Nuclear Receptor Research
Vol. 2 (2015), Article ID 101188, 30 pages
doi:10.11131/2015/101188

AgiAl Publishing House
http://www.agialpress.com/

Review Article

Peroxisome Proliferator-Activated Receptors: Features, Functions, and Future

Jihan Youssef and Mostafa Badr

University of Missouri-Kansas City, Kansas City, MO 64108, USA

Corresponding Author: Mostafa Badr; email: badrm@umkc.edu

Received 26 May 2015; Accepted 30 August 2015

Editor: Christopher Corton

Copyright © 2015 Jihan Youssef and Mostafa Badr. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract. In this review, the history of the peroxisome proliferator-activated receptors (PPARα, PPARβ/δ and PPARγ) discovery is briefly traced and major features of their structure and posttranslational modifications are presented. Furthermore, an overview of PPAR coactivators and corepressors as well as of endogenous and exogenous ligands is discussed. We have also summarized significant efforts underway to develop more effective and safer PPAR modulators as therapeutic agents to treat diseases such as diabetes, cancer, atherosclerosis, and inflammation. Finally, we share a hypothesis proposing how PPARs may control inflammatory events.

Keywords: PPARs; nuclear receptors; ligands; inflammation; endosalicylates

1. Introduction

In the course of attempting to delineate the mechanism(s) by which some chemicals induce peroxisome proliferation in rodents, a receptor, peroxisome proliferator-activated receptor (mouse PPARα), was discovered [1]. Shortly thereafter, two more PPAR subtypes, PPARβ/δ and PPARγ, were identified. Although the three receptor subtypes share a high degree of homology, they differ in tissue distribution and level of expression as well as in ligand specificity [2].

As research in the field progressed, it was discovered that PPARs regulate a variety of biological processes in various tissues. Among other effects, PPARα control lipid metabolism and inflammatory processes, while PPARβ/δ regulates glucose utilization, cell differentiation and inflammation. PPARγ is involved in adipocyte differentiation, glucose metabolism and inflammatory pathways [3].

The receptor activity is modified posttranslationally by phosphorylation, sumoylation and ubiquitination as well as controlled by a myriad of coregulators [4–6]. Research in the field continues to reveal new roles for these receptors in a variety of normal and disease conditions. In this review we trace the history of the receptor discovery and describe their identified features and posttranslational modifications.

Furthermore, an overview of PPAR coactivators and corepressors as well as endogenous and exogenous ligands is presented. We also present a plausible hypothesis stipulating how PPARs may control inflammation.

2. Historical Perspective

It has been well documented that an increase in size and/or number of peroxisomes in the rodent liver is caused by a group of structurally diverse chemicals known as peroxisome proliferators [7]. However, despite dissimilarity in the structure of these chemicals (Table 1), a receptor-mediated mechanism for peroxisome proliferation was postulated [8]. A peroxisome proliferator-binding protein was later purified from rat liver cytosol and was identified as a dimer protein which has a molecular weight of 140,000–160,000 KDa [9]. This protein was capable of binding to peroxisome proliferators structurally related to clofibrate and was suggested to play an important role in the regulation of peroxisome proliferator-induced pleiotropic response [9]. Further analysis of the isolated protein revealed that it was homologous with the heat shock protein HSP70 [10]. Eventually, PPARα was discovered [1] and subsequent studies indicated that Hsp72 and PPAR form a complex *in vivo*, suggesting that this protein may play a role in the activity of PPARs [11].

The cloned receptor was found to possess structural similarities to the steroid hormone receptors. Since the identified receptor was thought to mediate the peroxisome proliferative response to peroxisome proliferating chemicals, the receptor was named peroxisome proliferator-activated receptor (PPAR).

Following the discovery of mouse PPARα, the receptor was identified in other species, including rat [12] and human [13]. In addition, three related *Xenopus* receptors were cloned, PPARα, PPARβ and PPARγ [14]. PPARδ was later identified in human and was found to be closely related to PPARβ described earlier in *Xenopus*. These receptors bind to and are activated by numerous ligands, including fatty acids, eicosanoids and numerous xenobiotics; some of which possess therapeutic value [15–17]. Structures of representative ligands are presented in Figures 1 and 2.

3. PPARs: Genomics and Proteomics

3.1. Genomics.

3.1.1. PPARα. Several genetic variants of PPARα have been identified (Table 2). A variant lacking exon 6, found in human tissues, is generated by alternative splicing [18, 19]. The corresponding protein of this variant is localized exclusively in the cytoplasm and inhibits wild type PPARα protein activity [18]. In addition, the presence of two other PPARα variants has been revealed; one with a mutation at codon 162 (L162V) and the other with a less frequent mutation at position 131 (R131Q) [20, 21]. These variants possibly account for species-related differences in the response to PPARα activators (Table 3). It has also been suggested that the PPARα L162 V polymorphism is involved in liver tumor progression in patients with hepatocellular carcinoma [22]. Another variant, PPARα V227A, is considered a major polymorphism in the Japanese population [23]. An association has been described between this polymorphism and the pathogenesis of non-alcoholic fatty liver disease as well as with a protective role against obesity [24].

3.1.2. PPARβ/δ. A 3′ splice variant of human PPARδ (PPARδ2) has been reported [25]. This variant is a potential repressor of the PPARδ wild type receptor. The existence of a PPARδ +294T/C polymorphism (Table 2) has also been demonstrated [26], and this polymorphism is associated, in humans, with elevated levels of LDL and apolipoprotein B, lower levels of HDL and higher risks of coronary heart disease [27–29]. The +294T/C polymorphism of this receptor may be linked to an increase in fasting glucose levels in women with polycystic ovary syndrome [30].

3.1.3. PPARγ. It has been reported that alternate transcription start sites and alternative splicing are responsible for the generation of four types of PPARγ mRNA. However, it is believed that mRNAs of PPARγ 1, 3, and 4 are translated into an identical protein [31, 32]. The presence of PPARγ2 Pro12Ala variant (Table 2) in humans has been reported [33]. An association of this polymorphism with type2 diabetes, insulin resistance and obesity is controversial where conflicting data, regarding its effect in different populations, are available [34–38]; with gender differences as well as genetic factors potentially contributing to the discrepancy of reported results [39–41]. A meta-analysis study shows that the Ala allele is associated with a lower risk of developing type2 diabetes in Caucasians and with improved insulin sensitivity in overweight individuals [42].

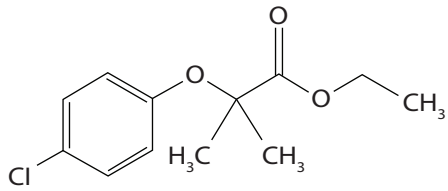
Studies have suggested that PPARγ Pro12Ala expression may increase the risk of cognitive impairment and dementia upon the development of diabetes [43], and this polymorphism may also play a role in the development of dementia at a younger age [44]. In addition, an association of this polymorphism with peripheral arterial disease has been reported [45]. Furthermore, involvement of the PPARγ Pro12Ala polymorphism has been mentioned in the development of gastric cancer [46–48] as well as endometriosis [49].

Another frequent PPARγ polymorphism (C1431T) was identified and found to be associated with higher plasma leptin levels [50]. While some studies reported no association between this polymorphism and body mass index (BMI) [50, 51], other investigations linked C1431T to higher BMI values [52]. Studies have also reported opposing effects of C1431T polymorphism and Pro12Ala polymorphism on BMI and diabetes [53, 54].

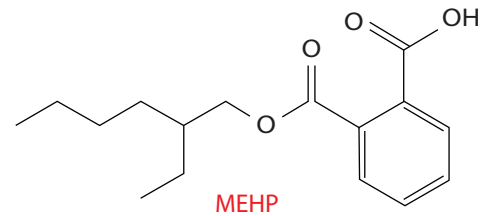
In addition to the above mutations, a PPARγ C190S mutation has been associated with partial lipodystrophy

Table 1: Representative Peroxisome Proliferators.

Fibrates	Nonfibrates	Miscellaneous
Bezafibrate	**Phthalic acid esters**	Aspirin
Ciprofibrate	Mono (2-ethylhexyl) Phthalate	Dehydroepiandrosterone
Clofibrate	Di (2-ethylhexyl) Phthalate	Ethanol
	Perfluorinated fatty acids	Valproic acid
	Perfluorooctanoic acid	
	Perfluorodecanoic acid	

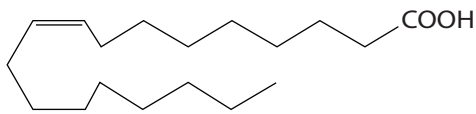


Clofibrate

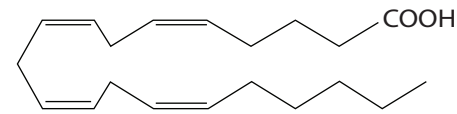


MEHP

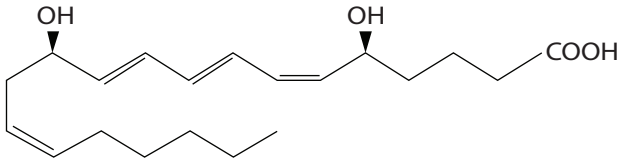
(a)



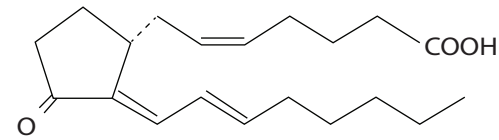
Oleic acid



Arachidonic acid



Leukotriene B_4



15-Deoxy-Δ12, 14-prostaglandin J_2

(b)

Figure 1: Representative PPAR Agonists: A, exogenous; B, endogenous.

