In addition, Genini et al. (182) showed that treatment of human lung carcinoma cells with PPAR β agonists induces VEGF gene expression through both direct transcriptional activation via binding to the VEGF promoter and nontranscriptional mechanism involving interaction between PPAR β and the PI3K regulatory subunit p85 α leading to PI3K activation and Akt stimulation.

PPAR β pathway activation also results in protection against endothelial cell apoptosis. Liou et al. (341) demonstrated that PPAR β activation by augmented PGI $_2$ production, carbaprostacyclin (cPGI $_2$) or specific synthetic agonist, suppresses H $_2$ O $_2$ -induced apoptosis in HUVECs. This antiapoptotic action of PPAR β activation appeared to be due to a direct transactivation of the 14-3-3 gene through interaction of PPAR β with a PPRE consensus sequence. Indeed, the PPAR β -driven induction of 14-3-3 protein is functionally efficient as it was shown that pretreatment of HUVECs with cPGI $_2$ or specific PPAR β agonists blocks the H $_2$ O $_2$ -induced Bad translocation into mitochondria and apoptosis (341).

Interestingly, PPAR β expression is modulated by H $_2$ O $_2$ treatment in endothelial cells as exposure of HUVECs to high concentrations of H $_2$ O $_2$ provokes a strong reduction of PPAR β protein (263), while repetitive treatments of HUVECs with low H $_2$ O $_2$ concentration promotes upregulation of PPAR β protein and protection against H $_2$ O $_2$ -induced apoptosis (262).

In addition to its effects on endothelial cell proliferation and survival and subsequent proangiogenic action, PPAR β is also involved in endothelial progenitor cells (EPCs) physiology and in vasculogenesis. EPCs are circulating bone marrow-derived cells able to proliferate, migrate, and differentiate into endothelial cells. EPCs play a crucial role in formation of new vessels in adult and have a great therapeutic potential in tissue ischemia (22, 433).

Han et al. (206) reported that treatment of human EPCs with specific PPAR β agonists induces their proliferation and protects them from apoptosis. Such a treatment also enhances EPC functions, such as transendothelial migration and in vitro tube formation. These effects appeared to be related to activation of the PI3K/Akt pathway. Furthermore, PPAR β activation displays an actual provasculogenic effect as demonstrated in two different in vivo mouse models, the hindlimb ischemic model and corneal neovascularization in which systemic administration of PPAR β agonist notably ameliorate EPC mobilization and vasculogenesis (206).

Pharmacological approaches have suggested that PGI $_2$, which is the main metabolite of prostaglandin synthesis in vascular tissue, could exert its proangiogenic action by PPAR activation (456). He et al. (220) established a central role for PPAR β in the regulatory control by PGI $_2$ of EPCs physiology by the findings that EPC-produced PGI $_2$ from the arachidonate/COX metabolic pathway activates PPAR β that, in turn, enhances EPC proliferation and proangiogenic functions both in vitro and in vivo.

An earlier study suggested that EPCs may also induce angiogenesis by producing and secreting unidentified angiogenic growth factors (470). A recent publication described a new aspect of PPAR β action on angiogenesis and myogenesis by inducing a paracrine effect from the EPCs toward endothelial cells and myoblasts. Indeed, Han et al. (205) found that PPAR β activation induces metalloproteinase-9 (MMP9) gene expression by a direct transcriptional mechanism in human EPCs. In vitro and in vivo experiments revealed that the PPAR β -induced MMP9 synthesis and secretion by EPCs affects the insulin growth factor (IGF) signaling pathway in target cells, such as endothelial cells and myoblasts, by proteolysis of IGF-binding protein 3 and subsequent increase in unbound IGF and demonstrated that this PPAR β /MMP9/IGF signaling pathway is involved in the activation of endothelial cells and myoblasts and the angiogenic/myogenic response taking place in the ischemic hindlimb mouse model (205).

Except for a few studies that would argue against a proangiogenic role for PPAR β , the majority of findings suggest that PPAR β plays a central role in angiogenesis and vasculogenesis and that its activation by naturally occurring molecules, such as PGI $_2$, stimulates the proliferation, survival,

and angiogenic functions of both EPCs and endothelial cells through changes in the expression levels of several proteins directly or indirectly implicated in the control of proliferation, apoptosis, or differentiation of these endothelial cell types. This PGI $_2$ /PPAR β signaling pathway is clearly implicated in physiological angiogenic responses, such as physical training-induced or ischemic-induced angiogenesis. Pharmacological activation of PPAR β may be a novel therapeutic intervention in pathological situations requiring angiogenesis, such as limb or cardiac ischemia.

III. PPAR β AND MUSCLE

A. PPAR β in skeletal muscle physiology and metabolism

Both RNA protection and quantitative-PCR assays showed that in rodent and human skeletal muscles, PPAR β expression is greater than that of PPAR α , while PPAR γ mRNA level is very low (112, 400). During the last decade, a large number of experimental evidence based on the utilization of pharmacological tools, cellular and animal models, including transgenic mouse models, have demonstrated that PPAR β plays a central role in the control of muscle metabolism, muscle functions, and adaptive response to environmental changes. These findings have quite important outcomes in muscle physiology and development of new pharmacological strategies for the treatment of metabolic disorders linked to physical inactivity and bad nutrition habits.

In the next section we present the main conclusions of the large body of literature on the topics of skeletal muscle structure, metabolism, functions, and adaptive responses to nutrition and physical activity behaviors.

1. Metabolic and functional diversity of skeletal muscle

The generic term *skeletal muscle* covers a large diversity of structural entities with different shapes and used for different tasks in an organism, such as ventilation, postural functions, sustained submaximal contractions, or short-term high-intensity workouts. To achieve these different physiological functions, mammalian skeletal muscles comprise a variety of muscle fiber types with different contractile and metabolic properties and, subsequently, diverse functional capacities (507). Muscle fibers display a specific expression pattern of the components of the contractile apparatus, and the distribution of these diverse fiber types within a specific muscle greatly affects its contractile performance. Among the major components of contractile apparatus are the myosin heavy chains (MHC) that contain the ATPase activity generating the energy required for contraction and determining the velocity of shortening of muscle fibers (472).

Based on the determination of predominant MHC isoforms, it has been established that rodents have four fiber types termed I, IIa, IIx, and IIb, while the majority of large mammal muscles, including human, contain three fiber types, I, IIa, and IIx (507). A significant percentage of fibers expressing more than one MHC isoform and termed “hybrid” fibers was observed in rodent (275, 555, 678) and human (86, 427) muscles. Other components of the contractile apparatus, such as myosin light chain isoforms, troponins, or troponins (50, 495, 621) and proteins implicated in Ca²⁺ sequestering (196, 354) also display a fiber type-specific expression.

In vitro studies on rodent and human skinned muscle fibers revealed clear mechanical differences among the various fiber types (68, 507). It is generally thought that both maximal contractile velocity and peak force are increasing in the following order: type I, type IIa, type IIx, type IIb in rodents (67, 174) and type I, type IIa, type IIx in humans (65, 66, 318, 640). As a consequence, muscles with a preponderance of type I fibers, such as postural muscles, have lower contractile force and velocity than muscles with more type IIa and IIx or IIb fibers, such as muscles implicated in resistance work. The fiber composition of rat hindlimb muscles illustrated this aspect since the soleus, which is implicated in postural and low-intensity workouts, is rich in type I fibers, while extensor digitorum longus, plantaris, and tibialis anterior muscles, who are employed for high-intensity work, consist mainly of type IIa, IIx, and IIb fibers (117).

Mechanical contractile activity of sarcomeres requires energy that is provided by the hydrolysis of ATP to ADP and inorganic phosphate catalyzed by the MHC ATPase activity. The energy must be delivered to the contractile apparatus in a well-appropriated manner in terms of amounts and duration of ATP supply to allow the different kinds of muscle efforts, such as high-intensity exercises that need huge amounts of ATP for a limited time and endurance exercises requiring less ATP for a longer period of time. Muscle fibers display huge differences in their energy consumption during contraction. For instance, during maximal isometric contraction, mouse extensor digitorum longus (EDL) muscle which contains mainly IIb myofibers, utilizes about fivefold more ATP than soleus muscle which consists mainly of type I fibers (29), while human type IIa and type IIx fibers utilize, respectively, 2.5 and 4 more ATP than type I fibers (493, 560). To comply with these energetic commitments, fibers utilize two main metabolic pathways for ATP provision of myofibrils.

Anaerobic glycolytic metabolism generates ATP by the catabolism of glucose to lactate. Energetic yield of anaerobic glycolysis is quite poor with the production of two molecules of ATP for one molecule of glucose used. Despite such a poor energetic yield, as the enzymes of anaerobic glycolysis are expressed at high levels, this metabolic pathway can

rapidly provide important amounts of ATP required for high-intensity exercises (210, 211). However, anaerobic glycolysis rapidly leads to muscle fatigue due to depletion of glycogen stores and production of deleterious metabolites and is ineffective to support muscle contraction for more than a few minutes (192, 414, 481).

ATP supply for sustained muscle contraction is provided by aerobic oxidative phosphorylation that takes place in mitochondria and consists of two coupled metabolic pathways, i.e., the citric acid, also known as the tricarboxylic acid cycle (TCA cycle) or Krebs cycle, and the electron transport chain. In skeletal muscle, carbohydrates and fatty acids are the major sources of acetyl-CoA for aerobic oxidative metabolism. Carbohydrates enter oxidative metabolism by decarboxylation of pyruvate, the end product of anaerobic glycolysis, to acetyl-CoA in an irreversible reaction catalyzed by the pyruvate dehydrogenase complex (PDC) (430, 469). Fatty acids activated into acyl-CoA provide acetyl-CoA to the citric cycle via breakdown by the fatty acid β -oxidation process that takes place in mitochondria. Aerobic oxidative phosphorylation is very efficient because when oxidative phosphorylation is totally effective (474), one molecule of either glucose or palmitate produces 38 and 129 molecules of ATP, respectively.

To cope with their energetic commitments for their contraction, type IIb and IIx mainly function on anaerobic metabolism, while type I and IIa display an oxidative metabolism. This metabolic fiber diversity is linked to higher mitochondrial content in type I and IIa fibers than in type IIb and IIx (179, 243, 432). From a large number of publications, it has been concluded that type I fibers display higher oxidative enzymatic activities [e.g., citrate synthase (CS) or succinate dehydrogenase (SDH)] and lower glycolytic enzymatic activities [e.g., lactate dehydrogenase (LDH) or phosphofructokinase (PFK)] than type IIb and IIx fibers, while type IIa fibers display an intermediate phenotype (145, 349, 549, 550). Transcriptomic analyses revealed a fiber-differential expression of several hundreds of genes, including those encoding key metabolic markers (90, 454). Fibers also differ in their ability to manage adequate oxygen availability for the oxidative metabolism. Indeed, muscles where type I and IIa are predominant contain high myoglobin amounts, while myoglobin contents are very low in muscles comprising a majority of type IIb fibers (294, 308, 378, 614). The microcirculation network is another important determinant for oxygen delivery, and several histological studies demonstrated that the capillary-to-fiber ratio is higher in oxidative muscles than in glycolytic muscles from several animal species (4, 74) and humans (252, 540). Fibers also differ by their content of substrate stores in the form of glycogen and triglycerides. Fast fibers contain more glycogen than slow fibers (194, 618) and, in contrast, neutral lipid content is 2–3 times higher in type I fibers than in type II fibers (145,

167, 610, 611) and ~1.5-fold higher in type IIa fibers than in type IIb fibers (356).

Adult skeletal muscles display an extraordinary high ability to adapt their morphological, functional, and metabolic capacities to prolonged changes in physical activity behaviors. There has been considerable effort to study this muscle remodeling process that appears as of considerable interest in sport science for performance improvement and, more recently, in the field of metabolic disorders and type 2 diabetes with the demonstration of beneficial effects of regular aerobic physical activity (23, 604).

Several strategies, aimed to increase or decrease muscle activity, have been used to establish the physiological adaptive responses of skeletal muscle to modifications in physical activity behaviors. Although adaptive responses are very different among species, type of muscle and experimental protocol, these studies showed that adaptive responses of skeletal muscle to physical activity are characterized by the modification in the expression profile of a very large panel of proteins, including key metabolic players and components of the contractile apparatus (507). In rodent and human muscles, long-term increase in physical activity, such as endurance training for several weeks, enhances oxidative metabolism with increased reliance on fat metabolism, lowered blood lactate concentration, and sparing of muscle glycogen during exercise (226, 234, 235). This metabolic remodeling is characterized by an increase in mitochondrial content, increment of enzymatic activities involved in the TCA cycle and in fatty acid and ketone oxidation pathways (32, 189, 233, 390, 644), and upregulation of the steady-state levels of mRNAs coding for the oxidative phosphorylation pathway (401, 402, 461) and fatty acid catabolism (397, 676). The metabolic adaptations to sustained increase in physical activity are accompanied by a progressive reduction of MHCIIb and IIx expression, and upregulation of MHCIa expression and, only in some circumstances, of MHCI (326, 327, 517). These adaptive responses of metabolism and contractile properties are more pronounced in severe models of muscle contraction, such as the chronic low-frequency electrical stimulation model (537, 538) or very robust endurance training paradigms (19, 208, 475), than in voluntary running rodent models (11, 225).

Skeletal muscle metabolism undergoes an adaptive response to decreased usage as shown in various models of muscle disuse, such as hindlimb suspension, space flight, and bed rest. Globally, this adaptive response is characterized by a reduction of fatty acid utilization and increased glucose utilization in rodent and human muscles (25, 54, 158, 315, 478). This shift in fuel metabolism from lipids toward glucose is related to augmented expression and activity of several glycolytic enzymes, such as PFK, hexokinase, and pyruvate kinase (47, 96, 536, 558, 574, 646), and decreased expression and activity of enzymes of FAO (227,

536, 558, 646). In contrast, mitochondrial oxidation capacity and expression of enzymes in the TCA cycle, such as CS, malate dehydrogenase, and SDH, are not (or only moderately) affected by hindlimb suspension or space flight (25, 47, 264, 574). In rodent models, reduction of neuromuscular activity is associated with a MHC remodeling characterized by downregulation of MHCI and concomitant upregulation of MHCIIx or MHCIIb (82, 419, 576, 577). MHC isoform remodeling appeared to be very limited in human muscles after reduced muscle activity by spaceflight (639, 680) or bed rest (26, 227).

2. Regulatory functions of PPAR β in skeletal muscle physiology

Based on the findings that PPAR α was involved in the transcriptional activation of genes implicated in hepatic and cardiac FAO, it has been proposed that this isoform was playing such a role in all tissues characterized by high fatty acid catabolism capacities, including skeletal muscle. To establish the requirement of PPAR α in the control of lipid metabolism in skeletal muscle, Muoio et al. (400) investigated the impact of PPAR α gene disruption on metabolism and gene expression in mouse in normal conditions or during metabolic challenges. The results of this study were surprising as PPAR α ablation did not affect FAO and expression of metabolic-related genes in muscles from mice maintained in standard conditions and did not change the metabolic and genic responses of skeletal muscles after 24 h of fasting or 2 h of treadmill running.

The use of both cellular models (mouse C2C12 and rat L6 myogenic cell lines, differentiated primary human myoblasts) and animal models (pharmacological treatment of rodents with specific PPAR β agonists and transgenic mouse models for muscle-specific overexpression or disruption of PPAR β) revealed that the PPAR β signaling pathway plays a central regulatory role in skeletal muscle metabolism and especially in the adaptive responses of this tissue to metabolic challenges, including fasting and sustained physical exercise, which are characterized by a shift toward lipid utilization for energetic metabolism.

A) PHYSIOLOGICAL REGULATION OF PPAR β EXPRESSION IN SKELETAL MUSCLE. The level of PPAR β expression in skeletal muscle is influenced by the nutritional status and level of physical activity. Holst et al. (238) reported a two- to threefold accumulation of PPAR β mRNA and protein in mouse gastrocnemius muscle after 24 and 48 h fasting, while PPAR α expression remained unchanged. This upregulation of PPAR β expression is totally reversed within 24 h of refeeding and does not occur in heart. A time course study by De Lange et al. (111) showed that in rat gastrocnemius muscle, PPAR β upregulation peaks at 6 h of fasting (6-fold increase) and then progressively declines for longer periods of time. This elevation of PPAR β expression is concomitant to that of PGC1 α and is followed by enhancement of the mitochon-

drial FAO rate. Data concerning PPAR β regulation in human skeletal muscle during fasting remains limited. One publication reported that a 48-h fasting reduces the expression of both PPAR β and PPAR α in healthy subjects, while expression of PGC1 and of several fatty acid metabolism-related genes remains unchanged (594).