Table 2: Common PPAR Variants

Variant	Reference
PPARα	
L 162 V	[20, 22]
R 131 Q	[20, 21]
V 227 A	[23, 24]
PPARβ/δ	
+294T/C	[26–30]
PPARγ	
P 12 A	[33]
C 1431 T	[50]
C 190 S	[55]
R 166 W	[56]
R 194 W	[56]

Table 3: Species Differences in Hepatic Peroxisomal β-Oxidation in Response to PPARα Activators *in vitro*[a].

Drug	Rat	Rhesus Monkey
Bezafibrate[b]	7.99	1.39
Ciprofibrate[b]	9.95	1.77
LY 17,1883[c]	5.44	1.44

[a]Fold increase in hepatic peroxisomal β-oxidation activity; [b]200 μM for 3 days; [c]100 μM for 3 days [300].

[55]. Other mutations, R166W in PPARγ1 and R194W in PPARγ2, are also associated with familial partial lipodystrophy and diminished transcriptional activity [56].

Screening for these mutations in various populations will undoubtedly facilitate the process of ascertaining susceptibilities to their linked diseases, aiding the determination of

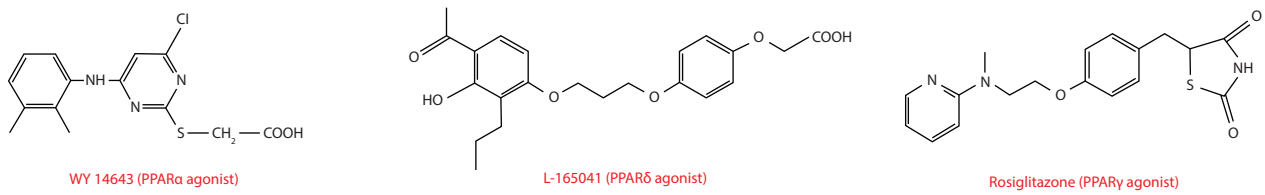


Figure 2: Representative PPAR Subtype-Selective Agonists.

individual disease risk and the consequent development of preventive measures and/or personalized medical treatments.

3.2. Proteomics. PPARs are composed of several domains [4], and interactions of these different domains are vital for the receptor functions (Figure 3 and Table 4). These domains are: (1) an N-terminal region (A/B domain), (2) a DNA-binding domain (DBD, C domain); (3) a flexible hinge region (D domain) and (4) the C-terminal region (E/F domain).

3.2.1. N-terminal (A/B domain). This domain contains a weak ligand-independent transactivating function (AF-1); a structure that is responsible for the constitutive transcriptional activity of PPAR-responsive genes in the absence of a ligand [57]. The N-terminus is a key determinant of subtype-selective target gene expression [58], where investigations have demonstrated that the N-termini limit the transcriptional activity of PPARs to their particular target genes [59].

3.2.2. DNA-binding domain (C domain), (DBD). This region contains two zinc finger-binding motifs, as well as amino acid motifs which recognize PPAR response elements (PPREs) located in the promoter region of target genes. The DBD may also participate in the dimerization of PPARs with RXRs, a process necessary for transcriptional activation [60]. In addition, DBD is involved in co-activator binding [61] and ligand-induced stabilization of PPARβ/δ [62]. The DBDs of PPARα and PPARγ contain phosphorylation sites which posttranslationally modulate the transcriptional activity of these receptors [63, 64].

3.2.3. Hinge region (D domain). This structure acts connects the DBD to the LBD, and acts as a docking domain for co-activators [65, 66]. Studies have suggested that the hinge region may contain a nuclear localization signal [18]. This region is also thought to modulate binding of the receptor to DNA as well as play an important suppressor role in PPARα function [67, 68]. The ribosomal protein rpL11 inhibits transcriptional activity of PPARα by associating to its hinge region; an interaction which is not seen with either PPARβ/δ or PPARγ [67]. Also, heat shock protein 90 (HSP90) interacts with the hinge region and the LBD of the PPARs; a phenomenon which occurs to a greater extent with PPARα than with PPARβ/δ or PPARγ. In addition, HSP90 acts as a repressor of both PPARα and PPARβ/δ activity [69]. Mutation at potential phosphorylation sites within the hinge region of PPARα blocks its phosphorylation and prevents heterodimerization [63].

3.2.4. Carboxyl terminal (E/F domain). This is the largest domain in the receptor, and its overall structure is common to the three PPAR subtypes. It contains a ligand-binding domain (LBD) [70]. The LBD is a Y-shaped hydrophobic pocket to which ligands bind to either activate or repress the receptor transactivation [71].

Although the overall domain structure of the three receptor subtypes is similar, X-ray crystal structure analyses have revealed that the LBD has some markedly different features among the receptor subtypes [70]. The binding pockets of PPARα and PPARγ are significantly larger than that of PPARβ/δ which may play a major role in determining ligand-binding selectivity [70]. Also, studies have revealed that the PPARα pocket is more lipophilic than either PPARγ or PPARβ/δ pocket, which may explain its higher affinity for saturated fatty acids [70].

In addition to ligand binding, The LBD domain is required for heterodimerization and interaction with transcriptional cofactors [72]. Studies have suggested that the PPARγ LBD cooperates with the DBDs of both PPARγ and RXRα to enhance binding to the response element [73]. Studies have also suggested that the extreme carboxyl-terminal amino acids of PPARα are required for the formation of PPAR-RXR heterodimers [74, 75].

The receptor carboxyl termini also contain a segment, ligand-dependent activation function, AF-2, which is engaged in the recruitment of PPAR cofactors [1]. Deletion of a short segment from the carboxyl terminus of PPARγ abolishes transcription activation [76]. The AF-2 domain in the latter receptor also mediates ligand-induced receptor degradation [77].

3.2.5. Post-translational modification of PPARs. PPAR activity is modulated by several post-translational modifications including phosphorylation, sumoylation, ubiquitination and nitration. Furthermore, it has been reported in the literature that activity depends on intracellular localization of the receptor where nuclear localization leads to *genomic* effects,

Figure 3: PPAR Domains.

while cytosolic or cell membrane localization promotes *non-genomic* effects [5, 6].

Subtype-specific phosphorylation of PPARs is mediated by MAPKS as well as by Cdk5, MEK, PKA, PKC and GSK3 [4, 6]. However, while activity of PPARα and PPARγ is modified by phosphorylation, that of PPARδ is not [4]. Furthermore, the phosphorylation site dictates the outcome of this effect. For example, while phosphorylation of serine 12 and 21 in the PPARα A/B domain enhances the transcriptional activity, phosphorylation of serine 76 leads to increased receptor degradation [4]. In addition, phosphorylation of serine 112 of PPARγ2 enhances transcriptional activity of the receptor [4]. Conversely, another study has shown that dephosphorylation of serine 112 of PPARγ enhanced the transcription activity of the receptor [78]. Similarly, phosphorylation of serine 82 in the PPARγ1 A/B domain inhibits both ligand-dependent as well as ligand-independent transactivation [4]. In addition, phosphorylation of PPARγ at serine 273 has been linked to obesity and lack of sensitivity to insulin [79]. Inhibition of phosphorylation at the latter site, both *in vitro* and *in vivo*, by antidiabetic PPARγ ligands was accompanied by improvements in obesity and responsiveness to insulin [79]. Phosphorylation of serine 273 is believed to influence the ability of the receptor to recruit coactivators and corepressors [79].

Both, sumoylation as well as ubiquitination of PPARs have also been reported [4, 6]. Interestingly, phosphorylation may reduce or enhance PPARα ubiquitination, depending on the phosphorylation site [4], whereas sumoylation of PPARγ has been shown to repress activity of this receptor subtype [4].

In addition to the above modifications, nitration of tyrosine residues of PPARs occurs when levels of nitric oxide are increased, e.g., during inflammation [6]. This post-translational modification blocks ligand-induced nuclear translocation of PPAR, and consequently inhibits its activity [6].

Another level at which the activity of PPARs is post-translationally regulated relates to the intracellular distribution of the receptor. As the genomic effects of the receptor require its presence in the nucleus, a nuclear-cytosol shift would be expected to diminish the genomic activity, while potentially enhancing its nongenomic functions [80]. In this regard, it has been reported that phosphorylation or sumoylation of PPARγ promotes exporting the receptor from the nucleus to the cytosol [4]. Furthermore, PPARs have been detected in the plasma membrane, subjecting the receptor to the influence of extracellular signals [6].

3.2.6. PPAR mode of action. Various postulates have been proposed to explain the mechanisms through which PPARs mediate their ascribed effects. As explained above, while modulating the expression of specific genes through these receptors (genomic effect) has been well established, a role not involving gene expression (nongenomic effect) has also been promulgated.

a- *Genomic pathways to PPAR effects*.