As previously mentioned, physical exercise affects PPAR β expression in rodent and human muscles. The contents in PPAR β protein are notably increased in mouse tibialis anterior after swimming training for 3 or 6 wk (353) and in human vastus lateralis muscle after 4 mo of moderate walking training (168). It has also been found that one bout of high-intensity and sustained exercise leads to an increase in PPAR β mRNA content within hours (355, 488, 633), while when high-intensity interval training is used such an augmentation of PPAR β mRNA muscular content becomes detectable only after several training sessions (437). However, it must be noted that these data should be confirmed at protein level to establish their physiological relevance.

Noteworthy, some publications reported a decreased expression of PPAR β and other transcriptional regulators of lipid catabolism-related genes, such as PGC1 α and PPAR α in muscles after space flight, hindlimb suspension, or spinal cord injury (10, 305, 405).

The molecular mechanisms and signals behind such modulations of PPAR β gene expression in skeletal muscle still remain mysterious. Clearly, the increase in fatty acid availability that occurs during fasting and physical exercise is not directly implicated as a signal, which is suggested by the lack of PPAR β gene induction upon treatment of myocytes in culture with a variety of saturated and unsaturated fatty acids (238), and as demonstrated *in vivo* by the findings that the blunting NEFA elevation by high-carbohydrate diet (488) or by nicotinic acid ingestion before a single bout of sustained high-intensity exercise (633) do not affect PPAR β upregulation.

Recent publications have described mechanisms resulting in PPAR β mRNA upregulation in various cellular contexts, including skeletal muscle. First, chromatin immunoprecipitation sequencing (ChIP-seq) and genome-wide transcriptional profiling have recently revealed that PPAR β binds to its promoter and activates in a ligand-independent manner the expression of PPAR β mRNA in mouse keratinocytes and human myofibroblasts (5, 286). The existence of such a positive regulatory loop in PPAR β expression in skeletal muscle during metabolic and physical exercise challenges remains to be directly demonstrated. Second, another publication provides very interesting observations linking the acute transcriptional activation occurring during physical exercise with changes in DNA methylation (34). Barres et al. (33) found that, in human muscle, the induction of PGC1, PDK4, and PPAR β mRNA expression during or just

after an acute bout of high-intensity exercise is accompanied or preceded by a marked, rapid, and transient reduction of methylation of the respective promoter, while the methylation remains unchanged for genes that are not induced by acute physical exercise, such as CS. Furthermore, the authors describe similar hypomethylation of PPAR β , PGC1, and PDK4 promoter both in isolated mouse soleus during electrical stimulation and in rat L6 myotubes treated with caffeine, e.g., through changes in cytosolic Ca²⁺ concentrations. Noteworthy, the alteration of cytosine methylation promoted by physical exercise is not occurring in the classical CpG context, but concerns cytosine located within a CpA, CpT, or CpC context. Rapid and reversible changes in non-CpG methylation have been already shown to play a role in gene reprogramming during differentiation of stem cells (342) and in the control of PGC1 α gene expression in myoblasts exposed to fatty acids or TNF- α (33). Future studies are needed to appreciate the real importance of this epigenetic mechanism in the global modulation of gene expression in response to physical exercise, to identify the mechanisms and signals involved in the hypomethylation of specific genes in such physiological conditions, and to verify the impact of this regulatory mechanism at the protein level for the different markers.

B) PPAR β -REGULATED SIGNALING PATHWAYS IN SKELETAL MUSCLE METABOLISM. There are several direct experimental demonstrations of the implication of PPAR β in metabolic regulations in skeletal muscle.

Data obtained from myoblastic cell lines and skeletal muscle cells in primary culture revealed that treatment with specific PPAR β agonists leads within 8–24 h to increased expression of several genes implicated in fatty acid uptake, such as FAT/CD36 (238, 551, 581), fatty acid handling and activation, such as FABP (135, 238) and ACS (135, 581), fatty acid mitochondrial uptake, such as carnitine-palmitoyl transferase 1 (CPT1) (135, 400, 551, 581) and fatty acid β -oxidation, such as acyl-CoA dehydrogenase (ACAD), 3-ketoacyl-CoA thiolase and 3-oxoacyl-CoA thiolase (581). Robust increases in uncoupling protein 2 and 3 (UCP2 and UCP3) mRNA (95, 135, 400) and in PDK4 mRNA (135, 400, 551, 581) were also reported by several authors in muscle cells exposed to PPAR β agonists. Treatment of myogenic cells with a PPAR β agonist promotes the expression of two transcriptional regulators that play important roles in muscle oxidative metabolism, PGC1 α (127, 240, 581) and Foxo1 (406). Not surprisingly, the metabolic impact of upregulation of these genes is an enhancement of FAO rate after treatment of myogenic cells with PPAR β agonists (238, 400, 581).

In vivo pharmacological activation of PPAR β confirmed these observations. The first study describing the genetic and metabolic impacts of pharmacological activation of PPAR β was carried out in mice fed a normal diet or a

high-fat diet (HFD) and receiving the specific PPAR β agonist GW501516 for several weeks (581). As previously described in myoblastic cell models, this study showed that pharmacological activation of PPAR β results in overexpression of a variety of genes implicated in fatty acid catabolism, including FAT/CD36, ACS, CPT1, hydroxyacyl-CoA dehydrogenase (HAD), UCP3, and PDK4. This study also revealed that pharmacological activation of PPAR β promotes after 1 wk a dose-dependent and robust (~2-fold at the maximal dose) increase in palmitate oxidation in skeletal muscle, but not in liver. Interestingly, treatments with PPAR α and PPAR γ agonists have no effects on FAO in skeletal muscle, while treatment of mice with the PPAR α agonist elevates FAO in liver. Moreover, the authors also found a net increase in PGC1 mRNA muscle content and detected by electron microscopic analysis a notable augmentation of mitochondria number in skeletal muscle. Importantly, treatment with the PPAR β agonist reduced the development of obesity, prevented lipid accumulation in liver and skeletal muscle, and improved glucose tolerance and insulin sensitivity in mice fed a HFD.

Further studies confirmed only partially these observations by demonstrating that pharmacological activation of PPAR β induces FAO and the expression of genes involved in fatty acid catabolism but failed to show any change in expression of PGC1 α and mitochondrial biogenesis (45, 107, 295, 407). For instance, Kleiner et al. (295) showed that treatment of mice with a PPAR β agonist for 3 wk increases the mRNA levels of CPT1, UCP3, and PDK4 but did not observe variations in expression levels of mitochondrial biogenesis markers, such as PGC1 α , PGC1 β , cytochrome *c*, and cytochrome *c* oxidase 5a. To further explore the relationships between PPAR β and PGC1 α , these authors explored the genic and metabolic effects of pharmacological activation of PPAR β in primary myoblasts isolated from PGC1 α -KO, PPAR β -KO, and control mice. They demonstrated that PGC1 α KO does not suppress the PPAR β -induced FAO and induction of fatty acid catabolism-related genes, but that PGC1 α potentiates these effects in a PPAR β ligand-dependent manner. Moreover, this study showed that the PGC1 α -induced mitochondrial biogenesis does not require PPAR β . However, a role in PPAR β in the control of PGC1 α gene expression cannot be excluded as Schuler et al. demonstrated a direct transactivation of the PGC1 α gene through binding to a PPRE identified in the PGC1 α promoter sequence (516).

Globally, these studies revealed that PPAR β activation promotes in skeletal muscle an impressive remodeling of gene expression known to result in a metabolic transition favoring lipid utilization and limiting carbohydrate oxidation. The balance between carbohydrate and lipid utilization for skeletal muscle aerobic metabolism is a physiological process controlled by several mechanisms to cope with both demand of energy and substrate supply. Deregulation of

this metabolic balance has been linked to muscle insulin resistance (173). Noteworthy, PPAR β activation promotes induction of several genes playing crucial roles in skeletal muscle fuel preference, such as FAT/CD36, CPT1, and PDK4.

FAT/CD36 was first identified as a fatty acid facilitating transport protein in rat adipocytes (3) and in other tissues, including skeletal muscle (59). Several studies have demonstrated that FAT/CD36 is an important actor in fatty acid metabolism for several organs, and gain- and loss-of-function experiments demonstrated the relationship between expression levels of FAT/CD36 and FAO capacity in skeletal muscle (102, 103, 250). The upregulation of PPAR β expression is parallel to that of FAT/CD36 in mouse skeletal muscle (238). Furthermore, muscle contraction promotes acute subcellular redistributions of FAT/CD36 protein that are important for FAO during muscle activity. Muscle contraction promotes translocation of FAT/CD36 from the intracellular compartment to the surface membrane, increasing both fatty acid uptake and FAO (58). In skeletal muscle, FAT/CD36 translocation to surface membrane is not related to AMPK signaling as demonstrated for cardiomyocytes (261, 351), but may possibly involve the calmodulin/Ca²⁺ signaling (314). Muscle contraction also promotes relocation of FAT/CD36 to the outer mitochondrial membrane, and various approaches demonstrated that mitochondrial FAT/CD36 plays a crucial role in fatty acid uptake into mitochondria and FAO during physical activity (85, 236, 544).

CPT1 is one of the components of a multienzymatic system facilitating long chain acyl-CoA entry into mitochondria. CPT1 is located at the outside of the outer mitochondrial membrane and catalyzes the transformation of acyl-CoA and carnitine to acyl-carnitine that is then translocated to the inner mitochondrial membrane and converted by CPT2 into acyl-CoA and carnitine which relocates to the cytoplasm by diffusion (372, 465). CPT1 is considered as the rate-limiting step of fatty acid entry in mitochondria (466), and induction of its expression correlates with increased FAO rate in skeletal muscle (111, 368, 449, 497). In addition to induction of its expression, PPAR β activation could also regulate CPT1 activity by reduction of its inhibition by malonyl-CoA. Several studies have shown that malonyl-CoA acts as a natural inhibitor of CPT1 (348, 372, 379, 492). In skeletal muscle, malonyl-CoA concentrations are reduced in physiological situations in which fatty acids are preferentially used as substrate for ATP synthesis, such as fasting (373), glucose depletion (490, 491), or physical exercise (137, 491, 643). Conversely, malonyl-CoA accumulates in rat soleus muscle during inactivity induced by denervation or after incubation with high concentration of glucose, situations favoring glucose utilization (490). Malonyl-CoA is synthesized by the decarboxylation of acetyl-CoA catalyzed by acetyl-CoA decarboxylase (ACC). Two

ACC isoforms, ACC1 and ACC2, encoded by separate genes have been identified, and various loss-of-function experiments clearly indicated that malonyl-CoA from ACC1 is a substrate for lipogenesis, whereas malonyl-CoA from ACC2, predominantly expressed in skeletal muscle, is implicated in CPT1 inhibition (2, 99, 501). ACC1 and -2 are controlled by various mechanisms including phosphorylation on serine residue by AMPK (322) which almost totally suppresses their activity promoting reduction of cytosolic malonyl-CoA concentration and enhancement of FAO (139, 284, 310, 645). AMPK is activated by several AMPK kinases, such as the liver kinase B1 (217, 218, 347), which is activated by high AMP/ATP ratio (209) or ADP/ATP ratio (417, 650), and calcium/calmodulin kinase kinases (CAMKK) (219, 249) sensitive to Ca²⁺ concentration change. As several studies have demonstrated that PPAR β stimulation promotes activation of AMPK and phosphorylation of ACC2 in skeletal muscle (306, 307, 328), it can be proposed that this results in reduction of malonyl-CoA concentration and enhancement of CPT1 activity.

PDC catalyzes the transformation of pyruvate into acetyl-CoA and is crucial for oxidative metabolism of carbohydrates. PDC activity is controlled by phosphorylation-dephosphorylation of the E1 subunit of the multienzymatic complex. Phosphorylation, leading to inactivation of PDC, is catalyzed by diverse pyruvate dehydrogenase kinases (PDK) and dephosphorylation by pyruvate dehydrogenase phosphatases (PDP) reactivates the multienzymatic complex (340). PDK4 is the predominant isoform expressed in mammalian skeletal muscle (69), and it has been established that its activity is controlled by metabolites and by transcriptional regulation. Several physiological situations in which glucose oxidation for aerobic metabolism is low are characterized by increased PDK4 mRNA expression (237, 552, 564). Thus the PPAR β -induced expression of PDK4 can be a main cause of inhibition of glucose oxidation in skeletal muscle.

Indeed, the PPAR β -induced modifications in gene expression are very reminiscent of that occurring during metabolic adaptive responses of skeletal muscle to long-term changes in the nutritional status and changes in physical activity behavior. For instance, situations characterized by reduction of glucose availability for a long period of time, such as prolonged fasting or continuous reduced carbohydrate content of the diet, result after several hours or days in decreased glucose oxidation and increased FAO in skeletal muscle (89, 513, 546). These metabolic adaptive responses are physiologically important for the glucose conservation and are related to modifications of expression levels of several genes encoding proteins implicated in metabolic regulations. For instance, PDK4 protein content (564) and PDK4 mRNA levels (552) are enhanced in skeletal muscle after several hours of fasting, while expression levels of the other PDK isoforms remain unchanged. Moreover, fasting

promotes expression of a large panel of genes related to fatty acid oxidative metabolism, such as lipoprotein lipase (LPL), FAT/CD36, CPT1, ACAD, ACS, or UCP3 in rodent and human muscles. These effects are robust (2- to 7-fold induction depending on the studied gene) and take place within a similar window of time (6–24 h of food depletion) in both rodent and human muscles (111, 112, 238, 449, 497, 598).

Increased availability of lipids by increasing the relative percentage of fat versus carbohydrate in the diet also leads to overexpression of lipid catabolism-related genes in skeletal muscle. Numerous studies demonstrated that feeding an eucaloric high-fat/low-carbohydrate diet promotes induction of FAT/CD36, CPT1, ACAD, and HAD mRNA in rodent (368, 459, 599) and human muscles (84, 157). These inductions can be observed after 5 days (84) and are sustained for several months as long as high-fat feeding is maintained (459). Similarly, PDK4 protein and mRNA contents are notably enhanced in human and rodent muscles after a shift for several days or weeks on an eucaloric high-fat/low-carbohydrate diet when compared with those detected with standardized diets (237, 445).

Aerobic physical training also results in upregulation of the same set of genes in both human and rodent skeletal muscle. For instance, training increases markedly the activity of HAD, a rate-limiting enzyme of β -oxidation (288, 397, 505), and the expression levels of CPT1 (270, 397, 676) and FAT/CD36 (302, 436, 575). Endurance exercise training promotes upregulation of a set of genes encoding proteins involved in triglyceride metabolism, including LPL implicated in hydrolysis of circulating triglyceride-rich lipoproteins (204, 521), adipocyte triglyceride lipase (ATGL) implicated in hydrolysis of intracellular triglycerides (13, 669), and perilipins 2 and 5 implicated in intracellular lipid droplet structuration and lipolysis regulation (446, 528). Upregulation of the expression of these proteins could explain the training-induced improvement of triglyceride synthesis and degradation observed in rodent and human muscles (190, 248, 288). Noteworthy, in muscle cells, PPAR β activation upregulates the expression of several proteins involved in triglyceride metabolism, such as LPL (135), hormone-sensitive lipase (HSL) (553, 581), and perilipins (49, 114).

Several lines of evidence have suggested that these adaptive responses of skeletal muscle to fasting and high-fat diet are related to the concomitant increases in circulating concentrations of NEFA. Indeed, during intralipid infusion, the induction of FAT/CD36 mRNA in rat muscle coincides with the raise of NEFA circulating concentrations (147, 615). Moreover, in rat soleus, a strict parallelism exists between PDK4 expression levels in soleus muscle and changes in circulating NEFA concentrations during the light (inactive) and dark (active) phases in animals fed either

chow or high-fat diets (556). To directly address the question of a causal role of NEFA in the transcriptional adaptive response of skeletal muscle, experimental approaches aimed to ablate elevation of NEFA levels during fasting have been carried out and provided mitigated results demonstrating huge differences between oxidative and glycolytic muscles. Indeed, treatment of fasting rats with nicotinic acid, that prevents the elevation of NEFA circulating concentration by inhibiting adipose tissue lipolysis (88), results in a total blunt of the fasting-induced expression levels of mRNA for UCP2, UCP3, CPT1, and medium-chain acyl-CoA dehydrogenase in oxidative muscle (soleus), while the responses are not modified in more glycolytic muscles (496, 497). Taken together, these observations indicate that elevation in circulating fatty acid concentration is a major signal for the transcriptional adaptive response toward lipid utilization, although some differences could exist between oxidative and glycolytic fibers.

Collectively, these findings strongly suggest that the activation of the PPAR β signaling pathway, occurring through upregulation of PPAR β protein and/or PPAR β activation by endogenous ligands, plays a central role in the adaptive metabolic responses of skeletal muscle to the nutritional status, e.g., fasting or high-fat feeding and to enhanced physical exercise (FIGURE 3).

In addition to direct actions in skeletal muscle, PPAR β can affect muscle lipid utilization by modifying gene expression in other organs. The work by Liu et al. (345) illustrates such kind of PPAR β -dependent interorgan metabolic regulations. It was previously shown that PPAR β activation leads to upregulation of several genes involved in lipogenesis in liver (346) and that PPAR β expression was in a diurnal rhythmic cycle with a maximum during the dark phase (665). The utilization of a mouse model with liver-specific PPAR β gene disruption confirmed these observations but also revealed that these mice display a defective lipid utilization in skeletal muscle related to decreased expression of proteins implicated in fatty acid uptake and handling, such as FAT/CD36 and FABP3, only at night, i.e., when hepatic PPAR β expression is maximal. The authors provided some experimental data suggesting that PPAR β activates during the dark phase the hepatic production and secretion of 1-stearoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (18:0/18:1-GPC) which acts as a specific activator of PPAR α in skeletal muscle leading to upregulation of FAT/CD36 and FABP3 and subsequently increased fatty acid uptake and utilization in this tissue. Very interestingly, it was also shown that treatment with 18:0/18:1-GPC improves metabolic parameters in *db/db* mice, while high-fat feeding reduced diurnal production of 18:0/18:1-GPC (345). Although many issues still remain to be clarified to fully validate such a model, this integrated regulatory pathway involving two different tissues and two different PPAR isoforms could have important implications for understanding

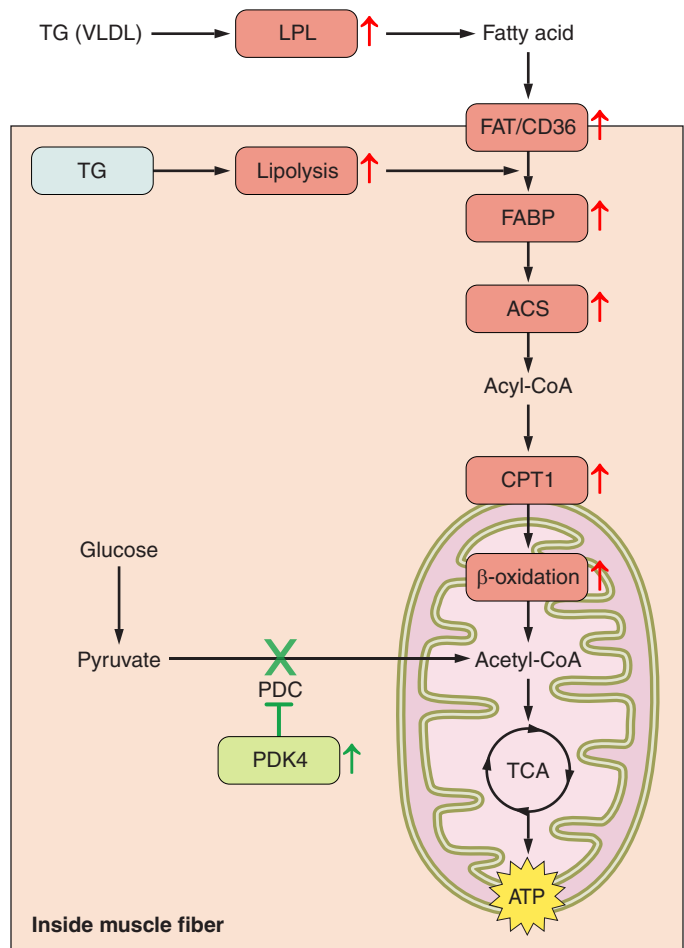


FIGURE 3. Regulatory functions of PPAR β activation in energetic metabolism in skeletal muscle. PPAR β activation enhances fatty acid catabolism by upregulation of the expression of several proteins involved in fatty acid availability, handling, activation, entry into mitochondria, and β -oxidation (red symbols). PPAR β activation also reduces carbohydrate oxidation by induction of PDK4 expression, which limits this metabolic pathway by decreasing PDC activity (green symbols). The metabolic impact of these regulations is an enhancement of fatty acid utilization for the oxidative metabolism of skeletal muscle.

the diurnal physiological regulation of lipid metabolism in the body and for optimizing treatment of metabolic diseases by PPAR β and PPAR α activators.

B. Regulatory Functions of PPAR β During Adaptive Responses of Skeletal Muscle to Endurance Exercise

1. Regulatory roles of PPAR β on fiber type transition and endurance performances

Studies based on the utilization of transgenic animal models for muscle-specific overexpression or invalidation of PPAR β gene have confirmed the role of the nuclear receptor on the regulation of muscle metabolism, but also revealed that PPAR β is a central player in the regulation of the train-

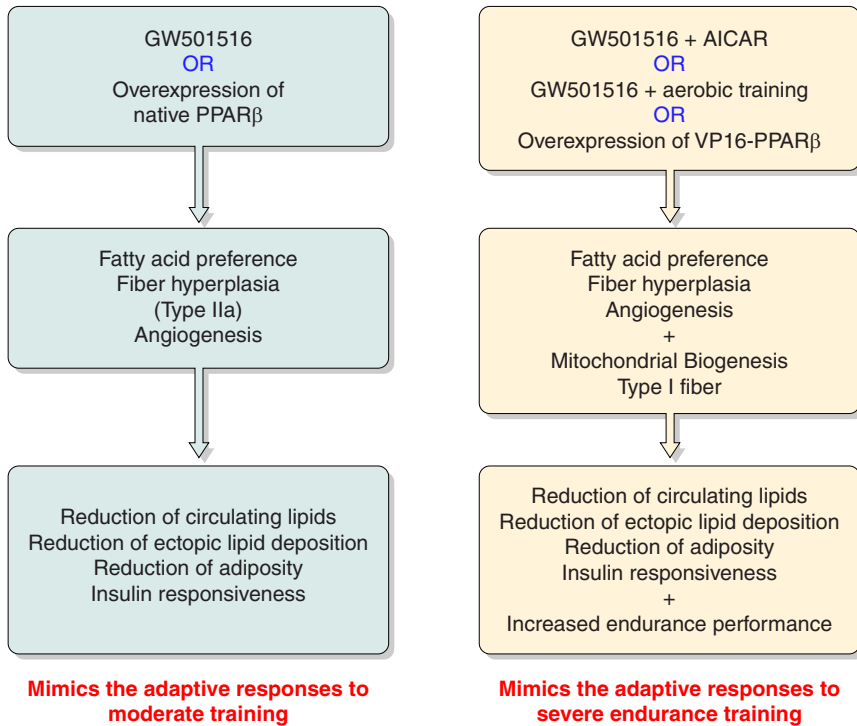


FIGURE 4. Interaction between PPAR β , AMPK, and exercise-induced signaling pathways in muscle remodeling and modulation of endurance performance. In sedentary mice, activation of the PPAR β pathway promotes a muscle remodeling reminiscent of that taking place after several weeks of moderate training. In exercised mice or mice treated with an AMPK activator, PPAR β activation promotes a stronger muscle remodeling and acquisition of a “long distance running” phenotype.

ing-promoted muscle remodeling and of muscle performance during endurance exercise.

The first mouse model for muscle-specific overexpression of PPAR β (353) was obtained by the Cre/Lox-promoted transcriptional Stop excision strategy previously described by Lakso et al. (313). Briefly, mice harboring a transgene consisting of the ubiquitously active CAG promoter followed by a transcriptional Stop cassette flanked by two LoxP sites and the mouse PPAR β coding sequence were crossed with mice harboring the bacteriophage P1 Cre recombinase under the control of human skeletal actin (HSA) promoter that exhibits stringent muscle-restricted expression. As expected, due to the presence of the transcriptional Stop cassette, no expression of transgenic PPAR β was detected in animals harboring only the CAG-Stop-PPAR β transgene, while PPAR β overexpression was found in skeletal muscles from double transgenic animals (i.e., harboring both Cre and PPAR β transgenes) and expressing in their muscles high amounts of Cre recombinase. Indeed, the abundances of PPAR β mRNA and protein are much higher (~20- and 6-fold, respectively) in oxidative, glycolytic, or mixed skeletal muscles from double transgenic animals than in muscles from control animals (wild-type and harboring either the HSA-Cre or CAG-Stop-PPAR β transgene), whereas no Cre expression and thereby no PPAR β overexpression were detected in adipose tissue, liver, or heart from double transgenic mice (353). Biochemical analyses of these transgenic mice revealed that overexpression of the native PPAR β results in increased oxidative capacities of skeletal muscle due to a mild enhancement of oxidative enzyme activities, such as CS and HAD (47 and 58%, respectively) with no detect-

able change in glycolytic enzyme activities and a twofold elevation in steady-state levels of mRNA encoding proteins implicated in fatty acid catabolism, such as FABP and UCP2. However, the levels of FAT/CD36 and PGC1 α mRNA were not affected in PPAR β -overexpressing animals compared with their control littermates. Histological analyses showed that PPAR β overexpression promotes a remodeling of the fast-twitch muscles characterized by an impressive increased number of SDH-positive fibers and parallel decrease in SDH-negative fibers and a net augmentation of total fiber number, mainly in tibialis anterior muscle. However, PPAR β overexpression did not promote appearance of actual type I fibers in these muscles. This remodeling of skeletal muscle was very reminiscent of that promoted by voluntary running in fast-twitch mouse muscles (11) and much milder than those promoted by severe endurance training (119) or overexpression of calcineurin (410) or PGC1 (338) characterized by appearance of type I fibers (FIGURE 4). Another phenotype induced by muscle-specific PPAR β overexpression is the important reduction of adipose mass primarily due to a decrease of adipocyte volume. As the transgene was not observed in adipose tissue and as food intake is not changed in transgenic animals, this observation demonstrated that the metabolic (increased fatty acid flux toward muscles) and/or the signaling (changes in myokine secretion) cross-talk between skeletal muscle and adipocytes are profoundly modified.

Wang et al. (631) developed a transgenic mouse model harboring a transgene consisting of the VP16 transactivation domain fused with the PPAR β coding sequence placed under the control of the muscle-specific HSA promoter. It was

previously shown by the same laboratory that the VP16-PPAR β protein displays a strong ligand-independent transcriptional activity (630). Muscle-specific overexpression of the VP16-PPAR β protein promoted a stronger remodeling of the fast skeletal muscles compared with what was previously observed by overexpression of native PPAR β (353), with a twofold elevation in type I fibers, evidenced by histological analysis and overexpression of the slow troponin isoform, and a mitochondrial biogenesis characterized by increased mitochondrial DNA content (2-fold) and enhanced expression of mitochondrial markers, such as those of the electron transfer cytochrome *c* and cytochrome *c* oxidase II and IV (1.5- to 2-fold increase). However, this mitochondrial biogenesis appeared to be not related to PGC1 α overexpression as PGC1 α mRNA amounts remained unchanged in muscles from VP16-PPAR β transgenic mice. As previously described for pharmacological PPAR β activation in wild-type mice (581), muscle-specific overexpression of the activated VP16-PPAR β form results in protection against diet-induced obesity with reduction of weight gain by 50% after 7 wk of high-fat diet in transgenic animals compared with their control littermates. It must also be noted that overexpression of the VP16-PPAR β protein promoted by somatic gene transfer in adult rat EDL muscle leads after 2 wk to an impressive shift from type IIb toward oxidative type I/IIa and type IIa fiber (352), demonstrating that, to exert its action on muscle remodeling, VP16-PPAR β overexpression is not required during early steps of muscle differentiation but is also able to promote a fiber transition toward oxidative metabolism in preexisting fibers.

The effects of overexpression of the activated VP16-PPAR β are clearly stronger than those observed after overexpression of the native PPAR β (353) and mirrors the effects of severe endurance training with fiber type transition toward type I fibers and active mitochondrial biogenesis (FIGURE 4). For the authors, these differential effects of overexpression of the native form and the activated form of PPAR β demonstrated the importance of endogenous activators of the signaling pathway on the muscle remodeling and suggested that severe endurance training more strongly affects the concentration and/or the nature of such endogenous activators than mild endurance training. However, it cannot be excluded that the phenotypes promoted in the muscles of the VP16-PPAR β mice are not only related to PPAR β overexpression but also related to the expression of the VP16 transactivation domain. Indeed, protein-protein cross-linking experiments have demonstrated that this VP16 transactivation domain interacts in vivo with several proteins implicated in transcriptional regulation, such as TATA-binding protein, TFIIB, and the SAGA histone acetylase complex (202) and also interferes with the muscle determination factor myogenin (519).

Wang et al. (631) also reported that, while VP16-PPAR β muscle-restricted overexpression does not affect daily physical activity, it results in enhancement of physical performance in animals submitted to physical challenges, such as treadmill running. In these conditions, transgenic mice are able to run more (67% in running time and 92% in running distance) than controls. Later on, such a “long-distance running” phenotype associated with high mitochondrial density and high number in type I and type IIa fibers in skeletal muscles was described in other mouse transgenic models for muscle-restricted overexpression of either phosphoenolpyruvate carboxykinase (201), PGC1 α (83), calcineurin A (265), or estrogen receptor-related receptor γ (ERR γ) (408) and for muscle-specific knockout of calsarcin-2 (165).

Studies based on transgenic animals with PPAR β gene disruption have also demonstrated the important role of the nuclear receptor in skeletal muscle metabolism, fiber composition, and functions. For instance, Schuler et al. (516) showed that muscle-selective PPAR β ablation in mice results in a strong decrease in muscle oxidative capacities due to global reduction in expression levels of mitochondrial enzymes of the TCA cycle, such as CS and NADH-tetrazolium reductase, and of several components of the respiratory chain. Although gastrocnemius mitochondria density was not affected by PPAR β ablation, mRNA levels of mitochondrial transcription factor A and PGC1 α , which are master regulators of mitochondrial genes, were reduced. A general decrease in the expression levels of proteins implicated in fatty acid uptake, handling, activation, and beta oxidation was also observed as well as a slow to fast fiber transition characterized by a reduced expression of markers of type I fibers, such as MHCI and slow-troponin and a parallel increase in type IIb markers, MHCIIb and fast-troponin. Muscle-specific PPAR β knockout animals display reduced endurance performance during treadmill running tests, but do not show changes in their spontaneous physical activity. These transgenic mice display adipose tissue hypertrophy with age and gain more weight than control littermates in response to high-fat diet. Metabolic tests showed that muscle-ablated PPAR β mice develop an age-dependent insulin resistance and glucose intolerance. This impact of muscle-restricted PPAR β ablation on metabolic parameter was recently confirmed as PPAR β gene disruption induced in muscle progenitor cells also results in obesity and insulin resistance at the adult age (20).

Collectively, the data coming from the utilization of transgenic animal models for gain-of-function or loss-of-function have established an important regulatory function of PPAR β in the control of transcriptional regulation of genes involved in oxidative metabolism and lipid catabolism. Muscle-restricted PPAR β gene disruption induces a phenotype that mimics the effects of long-term and severe physical inactivity both on metabolic and functional parameters in

skeletal muscle and in the whole body with augmented adiposity and impairment of insulin response, while PPAR β overexpression imitates the effects of exercise training and its beneficial action on metabolic parameters.