The transcriptional activities of PPARs and other members of the nuclear receptor (NR) superfamily are controlled by a large group of proteins known as transcriptional coregulators. These coregulators modify chromatin structure or interact with the components of cellular transcription machinery to enhance or inhibit transcription of NR target genes [81].

Prior to ligand binding, PPARs heterodimerize with retinoid x receptor (RXR), forming a complex [2]. This complex is required for binding to specific DNA sequences, known as PPAR response elements (PPREs), in the promoter region of target genes. Upon binding to their ligands, PPARs undergo conformational changes allowing recruitment of co-activators and release of co-repressors, followed by the activation or repression of transcription [2, 82]. Coactivators recruited and/or corepressors released determine the direction of the expressed effect; activation or repression of transcription. In some cases, a "ligand-independent" repression of target genes takes place [6].

b- *Transcriptional factor coregularors (Figure 4 and Tables 5 and 6)*.

Transcriptional coregulators of nuclear receptors are subdivided into coactivators which potentiate transcription and corepressors which silence or inhibit gene expression. In most NR-coregulator interactions, unliganded receptor remains associated with corepressor until conformational changes are imparted on the receptor by agonist binding. The chemical structure of a given ligand determines the conformational state of the receptor and its interaction with different coregulators [83]. As a result of these conformational changes corepressor dissociates from NR and coactivator binds to the receptor. However, some corepressors target agonist-bound receptors to reduce receptor-mediated gene transcription and in some cases coactivators may stimulate NR in the absence of a binding agonist. PPAR coregulators play key roles affecting physiological and pathological functions of the receptor and as such represent potential therapeutic targets for novel drug design.

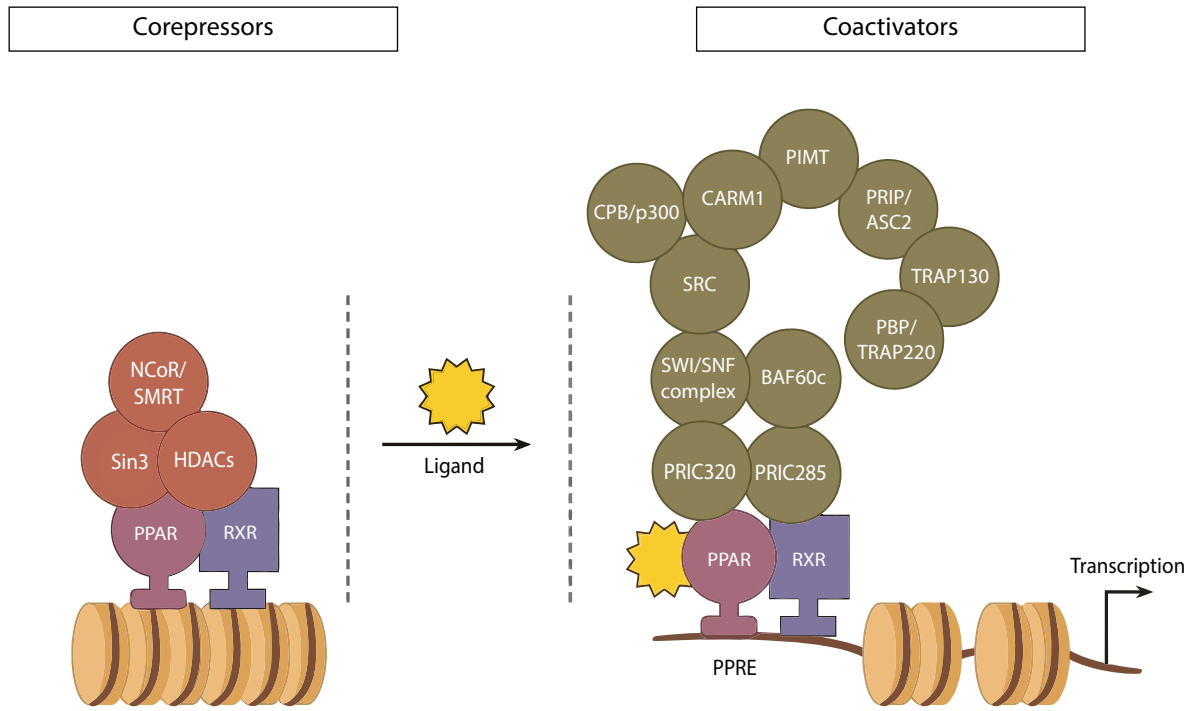


Figure 4: A Schematic Depiction of Coregulator Recruitment.

3.3. PPAR coactivators (Figure 4 and Table 5). Several nuclear receptor coactivators have been identified as essential for PPAR transcriptional activity. Some of these coactivators are recruited to ligand-bound receptor and enhance transcription activation by modifying the chromatin organization *via* intrinsic histone acetyltransferase or methyltransferase activities [84]. Other coactivators possess no enzymatic activity but enhance PPAR transcriptional function by stabilizing transcriptional complexes [84]. The assembly of coactivator complexes with multiple possible configurations allows the liganded PPAR to activate the transcription of specific target genes in a tissue/cell-specific manner. Most coactivators possess one or more short amphipathic leucine rich motif (LXXLL; L: leucine and X: any amino acid) known as the NR box, some of which may interact with a coactivator-binding groove located within the ligand-binding domain of nuclear receptor [85].

3.3.1. PPARγ coactivator-1 (PGC-1). This family of coactivators includes PGC-1α and PGC-1β which share extensive sequence homology, but contain distinct binding sites for different transcription factors. Both PGC-1α and PGC-1β play important roles in the regulation of mitochondrial functions by enhancing transcriptional activity of nuclear receptors, including PPARs [86, 87].

Studies have shown that PGC-1α is induced in a tissue-specific manner under conditions such as cold, fasting and exercise [6] and regulates the expression of mitochondrial genes involved in adaptive thermogenesis [88, 89], as well as mitochondrial biogenesis during exercise and caloric restriction [90]. PGC-1α knockout mice have a reduced expression of mitochondrial genes in several tissues including brown adipose tissue (BAT), skeletal and cardiac muscles as well as in the brain. These animals exhibit an impaired metabolic response to cold exposure and starvation [91]. PGC-1β knockout mice display an impaired expression of a large number of genes involved in mitochondrial and metabolic functions in multiple tissues including BAT, liver, brain, skeletal and cardiac muscle. These animals develop abnormal hypothermia and morbidity after acute cold exposure and, unlike the hyperactive PGC-1α knockout mice, PGC-1β knockout mice show a greatly decreased activity during the dark cycle [92].

Binding of PGC-1α to nuclear receptors is usually ligand-dependent; as is the case with PPARα. This binding involves an interaction between PGC-1α LXXLL domain and the AF2 region of PPARα [93]. Evidence demonstrates that PGC-1α acts as a coactivator of PPARα in the transcriptional control of mitochondrial genes involved in fatty acid oxidation [93]. A study has shown PGC-1β to physically interact with and potently coactivate hepatic PPARα [87]. However, other studies have demonstrated that overexpression of hepatic PGC-1β *in vivo,* induced by increasing dietary fat, does not potentiate PPARα–mediated fatty acid oxidation. Indeed, PGC-1β overexpression blunted the effects of agonist-mediated PPARα activation on gene expression and fatty acid oxidation [94].

Table 4: PPAR Domain Functions.

N-terminal	DNA Binding domain	Hinge region	Carboxyl terminal
transactivating function (AF–1)	Zinc finger binding motifs	Nuclear localization signals	Ligand – independent Largest domain
Phosphorylalion sites	Recognize PPREs	Phosphorylation sites required for dimerization (PPARα)	Contains LBD
Determines subtype-selective gene expression	Phosphorylation sites (PPARα & PPARγ) Dimerization	Interacts with HSP90 (PPARα more than PPARβ/δ or PPARγ)	Interacts with HSP90 (PPARα more than PPARβ/δ or PPARγ)
	Ligand-induced stabilization (PPARβ/δ)	Ribosomal protein rpL 11 inhibits activity Coactivator binding of PPARα	AF-2; for cofactors recruitment
		Modulates binding to DNA	Dimerization
		Docking domain for coactivators	Contains nuclear localization sequence

A strong physical interaction between PGC-1α and PPARβ/δ has been demonstrated [89]. Although this interaction is enhanced in the presence of PPARβ/δ agonists, PGC-1α acts as a powerful coactivator of PPARβ/δ even in the absence of an agonist. Studies have shown that cooperation between PGC-1α and PGC-1β appears essential for maximizing PPARβ/δ-mediated mitochondrial fatty acid oxidation [95].

Interaction of PGC-1α with PPARγ is ligand-independent and is mediated also through an LXXLL motif necessary for PGC-1α to coactivate PPARγ [96].