Narkar et al. (407) showed that the treatment of mice with a PPAR β agonist (GW501516) does not promote a shift toward type I fibers and mitochondrial biogenesis in skeletal muscles and does not augment running performance, while when combined with 4 wk of endurance training, pharmacological activation of PPAR β results in augmentation of all of these parameters. Indeed, combination of training and PPAR β pharmacological activation copies the phenotypes induced by muscle-restricted overexpression of the activated VP16-PPAR β as confirmed by metabolic tests, physical performance measurements, and transcriptomic analyses. These authors also reported that pharmacological activation of AMPK by treatment with the cell-permeable AMP analog AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) can substitute for endurance training, as co-treatment of sedentary wild-type mice with GW501516 and AICAR for 6 days reproduces the effects of combined training/GW501516 or VP16-PPAR β overexpression. Treatment of sedentary mice with AICAR alone for 4 wk increases the expression of genes related to lipid metabolism and increases moderately endurance performance. These effects of AICAR are dependent on PPAR β , as they are totally lost when the PPAR β gene is disrupted. Collectively, these data strongly suggest that a strong activation of AMPK induced by AICAR treatment (407) acts in a synergistic manner with pharmacological PPAR β activation to promote a genetic muscle reprogramming mimicking the adaptive responses of skeletal muscle to severe endurance training, with mitochondrial biogenesis, transition toward type I fibers, and increased endurance performances (**FIGURE 4**). The molecular mechanisms leading to a synergistic action of AMPK and PPAR β are not yet fully characterized, but multiple cross-talks between the two signaling pathways have been experimentally demonstrated. For instance, AMPK physically interacts with PPAR β in nuclei of muscle cells and, despite no evidence of change in PPAR β phosphorylation, such an interaction stimulates both basal and ligand-dependent PPAR β transcriptional activity (407). Moreover, AMPK can stimulate the activity of PPAR β by acting on its transcriptional coactivator PGC1 α . Indeed, AMPK activation leads to increased expression of PGC1 α mRNA and protein in rat muscle (568, 585) and enhances PGC1 α cotranscriptional activity by phosphorylation (258). Reciprocally, PPAR β activation can promote changes in AMPK signaling pathway. Treatment of both skeletal muscle cells (258, 306) and sedentary mice (328) with PPAR β agonist induces a transitory activation of the AMPK pathway, although to a lesser extent compared with AICAR treatment. Furthermore, pharmacological PPAR β activation results in a very rapid remodeling of skeletal

muscle AMPK, by affecting the expression level of AMPK γ subunit isoforms.

AMPK is a heterotrimeric kinase comprising a catalytic subunit and two regulatory subunits β and γ . Various isoforms of each subunits, namely, $\alpha 1$ and $\alpha 2$, $\beta 1$ and $\beta 2$, $\gamma 1$, $\gamma 2$, and $\gamma 3$ have been described in mammals, but of the 12 potential trimers, only 3 active AMPK heterotrimers, $\alpha 1/\beta 2/\gamma 1$, have been found in human muscle (169, 647). AMPK acts as a sensor of cellular energy homeostasis and has been implicated in the switch between anabolic to catabolic metabolism in several tissues. The γ AMPK-subunit contains sites for reversible binding of ATP or AMP and binding of AMP promotes moderate activation of the kinase (87, 567). Stronger activation of AMPK is obtained by AMP and ADP-controlled phosphorylation at threonine residue within the activation loop in the α subunit. It has been established that binding of AMP (567) and more recently of ADP (417, 650) to specific domains called Bateman modules of the γ subunit both increases the phosphorylation of the α subunit by several AMPK kinases and protects against dephosphorylation by phosphatases.

It has been reported that treatment of mice with GW0742 leads to downregulation of the $\gamma 3$ subunit and upregulation of $\gamma 1$ subunit leading to a notable and sustained shift between $\gamma 3$ -containing AMPK toward $\gamma 1$ -containing AMPK trimer in skeletal muscle (328). In that respect, PPAR β activation mimics the effects of training (169, 328, 647) and fasting (328) on AMPK subunit composition in skeletal muscle. To date, the physiological impact of such remodeling of AMPK trimers on AMPK activation remains largely unknown. However, this remodeling could result in a differential sensibility to AMP as it has been reported that the $\gamma 1$ -containing trimer displays greater AMP-dependence than the $\gamma 3$ -containing trimer (94).

PPAR β and AMPK pathways also converge to regulate glucose utilization during high-intensity exercise. Recently, Gan et al. (177) confirmed that the muscle-specific overexpression of PPAR β activates the expression of several genes involved in fatty acid metabolism but also increases the expression of genes implicated in glucose metabolism, including those for lactate dehydrogenase B (LDHB or LDH2), which converts lactate to pyruvate providing substrate for the mitochondrial TCA cycle, for the glycolytic enzymes fructose-biphosphatase aldolase A and B, and for the glucose transporter Glut4. The metabolic consequence of these upregulations is an enhanced capacity for glucose oxidation in muscles from PPAR β overexpressing animals during high-intensity exercise, and the functional consequence is an improvement of the sprint running performance by coupling glycolysis to glucose oxidation and enhancing the energetic yield of glucose catabolism. Molecular analyses revealed that transcriptional activation of LDHB by PPAR β is ligand independent and involves an

interaction between PPAR β , AMPK, and the transcription factor myocyte-specific enhancer factor 2A (MEF2A), resulting in enhanced binding capacity of MEF2A to its responsive element within LDHB promoter. Further studies are clearly required to have a complete molecular understanding of these changes in skeletal muscle metabolism and to demonstrate the physiological importance of this regulatory mechanism that is to date restricted to transgenic over-expression of PPAR β , which is much stronger than that taking place during adaptation to physical training. Moreover, pharmacological activation of PPAR β does not promote similar effects. In fact, it has been shown that treatment of rats with GW0742 for 6 days notably reduces tension development during sustained contraction at exercise intensities requiring glucose oxidation that is an expected consequence of the PPAR β -driven activation of PDK4 expression on limitation of carbohydrate oxidative metabolism (106).

To date, the effects of PPAR β pharmacological activation in human muscle have been poorly described. However, some data strongly suggested that, as described for rodents, the nuclear receptor is also involved in metabolic regulation in human muscle. For instance, metabolic explorations revealed that treatment of moderately obese men with GW501516 for 2 wk enhances skeletal muscle fatty acid catabolism and increases the expression of CPT1 mRNA in muscle biopsies (477). Moreover, genetic association studies also suggested an implication of PPAR β in the metabolic and functional adaptive responses of human skeletal muscle to physical training. Several single-nucleotide polymorphisms (SNPs) in various introns and exons of PPAR β gene (*PPARB*) have been identified, but the functional impacts of such SNPs remain largely unknown. However, transfection studies showed that the +294T/C polymorphism (SNP rs2016520) located in the exon 4 of *PPARB* results in higher transcriptional activity for the minor C allele (541), suggesting, despite the lack of direct evidence, an over-expression of PPAR β mRNA in tissues of carriers of this SNP.

Hautala et al. (216) reported that, within a healthy and sedentary subject cohort, carriers of the minor C allele for the SNP rs2016520 display a reduction of training-induced increases in maximal oxygen consumption and maximal power output compared with carriers of the major allele (216). Other genetic association studies were conducted within the Tuebingen Lifestyle Intervention program cohort. This study aimed to investigate the effects of 9 mo of dietary changes and moderate increase of aerobic physical activity on metabolic and morphological phenotypes in subjects with an increased risk for type 2 diabetes. A first study showed that carriers of the minor SNP allele in *PPARB* exon 3 (rs1053049) exhibit a reduced enhancement of anaerobic threshold and insulin sensitivity induced by the lifestyle intervention when compared with homozygous carriers of the major allele. Very interestingly, in vitro anal-

yses revealed that young and healthy carriers of the minor SNP rs1053049 allele display a 40% reduction of complex II respiratory chain activity in skeletal muscle mitochondria when compared with carriers of the major allele (557). A second study showed that carriers of the minor allele for SNPs in intron 2 (rs6902123), intron 3 (rs2267668), or exon 9 (rs1053049) of the PPAR β gene exhibited reduced responses to lifestyle intervention, i.e., reduction of fat mass and hepatic lipids and increment in muscle mass (588). As the impacts of these SNPs on the expression level and functionality of the PPAR β protein remain totally unexplored, it is not possible to propose any molecular explanation for the associated metabolic phenotypes. However, these various observations strongly suggest that such SNPs in the PPAR β gene can be used as genetic markers to predict the efficacy of physical training in the prevention of type 2 diabetic disorders. There are also some interesting observations suggesting an association between PPAR β rs2016520 polymorphism and endurance performance. A first study in a Russian population revealed a higher frequency of the minor C allele for SNP rs2016520 in endurance athletes than in control individuals (8). A second study conducted in an Israeli population did not find statistical differences in the frequency distribution of SNP rs2016520 alleles between groups of endurance athletes, sprinters, and healthy control subjects or between the subgroups of elite level and national level of endurance athletes. However, the genotype combining the minor C allele of *PPARB* rs2016520 polymorphism and the Gly482 allele of SNP rs8192678 in the *PGC1 α* gene was more frequently found in the elite-level endurance athlete group (20%) than in the national-level endurance athlete group (2%) and in the control group (3%), suggesting that the genotype *PPARB* CC + *PPARGC1A* Gly/Gly is determining elite endurance performance capacity (146). Since it was reported that the *PPARGC1A* Gly/Gly genotype is associated with higher levels of *PGC1* mRNA (339), and since it is supposed that the CC *PPARB* rs2016520 genotype results in higher transcriptional activity of the PPAR β gene, it could be proposed that over-activity of these pathways in human muscle is the molecular explanation for such a predisposition to endurance performance. These observations are in good agreement with the data that showed a convergence of these two signaling pathways in the stimulation of muscle oxidative metabolism and endurance performance in rodents.

2. PPAR β and muscle angiogenic responses

Aerobic training and voluntary exercise promote an angiogenic response leading to a marked increase in muscle capillarity (140, 632). This physiological angiogenic response to sustained changes in the physical activity behaviors is controlled by several signaling pathways (199, 625), and it is now clear that PPAR β is involved in this regulatory network. Indeed, activation of the PPAR β pathway phenocopies the effects of physical training by inducing an enhancement of capillary density of mouse skeletal muscle. We re-

ported that treatment of adult mice with a specific PPAR β agonist promotes a modest but significant (1.5-fold) augmentation of capillary number in tibialis anterior muscle. This PPAR β agonist-induced angiogenesis is a very fast process taking place within 2 days and is preceded by robust and transient increases in expression levels of VEGF-A (~7-fold increase at 8 h) and other angiogenic markers (178). This angiogenic response is probably due to the capacity of PPAR β agonists to stimulate both proliferation and differentiation of endothelial cells as discussed in section IIE. However, activation of PPAR β in muscle cells appeared to be also involved in this angiogenic response as illustrated by the finding that myofiber-restricted PPAR β overexpression also results in enhanced muscle capillarity even at a lesser extent compared with PPAR β agonist-treated mice (178). This suggests that activation of the PPAR β pathway in myofibers generates angiogenic signals able to drive a capillary network remodeling. Moreover, it was demonstrated that the PPAR β -induced angiogenesis is restricted to specific tissues since it is taking place in skeletal muscle and heart, but not in other organs, such as retina or kidney (623).

C. PPAR β Activation and Muscle Pathologies

1. Myogenic functions of PPAR β

Several lines of evidence support the notion that the PPAR β signaling pathway is implicated in the regulation of myogenesis and that its activation could have beneficial action on muscular pathologies.

We have reported that both muscle-restricted overexpression of PPAR β and treatment of adult mice with specific PPAR β agonist promote the appearance of new myofibers in hindlimb muscles. This hyperplasia is mainly observed in tibialis anterior muscle with a 37% increase in total fiber number (178, 353). The appearance of these new fibers is a fast phenomenon since it is fully established in adult animals treated for 48 h with the synthetic PPAR β agonist. Hyperplasia is preceded by a sequential and transitory up-regulation of two regulatory transcription factors of myogenesis, myogenic factor 5 (Myf5; 70% increase after 5 h and back to control value after 24 h) and myogenic determination factor 1 (MyoD1; 3-fold increase from 8 to 48 h of stimulation and back to control values at 96 h). In that respect, it must be noted that activation of the PPAR β pathway copies the effects of several weeks of a voluntary exercise training program that also promotes appearance of new fibers in mouse hindlimb muscles, such as tibialis anterior and soleus (11). Another muscle phenotype induced by PPAR β activation is an augmentation of myonuclear number in fibers. Myonuclear density is a tightly controlled parameter that is affected by physiological situations such as aerobic training with an enhancement of myonuclear number per fiber (487, 545) and aging with decreased myo-

nuclear density (70, 76). Specifically, it was shown that treatment of adult mice with a PPAR β agonist promotes within 2 days an increase in myonuclear density. Interestingly enough, in 19-mo-old mice displaying both reduced myonuclear density and PPAR β expression, a 4-day treatment with a synthetic PPAR β agonist almost totally restored a myonuclear density identical to that found in young adult animals, indicating that PPAR β activation compensates the age-related loss of myonuclei (184).

Fiber hyperplasia and myonuclear accretion require proliferation and activation of satellite cells that fuse to form new fibers or incorporate into a preexisting fiber to increase myonuclear number. Such a process has been observed during electrostimulation, training, and voluntary running (334, 462, 547). Adult muscle contains quiescent satellite cells located between the basal lamina and the sarcolemma of the muscle fiber. In certain circumstances, these satellite cells are able to reinitiate proliferation and myogenic commitment to provide myoblasts for myofiber growth, repair, and maintenance. The processes controlling activation, proliferation, and differentiation of satellite cells are complex and implicate a highly orchestrated expression and repression of transcription factors (77, 547, 658). Briefly, stimulation by growth factors, such as fibroblast growth factor and hepatocyte growth factor, activates the proliferation of quiescent satellite cells, often characterized as expressing the paired box transcription factor 7 (Pax7), that start to express MyoD1 and Myf5. Terminal differentiation requiring cell-cycle withdrawal is characterized by expression of myogenin and concomitant decline of Pax7 and Myf5 expression and leads to myoblast fusion into multinucleated myotubes or with preexisting fibers. The observed increase in expression of Myf5 and MyoD1 preceding the fiber hyperplasia in PPAR β agonist-treated adult mice (178) suggested a possible regulatory role of PPAR β in the control of satellite cell proliferation and/or activation.

Indeed, two recent publications report strong evidence for such a direct implication of the nuclear receptor in these regulatory processes. Angione et al. studied the physiological impact of satellite cell-restricted PPAR β ablation in mice by using a Myf5-Cre/Lox strategy (20). Animals with PPAR β ablation in Myf5 expressing cells do not display changes in muscle composition up to 3 wk of age but show a 40% reduction of satellite cells and myonuclear density in both glycolytic EDL and oxidative soleus muscles at the adult age. Moreover, animals with satellite cell-PPAR β gene disruption display a delayed muscle regenerative response after muscle injury by cardiotoxin injection. In vitro experiments with myoblasts from transgenic and control mice showed that invalidation of the PPAR β pathway seriously reduces satellite cell proliferative capacities, while conversely pharmacological PPAR β activation of myoblasts from control animals stimulates their proliferation. Furthermore, Bonala et al. (57) reported that pharmacolog-

ical activation of PPAR β enhances the proliferation and differentiation of C2C12 myoblasts, while primary myoblasts from PPAR β -null mice display reduced proliferation and myogenesis capacities (57).

PPAR β could exert positive actions on satellite cell activation by several complementary pathways. The Ca²⁺/calcineurin/NFAT signaling pathway is implicated in the PPAR β -driven hyperplasia and myonuclear accretion in adult animals. Ca²⁺ signaling plays a central role in the coupling between neuronal excitation and fiber contraction and also in adaptive responses of skeletal muscle to changes in muscle use and disuse. Ca²⁺ signaling involves a large number of proteins regulating sarcoplasmic Ca²⁺ release and reuptake, Ca²⁺ handling, and Ca²⁺-sensitive phosphatases and kinases that couple prolonged changes in Ca²⁺ cytosolic concentrations to transcriptional modulations. Among them, the Ca²⁺-dependent protein phosphatase calcineurin promotes dephosphorylation and nuclear translocation of the nuclear factors of activated T cells (NFATs) that, in turn and in collaboration with other transcription factors, stimulate expression of genes implicated in skeletal muscle metabolism and fiber typing (42, 384, 385). The calcineurin/NFAT signaling pathway is also important for satellite cell activation and myogenesis (166, 242, 520). We found that inhibition of the calcineurin phosphatase activity by cyclosporine A almost totally blunts the PPAR β -induced expression of MyoD1 mRNA and increases in both fiber number and myonuclear density in adult mouse tibialis anterior muscle (178, 184). Importantly, PPAR β stimulates calcineurin activity as demonstrated by the rapid dephosphorylation and nuclearization of NFATC1 and NFATC2 in skeletal muscles of PPAR β agonist-treated adult mice (184). As PPAR β activation does not change the expression level of calcineurin, it can be hypothesized that another upstream step of the Ca²⁺ signaling cascade is affected by the nuclear receptor. The demonstration of a PPAR β -driven stimulation of the CAMKK, another protein sensitive to cytosolic Ca²⁺ concentrations is in favor of this hypothesis (177).