3.3.2. P 160 family of steroid receptor coactivators (SRCs). Three members of the p160/SRC family of coactivators have been identified, including (1) SRC-1/NCoA-1(nuclear receptor coactivator A-1), (2) SRC-2/TIF2 (transcriptional intermediary factor 2)/GRIP1 (glucocorticoid receptor interacting protein 1), and (3) SRC-3/pCIP (CBP-interacting protein)/RAC3 (receptor-associated coactivator-3)/ACTR (activator of thyroid and retinoid receptors)/AIB1 (amplified in breast cancer-1)/TRAM-1(thyroid hormone receptor activator molecule 1) [97].

SRC proteins are required for mediating the transcriptional function of nuclear receptors in a ligand-dependent manner. They possess intrinsic histone acetyltransferase (HAT) activity responsible for acetylation of histones and remodeling of chromatin structure resulting in increased levels of transcription [98]. SRC1, cloned and identified as the first authentic nuclear receptor coactivator, interacts with steroid receptors and markedly increases their transcriptional activity [99]. Subsequent studies revealed that SRC1 interacts with PPARγ in a ligand-dependent manner, potentiating the receptor transcriptional activity and playing a role in the PPARγ-mediated signaling pathway [100, 101]. The X-ray crystal structure of SRC1 and the liganded PPARγ complex revealed that binding occurs between highly conserved glutamate and lysine residues in the PPARγ ligand binding domain and the backbone atoms of the LXXLL helices of SRC-1 [101].

Studies have shown that PPARγ function is impaired in SRC-1 null mice and this impairment is manifested as reduced energy expenditure with increased sensitivity to high fat diet and predisposition to obesity [102]. Conversely, disruption of SRC-2 gene in the mouse reduces PPARγ function in white adipose tissue (WAT) leading to a reduction in fat accumulation and protection against obesity [102]. The latter mice display enhanced adaptive thermogenesis and resistance to diet-induced obesity due to increased function and development of brown adipose tissue (BAT), promoting energy expenditure with improved glucose tolerance and insulin sensitivity [102]. PGC1α is up-regulated in SRC-2-depleted BAT and the interaction between SRC-1 and PGC1α is facilitated in SRC-2null mice leading to an increase in the thermogenic activity of PGC1α in these animals [102]. It is suggested that SRC-1 and SRC-2 control the energy balance between WAT and BAT, whereby SRC-1 promotes energy expenditure via fatty acid oxidation in BAT, while SRC-2 represses this process by activating PPARγ in WAT [103].

Like SRC-1 and SRC-2, SRC-3 has an LXXLL motif through which it binds directly to PPARγ in a ligand-dependent manner [104]. SRC-3 null mice show reduced body weight and adipose tissue mass with a significant decrease in PPARγ expression, compared to wild type mice, indicating that SRC-3 plays an important role in adipocyte differentiation [105]. SRC-1 and SRC-3 double null mice are lean and resistant to high-fat diet induced obesity. These mice exhibit no BAT lipid storage with decreased uncoupling

Table 5: PPAR Coactivators.

Coactivator	Receptor	Condition	Outcome
PGC1α	PPARα	– ligand dependent	– Stimulation of FA oxidation, promotion of mito biogenesis
	PPARβ/δ	– ligand dependent and independent	– Mito FA oxidation
	PPARγ	– ligand dependent and independent	Mediation of adaptive thermogenesis and fiber type switching of skeletal muscle
PGC1β	PPARα	– ligand independent	– inhibition of PPARα transcriptional activity
	PPARβ/δ	– in cooperation with PGC1α	– maximize mito FA oxidation
SRC_1	PPARα	– ligand independent	
	PPARγ	– ligand dependent	– promotion of energy expenditure
SRC_2	PPARγ	– ligand dependent	– repression of energy expenditure, promotion of adipocyte differentiation
SRC_3	PPARα	– ligand independent	
	PPARγ	– ligand dependent	– promotion of adipocyte differentiation
CBP/P300	PPARα	– ligand dependent	– regulation of brown fat UCP-1
	PPARβ/δ	– ligand depentant	Fat-burning stimulation
	PPARγ	– ligand dependent and independent	
Med 1	PPARα	– ligand dependent	– hepatic cell and peroxisome proliferation
	PPARγ	– ligand dependent	– no effect on PPARγ transcriptional activity
Med 14	PPARγ	– ligand independent	– fatty acid storage and adipogenesis
PRIP	PPARα	– Ligand dependent	– no effect on PPARα transcriptional activity
	PPARγ	– ligand dependent	– adipogenesis
PRIC 285	PPARα PPARβ/δ PPARγ	– ligand dependent	Moderate stimulation of transcription
PRIC 320	PPARα PPARγ	– ligand dependent – lesser degree than with PPARα	
PRIC 295	PPARα PPARγ	– ligand dependent – ligand dependent	Enhance transactivation Enhance transactivation
SWI/SNF	PPARα		– FA oxidation and hepatic lipid metabolism
	PPARγ		– adipogenesis
BAF60 a	PPARα	– PGC1α dependent	– Mitochondrial and peroxisomal – β-oxidation
BAF60 C	PPARγ	– ligand independent	Enhance transcriptional activity
PIMT	PPARγ		
CARMI	PPARγ		– adipocyte differentiation

Table 5: Continued.

Coactivator	Receptor	Condition	Outcome
NcoA4/ARA70	PPARα	– in absence of RXR – in presence of RXR	– activation – repression
	PPARγ	– ligand independent	– antiinflammatory effect
PRDM 16	PPARγ		– activation of BAT selective genes and suppression of WAT selective genes
TLE3	PPARγ		– adipocyte differentiation blocks interaction with PRDM 16, promotes lipid storage, inhibits thermogenic gene expression
CCPG	PPARγ	– ligand independent	– adipogenesis
TRIP3	PPARγ	– ligand dependent	– adipogenesis

protein 1(UCP1) expression and defective adaptive thermogenesis due to a deficiency in the regulation of selective PPARγ target genes. The increased basal metabolic rates and enhanced physical activity in these animals result in a lean phenotype despite the higher food consumption [106].

SRC-2 and SRC-3 concomitantly promote human adipocyte differentiation and lipid accumulation by attenuating PPARγ phosphorylation at S114, an inhibitor of PPARγ transcriptional activity and adipogenesis. It is suggested that targeting the PPARγ–SRC interaction may present strategies for developing new therapeutics to prevent obesity associated with the treatment of type-2 diabetes [107].

In vitro studies have documented protein-protein interaction between PPARα and SRC-1 and SRC-3 and these interactions appear to be ligand- independent. However, SRC-1, SRC-2 or SRC-3 null mice treated with PPARα agonists displayed similar responses as wild type animals exposed to same agonists, suggesting that these coactivators do not play an essential role in PPARα-regulated transcriptional activation *in vivo* [98].

3.3.3. CREB binding protein (CBP) and p300. CBP and p300, proteins are universal coactivators that link transcriptional factors to the basal transcription apparatus and provide a platform to integrate multiple cofactors. A high degree of homology is shared between CBP and p300 that are usually referred to as CBP/p300 [108]. Both proteins possess HAT activity and have the ability to recruit other proteins having HAT activity to further enhance acetylation of the coactivator complex for efficient gene transcription [98].

CBP and p300 directly interact with the ligand-binding domain (LBD) of several nuclear receptors including PPARs. Studies have demonstrated that CBP is a component of PPARα-interacting cofactor (PRIC) complex that interacts with full-length PPARα in the presence of ciprofibrate and leukotriene B4 [109]. CBP also coactivates PPARα-dependent regulation of the brown fat UCP-1 gene promoter in the presence WY14643 [110]. In the intestinal cell line Caco-2, CBP and p300 interact with the ligand-binding domain of PPARα and PPARβ/δ in the presence of their specific ligands [111].

In addition, both p300 and CBP interact with PPARγ. This interaction is described as complex and involves multiple domains in each protein. p300/CBP bind in a ligand-dependent manner to the DEF region of PPARγ in addition to ligand-independent direct binding to a region in the AB domain. Studies have shown that p300/CBP enhance the transcriptional activities of both AF-1 and AF-2 domains [112].

3.3.4. Mediator complex subunits. Several proteins participate in the formation of a multisubunit complex called TRAP (thyroid hormone receptor-associated protein) /DRIP (vitamin D_3 receptor-interacting protein) /ARC (Activator-recruited cofactor)/Mediator complex. These subunits are thought to be lacking intrinsic enzymatic activity but the complex is involved in facilitating interaction of the RNA polymerase II machinery with other transcription coactivators containing chromatin remodeling enzymatic activities [113].

PPAR-binding protein is a component of the mediator complex and is alternatively referred to as PBP (PPARBP)/TRAP 220/DRIP 205/Med1 (Mediator 1) [114]. This protein binds to several nuclear receptors including PPARα and PPARγ, in a ligand-dependent manner *via* two conserved LXXLL motifs [115]. Conditional deletion of Med1 gene in the liver results in the abrogation of PPARα ligand-induced pleiotropic effects, indicating that Med1 is essential for PPARα signaling. Studies have shown that Med1 deficiency in liver parenchymal cells results in near elimination of PPARα ligand-induced peroxisome proliferation, liver cell proliferation, and induction of PPARα-regulated genes. Moreover, mice deficient in Med1 gene exhibited a severe impairment of liver regeneration following partial hepatectomy. Studies have also suggested that Med1

plays a key role in PPARα ligand-induced liver tumor development [116].

Although direct binding of Med 1 to PPARγ has been demonstrated, experiments utilizing cells depleted of different Mediator subunits indicate that Med1 depletion does not affect PPARγ-dependent activation of target genes or PPARγ-dependent recruitment of Mediator to target promoters [117]. In the same study, another Mediator subunit, Med 14, was identified as a critical component for PPARγ-dependent transactivation and Mediator recruitment. It was shown that Med14 interacts with the N-terminal domain of PPARγ in a ligand-independent manner both *in vitro*. The same study also demonstrated that knockdown of Med14 results in reduced PPARγ-mediated activation of target genes involved in fatty acid storage and impairment of adipogenesis in 3T3-L1 cells [117].

3.3.5. PPAR-interacting protein (PRIP/NCoA6). PRIP is also referred to as activating signal cointegrator-2 (ASC-2)/nuclear receptor activating protein 250 (RAP250)/nuclear receptor coregulator (NRC)/thyroid hormone receptor (TR)-binding protein (TRBP), (PIMT/NCoA6IP) and serves as a linker between the initial HAT complex of CBP/p300 and p160 coactivators and the downstream mediator complex [97].

Although it was shown that PRIP binds to PPARα and this binding is increased in the presence of specific ligands [118], subsequent studies have demonstrated that targeted deletion of PRIP gene in liver does not affect the induction of PPARα-regulated pleiotropic responses, including hepatomegaly, hepatic peroxisome proliferation, and induction of genes involved in fatty acid oxidation, indicating that PRIP may not be essential for PPARα-mediated transcriptional activity [119]. Alternatively, absence of PRIP may trigger the recruitment and binding of other cofactors to PPARα.

Studies have shown that PRIP potentiates the transcriptional activities of PPARγ in a ligand-dependent way and a truncated form of PRIP acts as a dominant-negative repressor [118]. It has been demonstrated that coactivation of PPARγ by PRIP is required for adipogenesis [120].

3.3.6. PPAR alpha-interacting cofactor 285 (PRIC285). PRIC285 is a component in the PRIC complex isolated from rat liver nuclear extracts. This complex interacts with full-length PPARα in the presence of synthetic and natural ligands and acts as a coactivator by moderately stimulating PPARα-mediated transcription in transfected cells [109]. PRIC285 binds to the DBD-hinge of the PPARs through its C-terminal region [121]. Human PRIC285 has been shown to enhance PPARγ-mediated transactivation. PRIC285 also coactivates PPARβ/δ [121]. Assessment of PRIC285 function *in vivo* suggests a functional redundancy of this coregulator in the general transcriptional machinery of PPARα and PPARγ. These results imply that loss of a single component of a multisubunit protein complex could be compensated *in vivo* by other members of this complex [97].

3.3.7. PRIC320. PRIC320 possesses a chromodomain helicase DNA (CHD)-binding function and is also known as CHD9 or CReMM (Chromatin Related Mesenchymal Modulator). Members of the CHD family of proteins interact with nucleosomes and modulate chromatin remodeling to control transcription [122]. Studies indicate that two isoforms of PRIC320, PRIC320-1 and PRIC320-2, interact with PPARα in a ligand-dependent manner [123]. PRIC320 also binds to PPARγ but to a much lesser degree than to PPARα suggesting a differential role for the cofactor in the regulation of downstream target genes [123].

3.3.8. PRIC295. PRIC295 has been identified and characterized as a novel coactivator protein that interacts with the Med1 and Med24 subunits of the mediator complex [124]. It binds to PPARα, PPARγ and other members of the nuclear receptor superfamily in a ligand-dependent manner and enhances the transactivation function *in vitro* [124]. However, the role of this cofactor as a regulator of nuclear receptor signaling *in vivo* is yet to be determined.

3.3.9. Switch/sucrose non-fermenting (SWI/SNF) ATP-dependent chromatin-remodeling complex. Chromatin remodeling complexes mobilize nucleosomes and function as important regulators of transcription factor function [125]. In mammals SWI/SNF complexes are present in multiple forms made up of several proteins refered to as BRG1-associated factors (BAFs) [126]. Studies have identified SWI/SNF as a regulator of genes involved in fatty acid oxidation and hepatic lipid metabolism through an interaction with PPARα mediated by BAF60a [127]. SWI/SNF complex is also recognized as a regulator of genes involved in adipocyte differentiation. Experimental evidence indicate that the SWI/SNF complex is recruited on the promoter of PPARγ to transactivate PPARγ during adipogenesis [128].

3.3.10. BAF(s) Family. The BAF(s) family represents a molecular link between transcription factors and SWI/SNF complexes [94]. *In vivo*, BAF60a induces expression of genes involved in both peroxisomal and mitochondrial fatty acid oxidation and ameliorates hepatic steatosis suggesting the existence of a cross talk between BAF60a and PPARα. This has been confirmed by experimental findings revealing a significant decline in of BAF60a transcriptional function in PPARα-null hepatocytes. In addition, activation of PPARα by WY14643 was found to increase the induction of fatty acid oxidation genes by BAF60a providing more evidence for the existence of a connection between BAF60a and the PPARα pathway [127]. PGC-1α was found necessary for the function of BAF60a as a regulator of fatty acid oxidation genes by mediating the recruitment of BAF60a to PPARα-binding sites, leading to transcriptional activation of peroxisomal

and mitochondrial lipid oxidation genes [127]. Studies have shown that PGC-1α interacts with PPARα and BAF60a through different domains suggesting the formation of a transcriptional complex, involving these three factors, in the vicinity of fatty acid oxidation genes promoters [127].

Another member of the BAF family, BAF60c binds to PPARγ and enhances its transcriptional activity in a ligand-independent manner [129]. Two isoforms, BAF60c1 and BAF60c2, are localized primarily in the cell nucleus to help recruit SWI/SNF complex to nuclear receptors and other transcription factors [129].

3.3.11. PIMT. PIMT (PRIP-interacting protein with methyltransferase domain), enhances the nuclear receptor transcriptional activity and its methyltransferase property is involved in the formation of the 2, 2,7-trimethylguanosine cap of non-coding small RNAs [130]. In addition to its interaction with PRIP, PIMT has been shown to interact with transcriptional coactivators, CBP, p300, and PBP under *in vitro* and *in vivo* conditions [131]. Studies have shown that while PIMT enhances PBP-mediated transcriptional activity of PPARγ, it represses CBP/p300-mediated transactivation of this receptor [131].

3.3.12. CARM1 (coactivator-associated arginine methyltransferease 1). CARM1 functions as a coactivator for many nuclear receptors and acts synergistically with the p160 family of SRCs [132]. Studies have shown that CARM1 promotes adipocyte differentiation by coactivating PPARγ [132].

3.3.13. Nuclear receptor co-activator 4 (NcoA4)/ ARA70. NcoA4 was initially identified as androgen receptor (AR)-associated protein 70 (ARA70) and was thought to be AR-specific, but subsequent investigations revealed that it interacts with a variety of nuclear receptors, including PPARα and PPARγ [133, 134]. Studies have shown that NcoA4 acts as a PPARα coactivator in the human prostate cancer cell line DU145 but functions as a PPARα repressor in adrenal Y1 cells [133]. It appears that the availability of PPARα heterodimer partner retinoic X receptor (RXR) determines the activity of NcoA4 toward PPARα, thus by acting as a coactivator in the absence of RXR and as a repressor in the presence of RXR [133]. It is suggested that an additional protein or complex of proteins in Y1 cells may interact with the PPARα:RXR-NcoA4 complex to mediate repression of PPARα transcription [130]. It is also proposed that phosphorylation of NcoA4 may contribute to its repressing activity in Y1 cells [133].

Studies have demonstrated that PPARγ interacts with NcoA4 in the absence of PPARγ ligands, but with enhanced transactivation in the presence of a ligand [134]. The antiinflammatory effect of PPARγ in the colon is thought to be mediated by NCOA4 [135].

3.3.14. PRDM16. PRDM16 is a zinc finger protein required for development and function of BAT and beige adipocytes [136]. It is also considered as an effective regulator of muscle cell metabolism [137]. Studies have shown that direct interaction of PRDM16 with PPARγ is critical for activation of brown fat-selective transcription program and promoting BAT-like phenotype in WAT [138]. Studies have also demonstrated that PPARγ agonists induce browning of WAT by stabilizing PRDM16 protein [139]. It has also been shown that PRDM16 suppresses the expression of certain WAT-selective genes [140].

Studies employing transgenic mice overexpressing PPARγ2 suggest that this receptor induces conversion of myogenic cells into adipocytes and PRDM16 mediates the browning of such adipocytes and thus may represent a potential target for prevention and treatment of obesity [141].

3.3.15. Transducin-like enhancer of split 3 (TLE3). TLE3 is a member of the Groucho/TLE family of corepressors and acts as an activator of adipogenesis as well as a suppressor of osteoblast differentiation [142]. Studies have demonstrated that TLE3 is a white fat selective PPARγ cofactor enhancing adipocyte differentiation by stimulating transcriptional activity of PPARγ [142, 143]. Experimental evidence indicates that TLE3 is a constituent of PPARγ containing transcriptional complexes but direct interaction between these two proteins is not apparent [143]. However, TLE3 is able to bind PRDM16 and compete for its interaction with PPARγ thereby inhibiting the co-occupancy of PRDM16 and PPARγ on adipocyte promotors [144]. Blocking the interaction between PRDM16 and PPARγ by TLE3 promotes lipid storage and inhibits thermogenic gene expression [144].