Another alternative or complementary mechanism of action of PPAR β on proliferation and differentiation of satellite cells through modulation of the myostatin pathway has been recently proposed. Myostatin is a secreted factor of the TGF- β superfamily that acts as a potent inhibitor of skeletal muscle growth, partly through binding to activin receptors and activation of the Smad protein complex, which in turn represses the transcription of genes involved in myogenesis, such as MyoD1 (12, 325). Myostatin represses myoblast proliferation (582, 589) and differentiation (316) and is a potent negative regulator of satellite cell in vivo (370). These combined negative actions exerted by the myostatin pathway explain the impressive hypertrophic and hyperplastic muscle development observed in transgenic myostatin-null mice (375) and in cattle and dogs that carry loss-of-

function mutations in the myostatin gene (376). Importantly, myostatin also plays a regulatory role in adult skeletal muscle physiology. For instance, short-term inhibition of myostatin increases satellite cell activation in aged mice (539). Furthermore, myostatin is also potentially involved in adaptive responses to physical exercise, as both endurance (303, 365) and resistance (467, 486) trainings reduce myostatin mRNA expression in skeletal muscles. The activity of circulating myostatin is controlled by direct interaction with proteins that prevent association with cellular receptors. The growth and differentiation factor-associated serum protein-1 (GASP-1) was identified as inhibiting myostatin cellular action in muscle cell (228). Expression levels of GASP-1 are increased during physical training leading to muscle growth (21, 500). Bonala et al. (57) reported that treatment of C2C12 and primary human myoblasts with a specific PPAR β agonist does not affect expression of myostatin but induces both mRNA and protein levels of GASP-1 through interaction with a PPRE consensus sequence within the proximal promoter region of the corresponding gene. Moreover, reduced expression of GASP-1 was observed in skeletal muscles from PPAR β -null animals compared with their control littermates. The functional impact of this GASP-1 overexpression in response to PPAR β activation on myoblast proliferation capacity was demonstrated by the fact that immunological blockade of GASP-1 totally prevents the PPAR β -induced stimulation of human primary myoblasts proliferation. From these data, these authors proposed a model in which the positive effects of PPAR β activation on satellite cell proliferation involves an inhibition of the myostatin signaling pathway by an increased expression of the regulatory protein GASP-1.

These experimental data clearly demonstrate a regulatory role for PPAR β in satellite cell physiology by activation of multiple myogenic signaling pathways and suggest that pharmacological activation of PPAR β may have therapeutic potential for the treatment of muscle wasting, such as age-related sarcopenia, and muscle repair after injury.

2. PPAR β activation in the treatment of genetic myopathies

In addition, PPAR β activation could also have beneficial effects in correction of metabolic and biochemical disorders that occur in certain genetic myopathies, as demonstrated for myopathies caused by defects in FAO or mitochondrial respiratory chain and by dystrophin mutations.

Inherited defects in FAO are characterized by abolition (loss-of-function mutations) or partial reduction (mutations resulting in enzyme with residual activity) in the activity of enzymes involved in fatty acid transfer into mitochondria, including CPT 1 and 2, and in fatty acid beta oxidation, such as acyl-CoA and 3-hydroxyacyl-CoA dehydrogenases. The symptoms of this class of diseases depend on the severity and the nature of the genetic defect and are

intensified in situations requiring oxidative fatty acid catabolism, such as fasting, prolonged physical exercise, or stress. The clinical presentations of these diseases are cardiomyopathy, liver dysfunctions, rhabdomyolysis, myalgia, and exercise intolerance (301, 554).

Given the established role of PPARs in the control of genes involved in fatty acid metabolism, the effects of bezafibrate, a pan-PPAR agonist clinically used as lipid-lowering treatment (584, 642), were first investigated on FAO in fibroblasts isolated from patients with partial or severe deficiencies of either CPT2 (130, 343) or very long chain acyl-CoA dehydrogenase (VLCAD) (129, 187). These experiments revealed that treatment with high dose of bezafibrate almost totally normalize FAO in fibroblast from patients with partial deficiency in CPT2 and VLCAD, but not in fibroblast from severely affected patients. These corrective effects are related to increases in mRNA and protein levels of FAO-related genes, including CPT2 and VLCAD. In myoblasts, very low doses of PPAR β agonist phenocopies the effect of bezafibrate, while PPAR α agonist is not efficient, demonstrating a crucial role of PPAR β isoform in correction of FAO deficiency in these specific inborn metabolic disorders (129, 438). Very encouraging results were obtained in a pilot trial designed to test the efficacy of bezafibrate on correction of metabolic and functional disorders in six adult patients with a mild form of CPT2 deficiency. Specifically, bezafibrate administration for 6 mo promoted a normalization of the FAO capacity in skeletal muscle coupled with important enhancement of CPT2 mRNA and protein expression levels. The treatment also notably reduced number and gravity of rhabdomyolysis episodes and improved physical activity and quality of life for all the included patients (343).

Pharmacological activation of the PPAR β pathway appeared to also have beneficial action in mitochondrial disorders. Mitochondrial disorders are relatively common inherited neuromuscular diseases due to defects in oxidative phosphorylation related to deficient activity of enzymes or assembly components of the mitochondrial respiratory chain (98, 504). Inborn mitochondrial dysfunctions are caused by mutations or epigenetic factors affecting both nuclear genome and mitochondrial genome mutations (97, 359). The clinical presentations of mitochondrial disorders are very diverse with multisystemic or tissue-restricted forms, any age of onset, and ranging from severe lethal to mild forms (447, 502).

Bastin et al. (659) explored the effects of the pan-PPAR agonist bezafibrate or of specific agonists for the PPAR isoforms on the activity and mRNA expression levels of various components of the mitochondrial respiratory chain in fibroblasts from both control individuals and patients deficient in complex I, III, and IV of the respiratory chain (659). These authors reported that exposure to bezafibrate

or to a PPAR β specific agonist stimulates the expression of several components of the mitochondrial respiratory chain and increases respiration rates in fibroblasts from control individuals. Importantly, these treatments result in partial or total correction of respiratory chain functions in fibroblasts from 9 of 14 patient cell lines tested, while both PPAR α and PPAR γ agonists are ineffective. To date, there is no evidence for the presence of functional PPAR-responsive elements in the promoter sequences of respiratory component genes, an indirect implication of PPAR β in transcriptional regulation of such genes should be envisioned. Some observations strongly suggest an implication of PGC1 α in this regulatory pathway. By its actions on transcription factors and networks that govern the expression of mitochondrial proteins encoded by both nuclear and mitochondrial genomes, PGC1 α is considered as the master regulator of mitochondrial biogenesis and oxidative phosphorylation system (503, 635). It was found that bezafibrate treatment stimulates the expression of PGC1 α and of transcription factors playing a crucial role in the oxidative phosphorylation metabolic pathway, such as nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 α (NRF2 α), and transcription factor A (Tfam) in fibroblasts from control individuals and respiratory chain-deficient patients (40). Moreover, Wens et al. (636) showed that transgenic PGC1 α overexpression or bezafibrate treatment similarly result in a marked stimulation of the residual oxidative phosphorylation system and in prolonged life span in a mouse mitochondrial myopathy model caused by ablation of the COX10 gene encoding heme A:farnesyltransferase, an enzyme required for cytochrome *c* oxidase activity. However, two recent publications reported more mitigated data regarding the correcting effects of bezafibrate treatment in other mouse mitochondrial myopathy models provoked by constitutive ablation of Surf1 locus protein 1 (Surf-1), an important cytochrome oxidase assembly factor (77), and expression of a mutated dominant form of Twinkle-helicase, which is a protein involved in mammalian mitochondrial DNA maintenance and organization (658). In contrast to its effects in the COX10-KO animals, bezafibrate administration does not promote mitochondrial biogenesis and increase in mitochondrial respiration capacities in Surf1-KO mice (178) or mutated-Twinkle helicase-mice (20).

Collectively, these findings clearly indicate that activation of the PPAR β /PGC1 α pathway is a promising therapeutic intervention for certain forms of metabolic myopathies related to inherited FAO defects or mitochondrial respiration alterations by increasing directly or indirectly the expression of a large number of proteins involved in these metabolic pathways and consequently by stimulation of the residual capacity of mitochondrial oxidative metabolism. However, these beneficial actions are depending on the nature of the genetic defect and, not surprisingly, activation of PPAR β /PGC1 α is inefficient to correct metabolic disorders

caused by total abolition of an obligatory protein of the FAO and oxidative phosphorylation metabolic pathways.

Activation of the PPAR β signaling pathway has also been proposed for treatment of the Duchenne muscular dystrophy (DMD). DMD is a fatal recessive form of muscular dystrophy caused by mutations in the gene coding for dystrophin, a protein implicated in the linkage between the subsarcolemmal cytoskeleton and extracellular matrix via the dystroglycan complex. DMD is characterized by severe muscle wasting (42, 57) with a higher susceptibility of degeneration for oxidative than glycolytic fibers both in human (77) and in mdx mouse, a model of DMD (658). This fiber difference is probably due to many reasons, including greatest protection of oxidative fibers against oxidative and inflammatory stresses. In the DMD context, a very relevant difference between oxidative and glycolytic fibers is the expression level of utrophin A that is three to four times more abundant in type I and IIa fibers than in type IIx and IIb fibers in mouse skeletal muscle (20, 178). As utrophin A is considered as a dystrophin homolog in developing and regenerating muscles, it has been proposed that a high level of utrophin expression exerts a compensatory role for dystrophin deficiency in oxidative fibers and that strategies leading to high level of expression of utrophin A in skeletal muscle could compensate for dystrophin loss. Indeed, utrophin delivery using viral or transgene administration improves dystrophic phenotypes in mdx mice (42, 57), and upregulation of utrophin A gene expression by transgenic activation of the calcineurin/NFAT (385) or PGC1 α (384) signaling pathways improves muscle structure and function in mdx mice.

Miura et al. (388) demonstrated that PPAR β is implicated in the transcriptional regulation of the utrophin A gene by a direct transactivation mechanism through interaction with a PPRE consensus sequence in the utrophin A promoter and that treatment of mdx mice with a specific PPAR β agonist increases utrophin A expression and leads to improvement of structural and functional muscle parameters. These conclusions were confirmed by a more recent study showing that pharmacological activation of PPAR β reduces fiber degeneration and inflammation in skeletal muscles of mdx mice (166). Interestingly, AMPK activation, which stimulates the PPAR β pathway as previously discussed, exerts similar beneficial actions (242, 520).

Taken together, these data demonstrate that PPAR β pharmacological activation alleviates several structural and functional muscle disorders in the mdx mouse by increasing utrophin A expression and possibly by other mechanisms, such as reduction of metabolic and inflammatory stresses. Although these experimental observations must be confirmed in humans, they indicate that PPAR β synthetic agonists, such as bezafibrate that has been clinically used for many years without any safety

problems, could be proposed as a nonexpensive pharmacological therapy for DMD.

In summary, PPAR β is a central regulator of the use of lipids as an energetic substrate in skeletal muscle first by activating the expression of several proteins involved in rate-limiting steps of fatty acid catabolism and, second, by reducing the glucose oxidation through upregulation of PDK4 expression and PDC inhibition. These metabolic regulations are physiologically important to adapt the fuel utilization of skeletal muscle in particular situations such as fasting, characterized by high amounts of NEFAs and low glucose availability, or prolonged moderate physical activity, which requires a low rate of ATP synthesis sustained during a long period of time. PPAR β appears to be a central player in the metabolic and contractile adaptive responses of skeletal muscle to aerobic physical training. Activation of the pathway mimics the remodeling adaptation to moderate endurance training by an increase in type IIa metabolic and contractile phenotypes and promotion of angiogenesis, while abolition of PPAR β promotes a muscle remodeling resembling that induced by long-term inactivity, i.e., shift toward fiber IIb phenotype. Very interestingly, pharmacological activation of PPAR β also recapitulates the improving effects of regular aerobic exercise on metabolic dysfunctions in prediabetic subjects (178), including glucose intolerance, insulin resistance, and ectopic lipid accumulation. Such improvements of metabolic disorders upon PPAR β agonist administration have been observed in moderately obese humans and in various animal models of obesity, highlighting the usefulness of these molecules in the treatment of diabetic obese patients. Another impressive effect of PPAR β agonist treatment when coadministered with AICAR, an AMPK activator, or combined with endurance training is a muscle remodeling reminiscent to what was obtained after long-term and intense aerobic exercise with huge mitochondrial biogenesis, increased number of type I myofiber, and enhancement of endurance exercise performances in mice. Based on these observations, and since GW501516 is available from online retailers, often under the name of Endurobol, the compound has been added since 2009 to the prohibited list of substances by the World Anti-Doping Agency (www.wada-ama.org). Despite this interdiction, at least five cyclists have been provisionally suspended by sporting authorities for suspicion of use of GW501516 in 2013.

Finally, there is experimental evidence to support the idea that activation of the PPAR β pathway could be helpful in the treatment of several muscle disorders by its capacity to induce myonuclear accretion in ageing muscles, to boost the expression of genes implicated in some metabolic myopathies or to promote compensation for dystrophin mutation by utrophin A overexpression in DMD.

D. PPAR β in Heart Physiology and Metabolism

Cardiomyocytes express high amounts of both PPAR α and PPAR β , while PPAR γ is barely detectable in this cell type (184). During the past two decades, several studies have demonstrated that the two major cardiac PPAR isoforms play either redundant or different roles in the control of heart metabolism and in protection against inflammatory and metabolic stresses.

Under normal conditions, mitochondrial oxidative phosphorylation is the major metabolic pathway for ATP synthesis, with a minor (~5%) contribution of anaerobic glycolysis. FAO is the main source of acetyl-CoA for cardiac oxidative phosphorylation in basal conditions (~90%), while in physiological situations that require maximal cardiac power, oxidation of glycolytic metabolites, pyruvate and lactate, increase to account for up to 40% of ATP formation (177). These fuel preference patterns are perturbed in pathological states, such as ischemic and idiopathic dilated cardiomyopathy characterized by an increased dependence on glucose as substrate (325) or diabetic cardiomyopathy characterized by a greater reliance on fatty acids as energetic substrate (12). Evidence has emerged showing that PPAR α and PPAR β play important and not totally overlapping roles in adaptive transcriptional regulations of enzymes involved in heart fuel preference in response to physiological challenges and pathological states.

Early work established that PPAR α controls heart FAO by transcriptional regulation of several genes implicated in fatty acid uptake, activation, mitochondrial import, and mitochondrial and peroxisomal beta oxidation (589). PPAR α -null mouse hearts display a reduced FAO rate that is compensated by increased glycolysis and glucose oxidation for ATP production (316, 582). PPAR α deficiency does not affect cardiac functions under basal conditions (370), but results in age-associated myocardial damage, fibrosis, and impaired contractile function at high work load (375, 376). Conversely, cardiomyocyte-specific PPAR α overexpression leads to increased FAO and reduced glucose utilization for heart energetic metabolism, but surprisingly, promotes a phenotype that mimics that observed in the diabetic state characterized by cardiomyopathy with left ventricular hypertrophy and impaired cardiac functions (539). Several lines of evidence suggest that lipotoxicity is a major determinant in these altered cardiac phenotypes and that PPAR α overexpression promotes in heart an imbalance between fatty acid import and utilization leading to accumulation of deleterious lipid species (365).

Implication of the PPAR β pathway in regulation of cardiac FAO was initially demonstrated *in vitro* by the finding that treatment of cardiomyocytes with specific PPAR β agonists increases the expression of genes implicated in fatty acid catabolism and FAO rates and can restore, at least partially,

the altered metabolic phenotypes of PPAR α -deficient cardiomyocytes (467, 486). These observations were confirmed by the demonstration that cardiomyocyte-restricted deletion of PPAR β reduces cardiac expression of FAO-related genes and FAO rate and promotes cardiomyocyte lipid deposition, severe cardiomyopathy, and premature death (21). Thus both PPAR α and PPAR β are obligatory for appropriate cardiomyocyte FAO and for maintenance of normal cardiac functions in mouse, and, interestingly, the effects of PPAR β abrogation seem to be more detrimental to cardiac functions than that of PPAR α (228).