Transgenic mice lacking TLE3 gene exhibit enhanced expression of thermogenic genes in both BAT and WAT and have improved tolerance to cold [144]. It has been suggested that in cell types where both TLE3 and PRDM16 exist, the ratio between PPARγ-TLE3 and PPARγ-PRDM16 complexes may present an important determining factor of the extent of activation of particular promotors and these complexes may exist in equilibrium in beige adipocytes existing in WAT depots [144].

3.3.16. CCPG (Constitutive coactivator of PPARγ. CCPG interacts with the hinge region of PPARγ in a ligand-independent manner and enhances the receptor's transactivation function [145]. None of the four LXXLL motifs of CCPG were found to be essential for interaction with PPARγ. Studies have shown that CCPG is involved in the process of adipogenesis [145].

3.3.17. TRIP3 (Thyroid interacting protein 3). TRIP3 interacts with PPARγ in a ligand-dependent manner via an LXXLL motif [104]. Impaired adipocyte differentiation

Table 6: PPAR Corepressors.

Corepressor	Receptor	Condition	Outcome
NCoR/SMRT	PPARα	– In absence of ligands SUMOlyaltiom leads to recruitmmrnt of NCoR, but not SMRT	– downregulation of transcriptional activity
	PPARβ/δ	– Dependent of coactivator/Corepressor ratio	– decreased exercise endurance
	PPARγ	– In absence of ligand – Binding increases by SUMOlylation of PPARγ	– inhibition of adipogenesis, increase of inflammation, decreased insulin activity
HMGA 1	PPARγ	– Ligand-dependent	– loss of vascular protection
TRB3	PPARγ		– inhibition of adipocyte differentiation
LCoR	PPARγ	– Ligand-dependent – Acts as depressor at low levels	– inhibition of splenic macrophages
RIP 140	PPARα PPARβ/δ PPARγ	– ligand dependent activator and repressor depending on the relative level of RTP 140 in comparison to other cofactors	– Inhibition of mRNA expression of PPARα and PPARβ/δ and their target genes. – Suppression of BAT-specific genes in WAT
TNIP 1	PPARα PPARβ/δ PPARγ	– Ligand dependent	– partial repression
TAZ	PPARγ	– Ligand dependent	– attenuation of adipogenic gene expression and adipocyte differentiation
CoPR 1	PPARs	– Ligand dependent	– Partial repression
CoPR 2	PPARs	– Ligand dependent	– Partial repression
Brd 2	PPARγ		– Inhibition of adipogenesis

results from knock-down of TRIP3 indicating the importance of this coactivator in the process of adipogenesis [103].

Further research in the area of PPAR transcriptional coactivators may indeed prove valuable to the task of identifying new coactivators and/or pinpointing the exact role of each of the already discovered ones, with the ultimate goal of targeting these molecules/complexes as a therapeutic means to combat diseases. In addition, determining coactivator-specific involvement in the regulation of the excretion, secretion and effect of adipokines on energy expenditure is expected to be invaluable to the task of designing strategies to control the epidemic of obesity and related metabolic diseases.

3.4. PPAR corepressors (Figure 4 and Table 6). The corepressor proteins possess or recruit histone deacetylases (HDACs) and other enzymatic activities that participate in down regulating gene transcription by enforcing a tight chromatin structure [146]. Corepressors interact with unliganded nuclear receptors through amphipathic leucine-rich helices known as the corepressor/ nuclear receptor (CoRNR) boxes located within the corepressor [147]. A distinct group of corepressors target the agonist-bound receptor's activating function-(AF) 2 region to reduce receptor-mediated gene transcription. The latter group of corepressors also utilizes CoRNR boxes and may function to mediate a submaximal response during exposure to excess ligand [148].

3.4.1. Nuclear receptor corepressor (NCoR) and silencing mediator of retinoid and thyroid hormone receptor (SMRT). NCoR and SMRT proteins share a high degree of homology and interact with unliganded NRs through (CoRNR) boxes [147]. NCoR and SMRT possess three and two CoRNR boxes, respectively, and the release of the corepressor molecules upon ligand binding is due to reduced affinity of the receptor for the CoRNR box motif [147]. Studies have shown that NCoR and SMRT form multisubunit complexes that contain HDAC activities mediating repressive reactions [149]. Experimental evidence indicates that NCoR and SMRT act as repressors of PPARs and that the unliganded PPAR-RXR heterodimer remains bound to NCoR and SMRT mostly present in the corepressor complex [150].

Studies have also demonstrated that SUMOylation of human PPARα on lysine 185 downregulates its transcription

via the recruitment of NCoR, but not SMRT, leading to the differential expression of various PPARα target genes [151].

NCoR has been shown to act as a negative regulator of both muscle mass and mitochondrial oxidative metabolism. Enhanced exercise endurance in genetically modified mice with muscle-specific loss of NCoR is attributed, in part, to increased transcription activity of PPARβ/δ suggesting that NCoR acts as a repressor for this receptor [152].

Experimental evidence indicates that PPARγ recruits SMRT and NCoR in the absence of ligand resulting in down-regulation of the receptor-mediated transcriptional activity. The PPARγ-corepressor complex was dissociated when the agonist pioglitazone was introduced. Furthermore, 3T3-L1 cells deficient in SMRT or NCoR exhibit increased expression of adipocyte-specific genes and increased production of lipid droplets, as compared with control cells [153]. Further studies have demonstrated that NCoR promotes PPARγ ser-273 phosphorylation in adipocytes by recruiting cyclin-dependent kinase 5 (Cdk5/CDK5). NCoR deletion leads to adipogenesis, reduced inflammation, and enhanced systemic insulin sensitivity [154]. Genetically modified mice with a mutation in the nuclear receptor interacting domain of SMRT exhibit a number of metabolic changes which were attributed to enhanced PPARγ activity resulting from lack of association with the mutated SMRT [155].

3.4.2. High-mobility group (HMG). High-mobility group (HMG) proteins are ubiquitous chromatin-binding proteins consisting of three family members, HMGA, HMGB, and HMGN. These proteins induce structural changes in the chromatin fiber and regulate gene transcription. A carboxy terminus rich in acidic amino acids is a feature in all HMGs but each member is characterized by a unique functional motif and participates in distinct cellular functions [156].

Studies have shown that HMGA1 is involved in vascular smooth muscle cell PPARγ-mediated transrepression, by facilitating PPARγ SUMOylation through the rate-limiting SUMO E2 ligase Ubc9. Glitazone-mediated vascular protection through PPARγ activation is lost in HMGA1-deficient mice undergoing arterial injury [157].

3.4.3. TRB3 (Tribbles homolog 3). TRB3 was identified as a mammalian homolog of *Drosophila tribbles*. It is a 354–amino acid protein involved in multiple cellular pathways. Studies have shown that TRB3 downregulates PPARγ transcriptional activities through protein-protein interaction [158]. Expression of TRB3 in 3T3-L1 adipocytes results in decreased levels of PPARγ-target gene products and knockdown of TRB3 increased expression of these genes [158]. TRB3 was also found to inhibit PPARγ-dependent adipocyte differentiation [158]. These studies have provided evidence that TRB3 acts as a corepressor of PPARγ.

3.4.4. Ligand-dependent corepressor (LCoR). LCoR is an NR box-containing protein that interacts with the ligand binding domains of agonist-bound receptors and represses hormone-dependent transactivation [159]. It is widely expressed in human tissues and in addition to its histone deacetylase activity; it functions by recruiting a variety of proteins that mediate transcriptional repression [159, 160]. The type of repressor recruited by LCoR depends on the nuclear receptor with which it interacts or on the kind of tissue involved, allowing for a differential control of gene expression [160]. Studies have demonstrated that LCoR acts as a repressor of PPARγ in splenic macrophages [161].

3.4.5. Receptor interacting protein 140 (RIP140). Also known as NRIP1 (nuclear receptor interacting protein 1), RIP140 is another ligand dependent coregulator involved in both activation and repression of NR-mediated transcription [162]. The activity of RIP140 depends on the relative level of RIP140 expression in comparison with other cofactors. Post-translational modifications and interactions with other transcription regulators are addtional factors controlling the outcome of RIP140 binding [162]. RIP140 contains nine LXXLL motifs and four repression domains and acts primarily as a platform that links NRs to chromatin remodelling enzymes [163].

RIP140 recruits HDAC and represses the activity of various nuclear receptors including PPARs by competing with their coactivators [163]. Studies have suggested that RIP140 acts as a negative counterpart of the coactivator PGC-1α, by directly interacting with PGC-1α and blocking its binding to the nuclear receptors [164]. SUMOylation of PGC-1α enhanced its sensitivity to repression by RIP140 and disruption of SUMOylation increased the capacity of PGC-1α as a coactivator for PPARγ- dependent transcription [165]. Real-time PCR analyses revealed that mRNA expressions of PPARα, PPARβ and their target genes were repressed by RIP140 and induced by PGC-1α in a dose-dependent manner in neonatal rat cardiomyocytes [166]. Additional studies have reported that RIP140 interacts with PPARγ and suppresses brown adipose specific gene transcription in white adipose tissue [103].

3.4.5. TNIP1 (TNFα-induced protein 3-interacting protein 1). In addition to its NR repressing activity, TNIP1 functions as an NF-κB inhibitor [167]. TNIP1 contains transcriptional activation and repression domains and is widely distributed suggesting that it may play an important regulatory role in multiple tissues [167]. The regulatory effect of TNIP1 depends on its expression level and the expression of other regulators in NR and/or NF-κB signaling pathways [167]. Studies have shown that TINP1 interacts with agonist-bound PPARs and partially represses the receptor transcriptional activity without total loss of receptor function [168]. TNIP1 does not interact with the PPAR heterodimer partner retinoid X receptor (RXR) even in the presence of that receptor's ligand [169].

3.4.6. TAZ (transcriptional coactivator with PDZ-binding motif). TAZ acts as a transcriptional coactivator or corepressor and modulates the differentiation of mesenchymal stem cell (MSCs) into osteoblasts or adipocytes by stimulating the transcription factor RUNX2 (runt-related transcription factor 2) and repressing PPARγ-dependent transcription [170].

Investigating mechanisms of antiadipogenic activity of PPARγ ligand, KR62980 has indicated that this compound increases the nuclear localization of TAZ and augments the interaction between PPARγ and TAZ resulting in suppression of PPARγ activity and attenuation of adipogenic gene expression. Furthermore, KR62980 failed to suppress PPARγ-mediated adipogenic gene expression and adipocyte differentiation in TAZ knockdown 3T3-L1 cells suggesting that TAZ is an important mediator of KR62980 antiadipogenic effects [171].

The dietary flavonoid kaempferol (KMP) also has been found to enhance the association of TAZ with PPARγ resulting in suppression of PPARγ target gene expression and diminishing adipocyte differentiation. The effect of KMP on PPARγ activity was impaired in TAZ-null mouse embryonic fibroblasts and was regained by restoration of TAZ expression [172]. Another compound, TM-25659, a TAZ modulator enhanced nuclear TAZ localization and attenuated PPARγ-mediated adipocyte differentiation by facilitating PPARγ suppression activity of TAZ [173]. These studies suggest that TAZ modulators may prove to be beneficial in the control of obesity.

3.4.7. Comodulators of PPAR and RXRα (COPR1 and COPR2). COPR1 and its longer variant COPR2 are apparently derived by variant splicing of the same transcript resulting in a 50 amino acid difference between the two proteins. COPR1 and COPR2 utilize the LXXLL box and target the AF-2 domains of nuclear receptors to decrease, but not to completely silence, receptor function. A proline-rich autonomous activation domain (AAD) distinguishes CORP1 and CORP2 from other ligand dependent corepressors. Studies have reported that the COPR1 isoform has greater functional interaction with PPARs than does COPR2 [174].

3.4.8. Brd2. The double bromodomain protein (Brd2) can function as either a transcriptional coactivator or corepressor and regulates gene expression by controlling the activity of transcription complexes, interpreting the histone code and remodelling chromatin structure [175]. Studies suggest that Brd2 acts as a PPARγ corepressor; since Brd2 knockdown increases PPARγ activity and facilitates adipogenesis [176].

In light of the above brief presentation on coregulators of transcription, more research is required to identify the exact physiological function(s) of each of these molecules and their complexes and to characterize structural features involved in differential regulation of PPAR target genes. Such studies are expected to yield significant information essential for understanding the roles of gene regulation in various diseases and for designing preventive and palliative approaches for these diseases.

3.5. Nongenomic pathways to PPAR effects. Nongenomic PPAR-mediated effects occur within a much shorter time frame (minutes) compared with those effects mediated through the genomic pathway (hours). The nongenomic pathways involve the interactions of PPARs with extranuclear, fast-acting second messengers, e.g., kinases [5, 6, 80, 176]. In addition to kinases, evidence has been presented showing that PPARγ may also affect the activity of phosphatases, NADH cytochrome c reductase, as well as PKCα [6]. Furthermore, the existence of extranuclear, plasma membrane PPAR receptors has been advanced to support a nongenomic effects mediated by these receptors [178].

In support of a nongenomic effects, a study has shown that PPARγ agonists of various chemical structures rapidly diminished ERK phosphorylation in human microvascular endothelial cells in parallel to their known receptor binding affinity [178]. Similarly, our recent findings showing a *fast*, PPARα-mediated, enhanced cardiac muscle contractility and blood vessel relaxation is in support of the existence of such nongenomic receptor pathways [179]. Furthermore, a most recent study has demonstrated that pioglitazone, a PPARγ agonist, rapidly reduced neuropathic pain through non-genomic PPARγ mechanisms [180]. In addition, another recent study utilizing rat cardiac ventricular myocytes has shown that the PPARβ/δ specific agonist GW0742 attenuated ERK1/2 and Akt phosphorylation, an effect which was not blocked by the specific PPARβ/δ antagonist GSK0660 but was mitigated by the tyrosine phosphatase inhibitor vanadate [181]. The latter study suggests, however, that the effect of GW0742 maybe the result of an off-target action by the ligand.

Thus, effects such as inhibition of the production of reactive oxygen species and protein phosphorylation [178, 181] may represent nongenomic pathways through which PPAR agonists exert their beneficial effects. Whether these effects involve the PPAR receptor and/or other receptor(s) or are indeed totally receptor-independent are questions that await answers at this time.

4. PPAR Ligands

All three PPARs are activated by a variety of polyunsaturated long chain fatty acids and arachidonic acid derivatives [182, 183]. In addition to these physiological substances, numerous synthetic ligands of varying selectivity bind to and activate the various PPAR subtypes.

4.1. Endogenous ligands. These ligands are naturally occurring physiologically molecules that would be expected to have binding affinity to the receptor in the nanomolar

range under physiological conditions and modulate receptor activity (Table 7).

It is imperative, however, to state that experiments designed to identify endogenous ligands should consider the fact that results obtained in *ex-vivo* testing may prove physiologically irrelevant, unless evidence is presented showing that the intracellular concentration and location of the presumed endogenous agonist is consistent with physiological conditions. Therefore, whether many of these compounds satisfy the criteria of actual endogenous PPAR ligands remains to be determined.

4.1.1. PPARα. An example of the proposed endogenous ligands for this receptor is 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine; a FAS-dependent phosphatidylcholine [184]. While this molecule activates hepatic PPARα, arachidonic acid derivatives, e.g., Leukotriene B4 have strong PPARα-binding in immune cells [185].

Furthermore, oxidized phospholipids exert a phospholipase A2-dependent activation of PPARα in endothelial cells, suggesting that these phospholipids may be precursors of endogenous ligands [186]. In addition to the above physiological ligands, endocannabinoids are natural lipids included among endogenous PPARα ligands. Some endocannabinoids bind with relatively high affinity to PPARα and regulate lipid and glucose metabolism, as well as inflammatory responses [187]. *In vitro* experiments have identified other PPARα ligands including (8S)-hydroxyeicosatetraenoic acids, carbaprostacyclin and unsaturated fatty acids [188]. The physiological relevance of these findings is yet to be elucidated.

4.1.2. PPARβ/δ. Studies have demonstrated that PPARβ/δ is activated by prostacyclin (PGI2) [189–191]. In addition, experiments have demonstrated that although the vitamin A metabolite all-trans-retinoic acid (RA) binds to PPARα and PPARγ with a low affinity, this compound has a high affinity to PPARβ/δ [192]. C16 and C18 fatty acids have also been suggested as potential endogenous ligands for PPARβ/δ [193]. 4-hydroxynonenal (4-HNE), a lipid peroxidation product has also been reported as an endogenous ligand for PPARβ/δ [194].

4.1.3. PPARγ. Although PPARγ can be activated by prostaglandinJ2 (PGJ2) as well as by polyunsaturated and oxidized fatty acids, these compounds bind the receptor with low affinity [16]. Other PPARγ endogenous ligands have been described in more recent studies, including nitro-derivatives of unsaturated fatty acids [195], serotonin metabolites [196], farnesyl pyrophosphate [197] and some endocannabinoids [187]. Cyclic phosphatidic acid has been identified as an endogenous PPARγ antagonist [198].

4.2. Exogenous PPAR modulators.

4.2.1. Fibrates. Clofibrate was approved in the United States for the treatment of hyperlipidemia in 1967 [17]. Later it was noted that individuals with type 2 diabetes taking clofibrate for treatment of hyperlipidemia showed reduction in fasting blood glucose concentration [199]. Intensive research resulted in the discovery of fenofibrate [200]; demonstrated to be superior to clofibrate as a hypolipidemic agent. In the late 1970s and early 1980s, other fibrates, gemfibrozil, bezafibrate and ciprofibrate, were also introduced, and the beneficial cardiovascular effects of these drugs lead to their wide clinical use.