To further investigate the respective regulatory functions of the two PPAR isoforms in mouse heart, Burkart et al. compared the effects of cardiomyocyte-specific overexpression of either PPAR α or PPAR β on cardiac metabolism and functions (79a). These experiments revealed several differences in the phenotypes induced by the respective PPAR overexpression. First, in sharp contrast to PPAR α overexpression, PPAR β overexpression does not promote cardiomyocyte lipid accumulation and cardiomyopathy. This difference was explained by the finding that, while both models of PPAR overexpression display similar upregulation of genes of peroxisomal and mitochondrial FAO, overexpression of PPAR β does not promote increased expression of genes involved in fatty acid uptake, synthesis, and esterification as previously described for PPAR α overexpression (500). Furthermore, it must be noted that PPAR β , but not PPAR α , protects the heart against lipid overload by stimulation of the expression of ANGPTL4, which limits fatty acid delivery by inhibition of the LPL activity (57). Second, hearts from PPAR β -overexpressing animals, and also hearts from wild-type mice treated with a PPAR β agonist, display increased expression of genes involved in glucose metabolism, such as Glut4 and PFK and enhanced capacity of glucose uptake and oxidation, while hearts from PPAR α -overexpressing mice display the opposite phenotype. The molecular mechanism of the PPAR β -induced expression of glucose metabolism-related genes is not yet totally elucidated, but further analysis strongly suggests an indirect action through modification of transcriptional activity of Mef2A on the Glut4 gene (79a). This PPAR β -driven increase in glucose metabolism capacity has important potential therapeutic implications in pathological situations requiring an increased reliance on carbohydrate catabolism, such as ischemia (554). Indeed, Burkart et al. found that cardiac PPAR β overexpression exerts notable protective action against ischemia-reperfusion injury (79a), while cardiac PPAR α overexpression does not exert similar protective effects (301).

Transgenic models for inducible and cardiac-specific knockout or overexpression of PPAR β were used for the study of short-term alterations of the PPAR β signaling pathway in the adult mouse heart. These experimental approaches demonstrated that PPAR β plays a crucial role in

mitochondrial biogenesis in adult heart as short-term PPAR β deficiency results in decreased expression of transcriptional regulators of mitochondrial biogenesis, such as PGC1 α and PGC1 β , nuclear respirator factors 1 and 2 (NRF1 and NRF2), and reduction of mitochondrial DNA copy number, while short-term PPAR β overexpression leads to opposite phenotypes; increased mitochondrial biogenesis and enhanced cardiac performance (343, 584, 642). Moreover, PPAR β appears to be an essential determinant of the enzymatic antioxidant defense systems in the heart. It was initially shown that PPAR β activation inhibits the onset of oxidative stress-induced apoptosis by a direct transcriptional activation of catalase gene expression in H9c2 cells (438). Heart specific PPAR β loss- and gain-of-function experiments confirmed this observation and also demonstrated an essential role for PPAR β in the control of full expression of other key antioxidant enzymes, such as Cu/Zn superoxide dismutase (SOD1) and manganese superoxide dismutase (SOD2), and the prevention of oxidative damages (129, 343). Interestingly enough, generation of a mouse model for cardiac-specific PPAR β knockout in the PPAR α -null genetic background revealed that, while PPAR α plays a predominant role in the adaptive response of cardiac metabolic switch toward lipids during fasting, PPAR β is responsible for the control of mitochondrial biogenesis and protection against oxidative stress in heart independently of PPAR α (98, 504).

Activation of either PPAR α or PPAR β signaling pathways is also exerting cardiac protective actions by suppression of the NF- κ B proinflammatory and prohypertrophic pathway. NF- κ B plays a central role in the control of cardiomyocyte growth, and its activation mediates the effects of several hypertrophic agents, such as phenylephrine, endothelin-1, and angiotensin II (359). NF- κ B consists of a heterodimer of two subunits, p65 and p50, which binds with the inhibitor- κ B (I κ B) in the cytoplasm of nonstimulated cells. Exposition of cardiac cells to various inflammatory and hypertrophic stimuli promotes phosphorylation of I κ B resulting in its degradation and nuclear translocation of the p65/p50 heterodimer that transactivates the expression of several target genes (97).

It was initially demonstrated that PPAR α expression is reduced and its activity altered during heart hypertrophy (502). Moreover, it has been reported that pharmacological activation of either PPAR α (447) or PPAR γ (659) decreases cardiomyocyte hypertrophy, at least partly by inhibiting the NF- κ B signaling pathway. More recently, Planavila et al. (453) showed that PPAR β activation by specific agonists inhibits phenylephrine-induced and lipopolysaccharide-induced cardiomyocyte hypertrophy through physical interaction of the activated PPAR β with the p65 subunit of NF- κ B and subsequent reduction of the NF- κ B heterodimer binding on its DNA responsive elements. Interestingly, treatment of cardiomyocytes with liposaccharide (LPS)

strongly enhances the interaction between the NF- κ B p65 subunit and PPAR β and represses the transcriptional activation of PPAR β -regulated genes (452), suggesting a reciprocal antagonism between the PPAR β and NF- κ B signaling pathways in cardiac cells through direct physical interaction of the nuclear proteins. Antagonistic action of PPAR β on the NF- κ B pathway was shown to be involved in the cardiac lipid-induced inflammatory responses in mice fed a high-fat diet (15) and can also explain, at least partly, the preventing effects of PPAR β specific agonists on angiotensin II-induced cardiac hypertrophy (435, 531). Although other additional beneficial effects can be proposed in this specific model, as PPAR β activation suppresses the angiotensin II-induced intracellular Ca²⁺ increase and subsequent focal adhesion kinase (FAK) activation that is implicated in cardiac hypertrophy (323). Moreover, PPARs can also reduce the NF- κ B signaling pathway by stimulating the transcriptional expression of the inhibitor I κ B as suggested *in vitro* for the three PPAR isoforms and *in vivo* for PPAR α (81).

Finally, we have shown that PPAR β pharmacological activation promotes angiogenesis and moderate cardiomyocyte enlargement in adult mouse heart by activation of the calcineurin/NFAT pathway through a direct transactivation of calcineurin A gene. PPAR β -induced angiogenic and moderate hypertrophic responses take place within days and copy heart adaptation to several weeks of voluntary running (623). These observations suggest an important role for PPAR β in physiological adaptation of the heart to prolonged physical activity and also indicate that PPAR β pharmacological activation could have beneficial effects in pathological situations requiring cardiac angiogenesis.

In summary, intense research efforts have seriously improved our knowledge on the roles of PPARs in physiological control of cardiac metabolism and functions. As cardiomyocytes express high levels of both PPAR α and PPAR β , one of the main questions was to elucidate the respective roles of these PPAR isoforms in cardiac physiology. Today, it is clearly established that the two PPAR isoforms exert both shared and distinct actions on cardiac metabolism and on protection of the heart against inflammatory, ischemic, and oxidative stresses. Both PPAR isoforms control FAO in cardiomyocytes by exerting positive effects on the expression of proteins implicated in peroxisomal and mitochondrial fatty acid catabolism. PPAR α activation upregulates the expression of a subset of genes involved in lipogenesis, fatty acid uptake, and fatty acid esterification, while PPAR β activation leads to increased capacity of glucose uptake and catabolism. From these observations, it can be hypothesized that PPAR α has a predominant role in situations where fatty acid is the major energetic substrate, such as basal conditions or fasting, while PPAR β could be more important in situations requiring increased rates of ATP formation, such as enhanced heart work load, or in situations

where oxygen is limited such as ischemia. Interestingly, activation of PPAR β promotes a cardiac remodeling, e.g., angiogenesis, and moderate hypertrophy that mimics the adaptive response of heart to physical training and PPAR β also plays a crucial and specific role in the control of mitochondrial biogenesis and functions in cardiomyocytes.

PPAR α and PPAR β exert cardioprotective actions against inflammatory and oxidative stresses by several modes of action including impairment of the NF- κ B signaling and stimulation of the enzymatic defense systems against oxidative stress, although each isoform can also exert specific protective actions by affecting other signaling pathways.

IV. PPAR β AND INFLAMMATION

Like PPAR α and PPAR γ , PPAR β has been shown to play a role in a growing list of inflammatory conditions (FIGURE 5, previously reviewed in Refs. 52, 100, 246, 287, 289, 333, 360, 396, 511, 612, 626, 667). These conditions vary from acute to chronic inflammatory diseases and include several autoimmune diseases. Furthermore, PPAR β has been implicated in both the innate and adaptive immune system. Below, we discuss the inflammatory diseases in which PPAR β has been shown to play a role and subsequently describe the cellular and molecular mechanisms by which PPAR β is thought to regulate inflammation.

A. Septic and Nonseptic Shock

Zymosan is a nonbacterial, nonendotoxic agent derived from the cell wall of the yeast *Saccharomyces cerevisiae*. Intraperitoneal injection of zymosan, in mice or rats, leads to multiple organ failure in the course of 1 to 2 wk and is considered to be a model for nonseptic shock (619). With

the use of this model, it was shown that GW0742 attenuates the degree of zymosan-induced nonseptic shock in mice (176). Treatment with GW0742 led to a reduction of neutrophil infiltration caused by zymosan. Other inflammatory parameters measured, such as inducible nitric oxide synthase (iNOS) and its product nitric oxide, and the cytokines TNF- α and interleukin (IL)-1 β , were also lowered with agonist treatment. Furthermore, GW0742 administration reduced apoptosis-induced cell death triggered by zymosan treatment. Regarding a potential mechanism for these effects of PPAR β activation, the authors showed that GW0742 treatment prevented zymosan-induced I κ B α degradation and led to reduced levels of NF- κ B in the lung.

In another study using a cecal ligation and puncture (CLP)-induced polymicrobial sepsis model in rats, GW0742 treatment also provided beneficial effects (reduced systemic release of proinflammatory cytokines and neutrophil infiltration in lung, liver, and cecum) (684). Furthermore, the same study observed increased lethality in PPAR $\beta^{+/-}$ mice that were subjected to CLP. These mice exhibited severe lung injury and higher levels of circulating TNF- α and keratinocyte-derived chemokine (KC) than wild-type mice. The authors demonstrated that PPAR β activation inhibited NF- κ B at the nuclear level but this time without affecting the upstream cytosolic I κ B α degradation, suggesting that the protective effects of PPAR β activation are due to the fact that the initial sequence of inflammatory events, mainly production of proinflammatory mediators and recruitment of neutrophils in major organs, is interrupted through a negative modulation of NF- κ B-mediated transcription. More specifically, the authors observed that pretreatment with GW0742 of LPS-treated macrophages caused a dose-dependent reduction in the binding of the p65 subunit to the NF- κ B recognition site of the TNF- α promoter, in support of a mechanism described in more detail above and below where activated

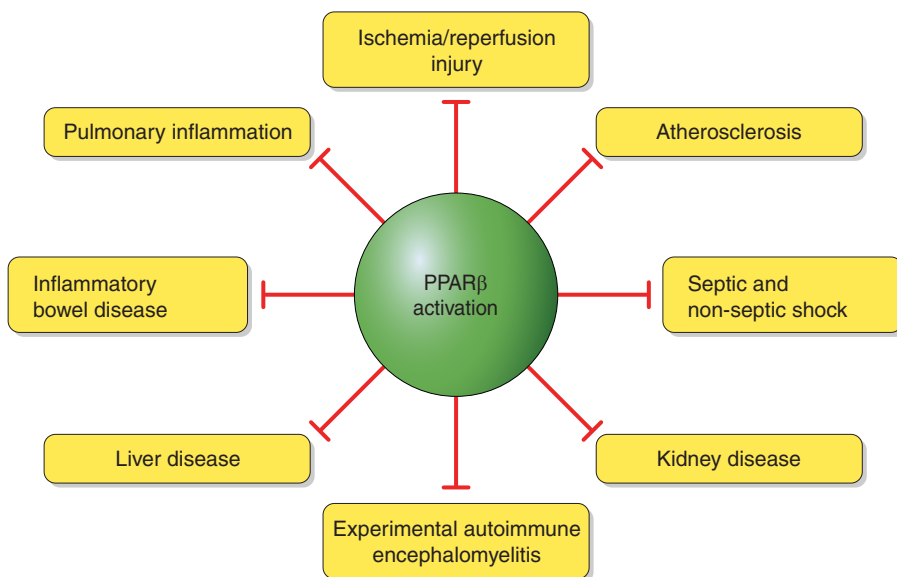


FIGURE 5. PPAR β in inflammatory diseases. PPAR β activation diminishes inflammation in a large variety of inflammatory conditions and is therefore an attractive therapeutic target.

PPAR β blocks NF- κ B action by binding to the p65 subunit (FIGURE 1, D AND E).

A similar study published around the same time demonstrated a protective role for PPAR β in two murine models of septic shock (LPS-induced organ injury and dysfunction and CLP-induced polymicrobial sepsis) (282). This study showed that complete PPAR β deletion worsened the cardiac and renal dysfunction, hepatic injury, and lung inflammation caused by endotoxemia. In contrast, GW0742 treatment attenuated organ dysfunction and inflammation in wild-type mice. These beneficial effects of GW0742 were weakened by the PPAR β antagonist GSK0660. Furthermore, treatment of PPAR $\beta^{-/-}$ mice with the PPAR β agonist alone or together with the antagonist did not have any effect on the cardiac dysfunction and lung inflammation caused by endotoxemia, indicating that these ligand actions were PPAR β dependent. Moreover, the effects of these ligands were sex independent.

In the BCL-6-dependent model of PPAR β action discussed earlier and in more detail below (see FIGURE 1, F AND G), BCL-6 remains free to act in the absence of PPAR β , similar to the ligand-induced dissociation of PPAR β from BCL-6. Therefore, PPAR $\beta^{-/-}$ mice should show the same phenotype as mice that were treated with PPAR β agonist. Since in this study PPAR β deficiency and ligand activation did not mimic each other but instead had opposite effects, the authors argued that PPAR β acts through other anti-inflammatory pathways. In fact, they showed that the protective effects of PPAR β activation against endotoxemia-induced effects in the heart may involve activation of Akt and downstream inhibition of GSK-3 β and NF- κ B. In addition, endotoxemia-induced phosphorylation of ERK1/2 and STAT-3 in the heart was decreased by GW0742 treatment in wild-type mice. This agonist-induced decrease in ERK1/2 and STAT-3 phosphorylation was counteracted by pretreatment with antagonist. Furthermore, endotoxemia-induced phosphorylation of STAT-3 was increased in PPAR $\beta^{-/-}$ mice. Lastly, agonist treatment attenuated the endotoxemia-induced increase of iNOS expression in the heart, and this again could be counteracted by antagonist treatment.

B. Atherosclerosis

Several studies have reported a role for PPAR β in atherosclerosis in different mouse models using multiple approaches. In one study, PPAR $\beta^{-/-}$ bone marrow was transplanted into LDL receptor (LDLR) knockout mice, which led to a decrease in atherogenic diet-induced atherosclerosis development in these mice compared with wild-type bone marrow recipient mice (320). Two other independent studies examined the effect of GW0742 treatment in LDLR $^{-/-}$ mice fed an atherogenic diet and demonstrated contradictory results (191, 332). While both studies observed a de-

crease in inflammatory markers, one study did not observe an effect on atherosclerotic lesion development (332), while in the second study GW0742 treatment reduced the lesion size (191). It was suggested that this discrepancy was due to the high level of hypercholesterolemia achieved in the former study, which may have dampened the impact of anti-inflammatory effects on lesion development (332). The latter notion was supported by another study that demonstrated that in LDLR $^{-/-}$ mice fed an atherogenic diet, where atherosclerosis was accelerated by angiotensin II (ANG II) infusion, GW0742 treatment attenuated the extent of atherosclerosis (572). ANG II infusion has been shown to profoundly increase inflammation in this accelerated atherosclerosis model (571). Furthermore, treatment with the PPAR β agonist GW501516 reduced atherosclerotic lesions in apoE $^{-/-}$ mice (31). Similarly, LDLR $^{-/-}$ mice fed an atherogenic diet exhibited decreased lesions and lesion macrophages when treated with GW501516 (56). GW501516 treatment in this model also attenuated pre-established hyperlipidemia, hyperglycemia, and hyperinsulinemia, as well as glucose and insulin intolerance. What was consistent throughout these studies was the observed reduction in inflammatory gene expression in the vessel wall upon PPAR β activation. Moreover, several of these studies demonstrated in *in vitro* assays that PPAR β deletion or activation repressed macrophage inflammatory responses (31, 191, 320, 572). The fact that both PPAR β deletion and activation result in the same macrophage phenotype would suggest involvement of BCL-6. Indeed, PPAR β was shown to control the inflammatory status in these macrophages in part by its direct interaction with BCL-6 (320, 572).

C. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by the destruction of the gut mucosa by the mucosal immune system (506). Two independent studies have shown that PPAR $\beta^{-/-}$ mice exhibit increased sensitivity to DSS-induced colitis (37, 232). DSS-treated PPAR $\beta^{-/-}$ mice exhibited increased expression of mRNA levels of the inflammatory markers interferon (IFN)- γ , TNF- α , and IL-6 in colon epithelium compared with similarly treated wild-type mice (232). Furthermore, mice deficient for PPAR β specifically in intestinal epithelial cells that received DSS in combination with AOM, a mouse model for inflammation-induced colon carcinogenesis, had more severe colon injury compared with wild-type mice (393). Interestingly, the latter study showed that targeted deletion of intestinal epithelial cell PPAR β alters T-cell populations and their activation status locally and systemically. CD8 $^{+}$ T-cell recruitment into mesenteric lymph nodes (MLN), CD11a expression by MLN CD4 $^{+}$ T cells, and splenic CD62L expression were down-regulated in mice lacking PPAR β in intestinal epithelial cells (393). Together, these studies suggest that PPAR β presence in the gastrointestinal tract has a protective function against IBD.

However, treatment with GW0742 in the DSS-induced colitis model had no effect regardless of genotype while the same agonist accelerated the onset of colitis in IL-10^{-/-} mice (232, 321). The latter mice spontaneously develop colitis (73). In contrast, treatment with the pan PPAR agonist puniceic acid protected wild-type mice against DSS-induced colitis, but its beneficial effects were abrogated in PPAR β ^{-/-} mice, suggesting that activation of PPAR β with puniceic acid ameliorates intestinal inflammation (37). Puniceic acid treatment increased the percentages of regulatory T cells in the blood of wild-type mice but not in PPAR β ^{-/-} mice (37). Together, these contradictory results from studies using PPAR β agonists demonstrate the need for further studies on the precise role of PPAR β in IBD. It is of interest to note that attempts to generate double-knockout mice for PPAR β and IL-10 were unsuccessful due to increased embryonic mortality of mice lacking both PPAR β and IL-10 (37).

D. Experimental Autoimmune Encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE), in which mice are immunized with the encephalitogenic myelin oligodendrocyte glycoprotein (MOG) peptide, is used as a model of multiple sclerosis (MS) (268). MS is a T cell-mediated autoimmune disease of the central nervous system (CNS) that results in the expansion of pathogenic T cells specific for myelin autoantigens associated with the destruction of myelin sheets and the inflammatory activation of glial cells.

It has been shown that oral administration of GW0742 reduces clinical symptoms in a mouse model of EAE (457). These protective effects were receptor dependent since no amelioration of EAE clinical scores was observed in PPAR β ^{-/-} mice treated with GW0742 (617). In addition, PPAR β deficiency resulted in a similar disease incidence and severity as wild-type mice, suggesting that PPAR β does not play a significant role in the early stages of EAE (617). The effects of GW0742 were only modest when the drug was provided simultaneously with MOG immunization, but a greater reduction was observed when GW0742 was administered during disease progression (457). Treatment of splenocytes with GW0742 either *in vivo* or *ex vivo* did not reduce IFN- γ production induced by either MOG peptide or concanavalin A (ConA) treatment, respectively. These latter findings are in contrast to other studies that will be discussed below. However, GW0742 reduced astroglial and microglial inflammation, since both IL-1 β and NOS2 activity were significantly reduced. Furthermore, treatment with GW0742 reduced IL-1 β levels in the EAE brain (457).

Two other PPAR β agonists, GW501516 and L165041, were also effective at ameliorating EAE (273). These agonists did not affect MOG-induced T-cell proliferation, but

in vivo treatment with L165041 or GW501516 resulted in a significant decrease in the expression of the cytokines IFN- γ , IL-17, and the transcription factor T-bet in the brains and spleens from EAE mice. In addition, the inhibition of EAE by PPAR β agonists was also associated with a decrease in IL-12 and IL-23 and an increase in IL-4 and IL-10 expression in the brain and spleen. IL-4 and IL-10 are typical Th2 cytokines, and IL-12 and IL-23 are known to drive Th1 and Th17 polarization, respectively. Furthermore, *ex vivo* and *in vitro* studies confirmed that these PPAR β agonists inhibit the expression of IFN- γ , IL-17, and T-bet in splenocytes. Together, these findings suggest that PPAR β activation ameliorates EAE in association with the inhibition of Th1 and Th17 responses in the CNS and lymphoid organs. Indeed, the same study showed that both PPAR β agonists inhibited Th1 and Th17 polarization *in vitro*, and the addition of L165041 also resulted in an increase in IL-4 secretion from spleen cells under Th2 polarizing conditions. The same investigators published a study a year later in which they demonstrated that PPAR β ^{-/-} mice develop EAE with similar day of onset and disease incidence compared with control mice but show prolonged EAE with resistance to remission and recovery (274). These findings were in line with the study mentioned above that observed no significant role for PPAR β in the early stages of EAE (617). These PPAR β knockout EAE mice expressed elevated levels of IFN- γ , IL-12, and IL-23 in their brain and spleen. Furthermore, MOG-induced secretion of IFN- γ , IL-12, IL-17, and IL-23 was increased in splenocytes from PPAR β ^{-/-} compared with wild-type mice. On the other hand, IL-4 expression was significantly lower in brain and spleen of PPAR β ^{-/-} compared with wild-type mice. These differences were in some cases gender specific. Similar to agonist treatment (273), PPAR β deficiency did not affect splenocyte viability and proliferation in this study. Together, these results show that PPAR β -deficient mice exhibit an augmented Th1/Th17 and an impaired Th2 response without affecting T-cell expansion in an EAE model.

Another study published just a few months before the latter study also observed resistance to remission in the EAE model in PPAR β ^{-/-} compared with wild-type mice (138). Also, MOG-induced secretion of IFN- γ , IL-17, and TNF- α was increased in PPAR β ^{-/-} compared with wild-type splenocytes, while no change was observed for IL-2, IL-12, IL-4, and IL-10 secretion. Similar to the study above (274), PPAR β deficiency led to an increase in IL-12 family cytokine expression in splenic cd11b⁺ cells and peritoneal macrophages. A common problem with the above-mentioned *in vivo* studies that either use agonist treatment, PPAR β knockout mice, or both is that it is impossible to define the specific contribution of specific cell types to a certain phenotype since the knockouts were global (i.e., in all cells) and agonist treatment was systemic. In this respect, the last study went further to analyze the specific role of CD4⁺ T-cell intrinsic effects of PPAR β signaling on EAE patho-

genesis by making chimeras by reconstituting T cell-deficient B6.RAG1^{-/-} mice with either wild-type or PPAR β ^{-/-} CD4⁺ T cells and subjecting these chimeric mice to the EAE model. The authors could reproduce the major phenotypes of global PPAR β ^{-/-} mice (higher IFN- γ and IL-17 production by splenocytes, resistance to remission). Furthermore, the investigators used *in vitro* reductive approaches to delineate the potential contribution of T cells to the observed phenotypes. When naive (CD62⁺) CD4⁺ T cells were subjected to Th0 skewing conditions (anti-CD3 and anti-CD28 stimulation), a higher proportion of PPAR β ^{-/-} than wild-type cells were expressing IFN- γ . Furthermore, the authors observed a more effective Th17 polarization in PPAR β ^{-/-} compared with wild-type naive CD4⁺ T cells. In addition, IL-2 and IL-10 were also elevated in PPAR β ^{-/-} T-cell cultures under Th0 and Th17 skewing conditions, respectively. At the level of transcription factors, the authors showed that while ROR γ T expression was similar, T-bet transcripts were enhanced in PPAR β ^{-/-} compared with wild-type Th0 cells. Regarding the role of PPAR β in T-cell proliferation, the authors observed higher CD4⁺ T-cell proliferation in PPAR β ^{-/-} compared with wild-type cells in response to anti-CD3 and anti-CD28 stimulation. This contradicts the two studies from one group of researchers described above that did not observe an effect of activation or deficiency of PPAR β on T-cell proliferation (273, 274). Perhaps this is due to a difference in mechanism of action between MOG- or anti-CD3/CD28-induced proliferation. Another contradiction mentioned above regarding the role of PPAR β in T-cell IFN- γ production might be explained by the observation that GW0742 treatment of wild-type Th0 triggered an increase in IFN- γ in the presence of 10% FCS but a decrease in serum-free media. The authors blame this difference on the presence of endogenous PPAR β ligands in bovine serum. Under serum-free conditions, the IFN- γ expression was higher in PPAR β -deficient than in wild-type T cells, and no effect of GW0742 was observed in the PPAR β ^{-/-} cells. The same was true for IL-12 expression by macrophages. A similar inhibitory effect of GW0742 treatment on IFN- γ expression was seen in human peripheral blood mononuclear cells grown in serum-free media. Together, these findings suggest that the use of PPAR β agonist-containing serum might explain the lack of effect of PPAR β activation on IFN- γ production by splenocytes in the study mentioned above (457). Lastly, the authors made the interesting observation that spleens from PPAR β ^{-/-} mice contain more memory (CD44^{high}CD62L⁻) or activated (CD69⁺) T cells compared with their wild-type counterparts.

On the basis of the studies discussed above, it has become apparent that the role for PPAR β in the EAE model can, for a large part, be attributed to its effects on T-cell biology. However, some studies have also demonstrated a role for PPAR β in EAE that are related to other cell types. For example, in a study using a three-dimensional brain cell

culture system consisting of microglial cells and astrocytes, but devoid of T cells, it was demonstrated that while GW501516 treatment had anti-inflammatory effects, it did not protect against antibody-mediated demyelination (115). Based on these findings, the authors concluded that the protective effects of PPAR β agonists observed *in vivo* can, in part, be attributed to their anti-inflammatory properties on microglial cells and astrocytes rather than to a direct protective or trophic effect on oligodendrocytes.

Another study investigating the role of the steroid receptor coactivator (SRC)-3 in the pathogenesis of MS suggested a role for PPAR β in regulating the activation state of spinal cord microglial cells in EAE mice (651). SRC-3 is a transcriptional coactivator that interacts with ligand-activated nuclear receptors to enhance their transactivation through its intrinsic histone acetyltransferase activity (655). In addition, SRC-3 has been reported to control the expression of PPARs (382). SRC-3 deficiency attenuated the disease severity of EAE, and this was not caused by any differences in T-cell reactivity and cytokine profile between SRC-3^{-/-} and wild-type mice (651). Instead, the SRC-3-deficient EAE mice exhibited a decrease in spinal cord inflammation compared with their wild-type counterparts. The authors demonstrated that during EAE disease process, PPAR β mRNA levels were increased in spinal cord but not in spleen of SRC-3^{-/-} compared with wild-type mice. Furthermore, microglia seem to be induced to an alternative activation state in SRC-3^{-/-} EAE mice. The investigators claimed, based on these findings, that SRC-3 deficiency specifically upregulates CNS PPAR β , which induces alternatively activated microglia to counteract CNS inflammation during the process of EAE. However, on the basis of the data presented in this study, it cannot be excluded that other (transcription) factors than PPAR β play a role in the phenotypes observed.

Nonetheless, it has become clear from the studies discussed above that PPAR β has been shown to play a significant role in the pathogenesis of EAE, mostly by regulating the inflammatory state in T lymphocytes and microglial cells.

E. Liver Disease

PPAR β has been shown to be protective in both a model for chemically induced liver toxicity and a HFD-induced model of nonalcoholic fatty liver disease (NAFLD), predominantly by regulating the immune response in these mouse models (280, 418, 525, 526). PPAR β knockout mice exhibit exacerbated hepatotoxicity in response to administration of AOM or carbon tetrachloride (CCl₄) compared with wild-type mice (525). In this study, a clear role for NF- κ B signaling was demonstrated. In the absence of PPAR β expression, enhanced activity of NF- κ B signaling occurs in response to CCl₄, which is consistent with increased expression of a number of NF- κ B target genes that mediate liver damage, such as TNF- α . In a follow-up study, the same

researchers showed that activation of PPAR β with GW0742 attenuates CCl $_4$ -induced hepatotoxicity in wild-type mice but not in PPAR β -deficient mice (526). Similarly, GW0742 treatment resulted in lower expression of CCl $_4$ -induced TNF- α and monocyte chemoattractant protein 1 (MCP-1) in wild-type mice, and these effects were not observed in PPAR β knockout mice. Furthermore, hepatocytes and hepatic stellate cells do not appear to be the direct cell types that mediate the protective effects of PPAR β activation. In contrast, enhanced CCl $_4$ -induced liver toxicity is reported to occur in rats when administered in combination with the PPAR β ligand L165041 (224). These discrepancies might be explained by species differences or the ligand used. In a similar model of CCl $_4$ -induced liver injury, PPAR β activation by KD3010, but not by GW501516, led to reduced hepatic inflammation (256). Similar observations were made in a bile duct ligation (BDL) model of liver injury (256). In this study, hepatocytes appeared to be the target for PPAR β ligand activation. In contrast to these findings, an earlier report demonstrated that administration of GW501516 is protective against steatohepatitis induced by methionine- and choline-deficiency which may be due to anti-inflammatory effects including reduced hepatic expression of TGF- β 1, IL-6, IL-1 β , MCP-1, TNF- α , and NF- κ B (404). Furthermore, GW501516 inhibited hepatic steatosis but not liver fibrosis in a choline-deficient, methionine-supplemental mouse model of steatohepatitis (300). In a model of copper-induced acute liver damage, GW0742 treatment led to reduced TNF- α and macrophage inflammatory protein 2 (MIP-2) expression (498). In the same study, the opposite effect was observed after treatment with the PPAR β antagonist GSK0660. Some of the discrepancies between the above studies using the same PPAR β agonists are probably due to the large differences (5-fold in some cases) in the dosage of compounds used.

The results from two studies using a HFD-induced mouse model of NAFLD would suggest that PPAR β activity in Kupffer cells (liver macrophages) might be responsible for many of the protective effects of PPAR β on liver inflammation (280, 418). In one study, *Ppard*^{flox/flox} mice were crossed with lysozyme Cre mice resulting in PPAR β deficiency in myeloid cells, including Kupffer cells (280). HFD feeding of these mice led to several phenotypes, among which was hepatosteatosis. In a second study, adoptive transfer of PPAR β ^{-/-} bone marrow into wild-type mice, resulting in the (partial) replacement of wild-type with PPAR β -deficient Kupffer cells, caused hepatic dysfunction after HFD feeding (418). Both studies demonstrated that PPAR β plays a crucial role in controlling the Th2 cytokine-induced alternative activation of macrophages. The incapacity of PPAR β -deficient macrophages to polarize towards this anti-inflammatory alternative activation (M2) state leads to impaired glucose tolerance and exacerbation of insulin resistance provoked by a HFD, accompanied by a fatty liver with increased lipogenesis and decreased oxida-

tive metabolism. Together, these studies suggest that the protective role observed for PPAR β in liver disease can largely be attributed to its function in liver macrophages (i.e., Kupffer cells). In support for the role of PPAR β as a modulator of Kupffer cell function, a transcriptional profiling study analyzing gene expression in liver from PPAR β knockout mice detected an elevation of Kupffer cell marker gene expression (499). Furthermore, the latter study showed that pathways upregulated in the liver by PPAR β deletion were connected to innate immunity and inflammation, including elevated expression of genes that are part of the NF- κ B pathway. In the Otsuka-Long-Evans-Tokushima-Fatty (OLETF) rat model of type II diabetes and obesity, GW0742 treatment led to a reduction of liver triglyceride content and expression of TNF- α and MCP-1 (324). Furthermore, overexpressing PPAR β in liver by means of PPAR β adenovirus infection of normal diet fed mice led to a reduction in liver expression of IL-1 β , TNF- α , IFN- γ , and MCP-1 and an upregulation of M2 macrophage markers (346), again supporting a role for PPAR β in Kupffer cell polarization. Interestingly, these differences in inflammatory gene expression lost statistical significance when the mice were put on a HFD, suggesting that high-fat feeding suppressed the beneficial effect of PPAR β overexpression in the liver (346). Taken together, these studies demonstrate that PPAR β has a protective function in liver disease predominantly as a result of its anti-inflammatory actions.

F. Other Inflammatory Conditions

Activation of PPAR β has also been shown to prevent the development of streptozotocin-induced diabetic nephropathy by inhibiting inflammatory processes, including chemokine/cytokine expression and macrophage infiltration (366). Treatment with GW0742 led to a reduction in macrophage infiltration into the glomeruli in this nephropathy model and decreased the expression of MCP-1, TGF- β , and osteopontin but not TNF- α or ICAM-2. In vitro studies with the RAW264.7 macrophage cell line suggest that the GW0742-induced decrease in MCP-1 and osteopontin expression involves BCL-6 (366). When streptozotocin-induced diabetic rats were subjected to renal ischemia/reperfusion (I/R) injury, PPAR β activation with GW0742 attenuated the renal dysfunction, leukocyte infiltration, and formation of IL-6 and TNF- α (105). These beneficial effects of GW0742 were attenuated by pretreatment with the PPAR β antagonist GSK00660. In another model of kidney disease (protein overload), GW501516 treatment attenuated macrophage infiltration and resulted in decreased MCP-1 and TNF- α mRNA levels (666). In vitro studies using cultured proximal tubular cells suggest that the GW501516-induced decrease in TNF- α and MCP-1 expression occurred through inhibition of the TGF- β activated kinase 1 (TAK1)-NF- κ B pathway (666).

In an I/R injury model in rat testis, PPAR β activation with L165041 was shown to inhibit TNF- α and IL-6 expression (387). Concomitant treatment with the PPAR pan-antagonist GW9662 reversed these protective effects of L165041. Similarly, I/R injury in the rat heart induced expression of IL-6, IL-8, ICAM-1, and MCP-1, which was attenuated by treatment with GW0742 (675). In a similar study, looking at I/R injury in the rat heart, GW0742 administration led to a decrease in nuclear translocation of NF- κ B p65 (281). GW501516 treatment was shown to abrogate HFD-induced expression of TNF- α , MCP-1, and IL-6 and NF- κ B activity in the mouse heart (15). In a mouse model of gut I/R injury, administration of GW0742 prevented the I/R-induced I κ B- α degradation and reduced the levels of NF- κ B p65, TNF- α , and IL-1 β in ileum tissue (126). Furthermore, the activation of PPAR β in this model led to reduction of neutrophil accumulation in the ileum. The same group later showed that GW0742 treatment attenuates pancreatic damage in two different experimental models of pancreatitis in mice: edematous pancreatitis induced by administration of cerulein at supramaximal doses, and a model induced by intraductal administration of sodium taurocholate (431). PPAR β activation resulted in a reduction in cerulein-induced TNF- α and IL-1 β expression and neutrophil infiltration in the pancreas. The same was true for taurocholate-induced IL-6 expression and neutrophil infiltration in the pancreas. GW0742 treatment prevented cerulein-induced I κ B- α degradation and reduced the levels of the p65 subunit of NF- κ B in the pancreas (431). In yet another inflammatory mouse model, lung inflammation induced by bleomycin or carrageenan, the same researchers demonstrated that treatment with GW0742 led to a decrease in cytokine production, leukocyte accumulation, I κ B- α degradation, and NF- κ B nuclear translocation (125, 175). Similarly, in a model of LPS-induced pulmonary inflammation, GW0742 pretreatment resulted in a decrease in leukocyte recruitment and IL-6, IL-1 β , and TNF- α expression (213).

Taken together, we think it is safe to conclude that PPAR β activation has protective effects in a large spectrum of inflammatory conditions. Next, we discuss the cellular and molecular mechanisms by which PPAR β can exert these anti-inflammatory effects.

G. Mechanisms at Cellular Level

Leukocyte extravasation from the bloodstream into inflamed tissue involves the rolling of these cells along the vessel wall, their firm attachment to the endothelial cell layer, and their subsequent transendothelial migration into the target tissue. Therefore, endothelial cells play potentially an important role in inflammation. PPAR β is expressed in endothelial cells, and activation of PPAR β has been shown to inhibit endothelial inflammatory responses both in vitro and in vivo by reducing the expression of

adhesion molecules (VCAM-1, ICAM-1, and E-selectin) and chemokines (MCP-1 and Gro- α) (53, 148, 335, 451, 479). As a result, PPAR β activation by GW501516 inhibits TNF- α -induced leukocyte rolling, adhesion, and transendothelial migration in vivo in the mouse cremasteric microcirculation (451). Similarly, in an in vitro assay, GW501516 treatment also inhibited rolling and adhesion of polymorphonuclear cells on TNF- α -activated HUVECs under physiological flow (451). A more indirect way PPAR β can have anti-inflammatory effects on endothelial cells is by protection against oxidative stress. PPAR β has been shown to induce 14-3-3 α , superoxide dismutase-1, catalase, and thioredoxin in endothelial cells (148, 341). More recently, activation of PPAR β was shown to prevent endothelial dysfunction by reducing NADPH oxidase-driven superoxide production and increasing nitric oxide production (109, 267, 463).

After a monocyte has rolled along, attached, and crossed the vessel wall, it will become a tissue macrophage. As discussed above, PPAR β has been shown to play a role in several aspects of macrophage biology. Most of the knowledge on the role of PPAR β in macrophages comes from studies on atherosclerosis. PPAR β activation inhibits the development of atherosclerosis in mouse models, and this is thought to occur predominantly through the inhibition of macrophage expression of inflammatory cytokines/chemokines and adhesion receptors (31, 191, 320, 572). Furthermore, as mentioned above, PPAR β has been shown to play an important role in the development of the alternatively activated anti-inflammatory M2 phenotype in macrophages (280, 418).

PPAR β was also shown to be expressed in T cells and, as discussed above, its function in T cells has mostly been studied in the context of EAE (138, 273, 274, 457, 512). PPAR β activation inhibited Th1 and Th17 polarization and augmented Th2 polarization, and the opposite was seen when PPAR β was deleted. The results regarding the role of PPAR β in T-cell proliferation are contradictory, and more research is needed to resolve this question.

The role for PPAR β in other inflammatory cell types (e.g., B lymphocytes and dendritic cells) has been largely unexplored. PPAR β is present at the mRNA level in human CD19⁺ B cells, and there is one study reporting anti-inflammatory effects of PPAR β activation in monocyte-derived dendritic cells (259, 512).

H. Molecular Mechanisms

The anti-inflammatory models of action of PPAR β do not often involve the induction of anti-inflammatory genes, which goes against what one would expect from a transcription factor. TGF- β has been described as a direct target gene of PPAR β in addition to several anti-oxidant

genes (i.e., 14-3-3 α , SOD, catalase, and thioredoxin), and regulators of G protein signaling-4 and -5 (31, 148, 293, 341). As discussed above, in the unactivated state (no ligand bound) PPAR β , in complex with RXR, is bound to PPREs and represses gene expression via interactions with a corepressor complex. As a consequence, absence of PPAR β (knockout models) would lead to a (modest) increase in transcription of target genes (known as derepression), which in the context of anti-inflammatory target genes would have an anti-inflammatory effect. Activation of PPAR β would obviously also lead to an increase in transcription of these anti-inflammatory target genes so in a sense both absence and activation of PPAR β would be anti-inflammatory according to this model. However, given the likely presence of endogenous ligands, the occurrence of PPAR β in the unactivated state probably is quite rare, and therefore, no anti-inflammatory derepression effect of knocking out PPAR β should be expected.

In addition to this transactivation of anti-inflammatory genes, PPAR β is best known to inhibit inflammation through transrepression of proinflammatory genes. In one model of transrepression, inactive PPAR β binds to the anti-inflammatory corepressor BCL-6 and, as a result, BCL-6 is not available to repress the transcription of proinflammatory target genes (320) (FIGURE 1, F AND G). Once PPAR β is activated (or in the absence of PPAR β protein), BCL-6 no longer binds to PPAR β and can perform its function as a corepressor. This means that in both knockout models of PPAR β and in the presence of PPAR β agonists, transcription of proinflammatory target genes of BCL-6 is repressed.

In a second model of transrepression, activated PPAR β binds to the p65 subunit of NF- κ B, thereby blocking the transcription of proinflammatory target genes of NF- κ B (452) (FIGURE 1, D AND E). In the absence of ligand or PPAR β protein, p65 is free and NF- κ B induced transcription of pro-inflammatory genes can occur. A big difference between this model and the transrepression through BCL-6 is that in the absence of PPAR β there will be an increase in transcription of proinflammatory genes (TABLE 3). In addition to the direct binding of PPAR β to P65, there are other mechanisms through which PPAR β has been shown to regulate NF- κ B. For example, it was

shown that PPAR β activation can inhibit NF- κ B activation through inhibition of ERK1/2 phosphorylation (482). Furthermore, another model describes how PPAR β activation leads to GSK-3 β phosphorylation through Akt activation, thereby inactivating GSK-3 β resulting in the inhibition of NF- κ B (281, 282). In another model, PPAR β activation leads to AMPK phosphorylation, which subsequently leads to inactivation of p300 by phosphorylation and SIRT1 activation (35). The transcriptional coactivator p300 has intrinsic acetyltransferase activity and the sirtuin SIRT1 is a protein deacetylase. As a result, this leads to a marked reduction in acetylation of p65 thereby inhibiting NF- κ B transcriptional activity. Taken together, a common feature of all the different mechanisms by which PPAR β has been shown to regulate NF- κ B is the fact that activation of PPAR β leads to a decrease in NF- κ B activity.

I. Conclusion on the Role of PPAR β in Inflammation

In almost all the inflammatory disease models discussed above, PPAR β activation or overexpression leads to a decrease in inflammation, and deletion of PPAR β leads to an aggravation of the inflammatory state. One rare exception is the observation that MCP-1, IL-1 β , and MMP-9 were downregulated in PPAR β ^{-/-} macrophages and upregulated in RAW264.7 macrophages that overexpressed PPAR β by transfection (320). While the latter findings are in support of a model of transrepression through BCL-6, they, at the same time, are not compatible with the models of PPAR β -mediated transrepression of NF- κ B and PPAR β -mediated M2 polarization. Hence, the role of PPAR β in macrophage biology and, likewise, the relevance of the different molecular mechanisms that are supposed to be involved, remain unclear. However, the fact that in a large majority of studies using PPAR β knockout models inflammation is aggravated, which goes against the BCL-6 model of action (see TABLE 3), would suggest that this molecular mechanism plays an irrelevant role in the protective effects of PPAR β against inflammation. What does however seem to be indisputable, and is compatible with all the proposed mechanisms of action, is the fact that PPAR β activation has anti-inflammatory effects. As a consequence, PPAR β presents an

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Table 3. Effect of PPAR β activation or absence compared with presence of inactive PPAR β on inflammation according the different mechanistic models of action

	Transactivation of Anti-inflammatory Genes	Transrepression Through BCL-6	Transrepression Through NF- κ B
PPAR β activation	↓ Inflammation	↓ Inflammation	↓ Inflammation
PPAR β absence	↑ Inflammation*	↓ Inflammation	↑ Inflammation

*Taking into account that a moderate decrease in inflammation as a result of derepression effect is unlikely to occur due to presence of endogenous ligand.

interesting therapeutic target in a large variety of inflammatory conditions (FIGURE 5).

V. CONCLUDING REMARKS

Modulation of gene expression is one of the means for the organism to adapt the physiological functions of the tissues to environmental or internal signals. In this respect, PPAR β is a good example of a transcription factor able to integrate multiple external and internal stimuli and modify the expression of a very large set of genes in several tissues to give an appropriate response to these signals. As PPAR β displays a broad pattern of expression among tissues, is activated by a great variety of natural molecules, and is able to regulate transcription of a great number of genes by different mechanisms of action, it is implicated in the regulation of a variety of physiological functions. Throughout this review, we presented the numerous experimental data illustrating the wide actions of PPAR β in the regulation of metabolism, differentiation, inflammation, angiogenesis, and other biological processes in a great diversity of tissues (FIGURE 6).

The multiple effects of modulations of the PPAR β transcriptional pathway have been well exemplified in skeletal muscle. In this tissue, PPAR β plays a crucial role in the adaptive response to the nutritional status by adapting the fuel preference to substrate availability and also in the response to physical activity behaviors to cope with the energetic demands for fiber contraction. These adaptive responses involve the modulation of a large set of genes in several cell types, such as myofibers, myoblasts, and endothelial cells, and result in a pertinent remodeling of muscle

structure, muscle metabolism, and capillary network. Additionally, in skeletal muscle, PPAR β also enhances the defenses against oxidative stress and reduces inflammation.

A large majority of the experimental evidence from animal models support the idea that treatment with PPAR β agonists might have therapeutic usefulness in the treatment of several metabolic syndrome-associated abnormalities. First, the potency of PPAR β to induce muscle fatty acid catabolism should be beneficial in pathological situations typified by chronic high circulating NEFA concentrations by a reduction of circulating lipids and, as a consequence, by attenuation of ectopic lipid accumulation that results in inflammation and insulin resistance in skeletal muscle and other insulin responsive tissues (371, 565). Second, PPAR β agonism should reduce the low-grade inflammatory status by a promotion of phenotypic modifications in macrophages and other inflammatory cell types and also by an inhibition of major proinflammatory signaling pathways. Lastly, activation of PPAR β should improve cholesterol homeostasis by increasing intestinal cholesterol excretion. To date, the first pilot clinical studies have confirmed some of these beneficial effects of activation of the PPAR β signaling pathway in obese and/or dyslipidemic subjects. Moreover, the use of PPAR β agonists should also be envisioned in other pathologies, such as inherited myopathies and autoimmune diseases.

However, clinical trials are now required to demonstrate the safety of long-term administration of potent PPAR β agonists as some of the experimental data have suggested that, when fully activated, the PPAR β pathway could promote or accelerate the incidence of severe pathologies, such as colorectal cancers and psoriasis.

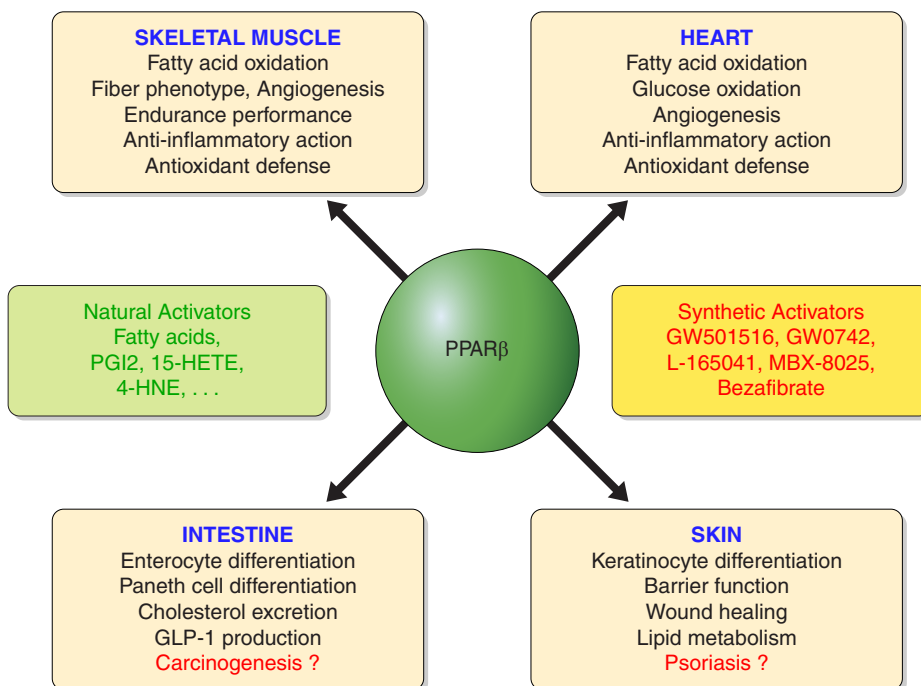


FIGURE 6. Summary of the main regulatory functions of PPAR β in skeletal and cardiac muscles, intestine, and skin. Activation of PPAR β by natural or synthetic agonists affects a large variety of different processes in skeletal muscle, heart, intestine, and skin.

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DISCLOSURES

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