4.2.2. Glitazones. Thiazolidinediones, also referred to as glitazones were discovered in the 1980s [201, 202]. Beside its hypolipidemic effect, ciglitazone was shown to normalize hyperglycemia and hyperinsulinemia in animal models of type 2 diabetes [203, 204]. The antidiabetic effect of ciglitazone, however, was too weak for clinical application. In addition, edema was found to be a significant problem associated with this agent.

In search for more potent insulin sensitizers with less serious side effects, two other glitazones, troglitazone [205] and rosiglitazone [206], were developed. However, troglitazone was rapidly withdrawn from the market because of its liver toxicity [207]. Rosiglitazone which normalizes blood glucose levels and improves tissue sensitivity to insulin with more potency and more selectivity than ciglitazone [208] was approved for clinical use in the United States in 1999 [17]. Unfortunately, due to association with significant side effects including weight gain, congestive heart failure and fluid retention, rosiglitazone was banned from the European market in 2010, while in the United State, the Food and Drug Administration limited its use to situations in which other medications are not effective, a decision that was later repealed in late 2013.

Pioglitazone was synthesized and evaluated for hypolipidemic and hypoglycemic activities. Clinical studies revealed that pioglitazone ameliorates the glucose and lipid profile of patients with type-2 diabetes. Although this drug is orally active, well tolerated and provides beneficial effects on insulin resistance [17], association with an increased incidence of bladder cancer has been raised.

4.2.3. Allosteric ligands. Interaction between a receptor and its ligands is traditionally considered to occur at the endogenous agonist-binding site in the receptor, the *orthosteric site* [209, 210]. However, there has been a marked increase in the discovery of ligands that interact with alternate sites on receptors, *allosteric sites* [209, 211–213]. Binding of ligands to these allosteric sites results in modifying the conformation of the receptor, with significant consequences related to its activity [209].

Table 7: Some Postulated PPAR Endogenous Ligands[a].

PPARα	PPARβ/δ	PPARγ
Endocannabinoids	All *trans* retinoic acid	Endocannabinoids
8-Hydroxyeicosatetraenoic acid (8-HETE)	Arachidonic acid	Farnesylpyrophosphates
Leukotrienen B4	Docahexanoic acid	15-Hydroxyeicosatetraenoic acid (15-HETE)
Oleoylethanolamide	4-Hydroxynonenal	13-Hydroxyoctadecadienoic acid (13-HODE)
Oxidized phospholipids	Prostacyclin	5-Hydroxyindole acetate
1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphatocholine	Linoleic acid	5-Methoxyindole acetate Nitro derivatives of unsaturated fatty acids Nitrolinoleic acid

[a][301, 302].

Although in comparison with other classes of receptors, developing allosteric ligands for nuclear receptors is lagging behind, efforts are in earnest to develop such ligands for various members of this receptor superfamily, including PPARs. In 2000, Camp et al., [214] observed that while only troglitazone was a partial agonist in transfected muscle and kidney cells, rosiglitazone, pioglitazone and ciglitazone exerted full agonistic effects. Furthermore, troglitazone and rosiglitazone produced different states of receptor conformation to a degree that allowed troglitazone to antagonize rosiglitazone-stimulated PPARγ transcriptional activity [214]. This effect was confirmed by limited protease digestion studies of PPARγ bound to either ligand as well as by in vitro coactivator association assays [214]. Although these surprising results were explained by possible agonist-induced variations in the affinity of cofactors to the receptor, the potential presence of PPARγ isoforms and/or undefined cell transfection-associated events, the possibility of different troglitazone and rosiglitazone binding sites was not raised by these authors [214]. More recently, however, the fact that agonists of both PPARα and RXRα exerted a synergistic effect on the activity of the PPARα/RXRα heterodimer lead investigators to speculate that there may be an allosteric communication between these two obligatory partner receptors in the heterodimer [215]. Indeed, molecular dynamic simulations as well as experimental evidence have revealed that RXRα ligands stabilize the PPARα coactivator binding site, via an *allosteric* effect that impacts the PPARα/RXRα heterodimer activity [215].

Subsequently, a novel *alternate* PPARγ ligand binding site was most recently identified [216]. These authors [216] have shown that, at pharmacologically relevant concentrations, synthetic PPARγ ligands bind to an *allosteric* receptor site, leading to unique receptor conformational changes that influence the receptor transactivation and target gene expression [216]. The reported ligand-receptor binding was not blocked by either antagonists or by endogenous agonists, indicating that binding was not occurring at the *orthosteric site* [216].

Since various known PPARγ agonists have shown varying potencies and/or efficacies in binding to the described receptor *allosteric site* [216], it is likely that these agonists will exert a corresponding range of different receptor conformation states and subsequent transcriptional activity. Thus, this relatively new allosteric binding and the documented subsequent alteration in receptor function have substantial promising implications for future drug discovery in the field of PPARs.

It is noteworthy in this regards to refer to a reported evidence pointing to the fact that a PPARγ ligand with minimal known agonistic activity exerted an antidiabetic effect comparable to, or better than, that produced by a full agonist [79]. This effect could not therefore be explained based on the classical concept of agonist-receptor interaction, but was explained by the ability of these ligands to inhibit the receptor-protein-phosphorylation at serine 273 by cdk5, through altering the receptor conformation making serine 273 inaccessible to the kinase [79]. The involvement of an *alternate* receptor binding site in the effect of the PPARγ ligand with minimal agonistic activity remains a possibility in attempting to explain its superior effect to the full agonist. This is particularly plausible in light of the fact that this agonist did induce receptor conformational changes that are different from those produced by the full agonist [79].

5. The Future of PPARs

5.1. Challenges facing PPAR research. Because PPARs control a plethora of cell functions in various organs, a variety of adverse effects may arise as a consequence of the activation or inhibition of these receptors. Indeed, significant therapeutic as well as toxicological profile differences have been observed with various PPAR agonists, presenting major challenges to researchers in the field.

5.1.1. PPARα. The PPARα agonists, fibrates, represent a valuable class of drugs for the treatment of dyslipidemia [217]. These drugs are generally well tolerated, and infrequently associated with major safety concerns [218]. To highlight a few untoward effects encountered with fibrates, one would have to refer, albeit rarely, to myopathy as the most serious safety risk associated with these drugs [219]. Furthermore, although some clinical trials have demonstrated a significant reduction in nonfatal myocardial infarction in

fibrate users, others have noted increases in cardiovascular and total mortality; a finding that has resulted in FDA-mandated warning about mortality in the fibrate package insert [218]. In addition, a small, but statistically significant, increased risk for pulmonary embolism and deep venous thrombosis due to fenofibrate has been reported [219]. Treatment with fibrates is also known to cause an increase in plasma homocysteine levels that increases the risk for hypercoagulability and coronary, cerebral, or peripheral vascular disease [218]. In addition, a higher incidence of pancreatitis has also been observed in patients treated with fenofibrate [200], and an increase in creatinine has been noted with other fibrates [218]. Furthermore, all fibrates appear to have the propensity to cause gallbladder disease [219].

5.1.2. PPARγ. Increased rates of bone fractures in women taking the PPARγ agonist, rosiglitazone has been reported and this effect was not observed in men [220]. Also, an increase in myocardial infarction with rosiglitazone versus placebo or other antidiabetic drugs, with no increase in mortality, has been observed [221]. The concern about the cardiovascular safety of rosiglitazone was confirmed by an internal FDA meta-analysis as well as in other studies [222–230]. Conversely, the RECORD study (rosiglitazone evaluated for cardiac outcomes and regulation of glycemia in diabetes) trial [231], one of the most important studies on the rosiglitazone cardiovascular safety issue [232], showed no increase in the primary endpoint of hospitalization or death from cardiovascular causes with rosiglitazone. Other studies [233–235] failed to observe this risk with rosiglitazone. However, these studies were also criticized for several limitations [232].

In July 2010, the FDA re-evaluated rosiglitazone cardiovascular safety data and a new internal FDA meta-analysis showed that total myocardial ischemia was significantly increased in patients receiving rosiglitazone [232]. A repeat meta-analysis by Nissen and Wolski also showed a similar trend [236] and other meta- as well as observational studies provided more evidence for increased cardiovascular events with rosiglitazone [225, 232]. Based on these discoveries, the FDA announced the restricted availability of rosiglitazone a decision that was rescinded in late 2013, based on the reevaluation of the RECORD trial [237]. In contrast, the European Medicines Agency has completely withdrawn rosiglitazone from the market [232], an action that remains in effect to date.

Weight gain is also a known side effect of glitazone treatment [238–240], an effect that is due to increased adipogenesis in the subcutaneous fat depot [241, 242] as well as due to fluid retention [243].

Clinical trials have shown that pioglitazone increases rates of congestive heart failure (CHF). This effect is further increased when pioglitazone is combined with insulin [232]. This untoward effect has prompted The American Diabetes Association and the American Heart Association to recommend against the use of any glitazone in patients with known class III or IV CHF [232]. It is generally accepted however, that pioglitazone does not cause an increase in myocardial infarction and may actually reduce the number of myocardial infarction and strokes [244].

A nonsignificant trend towards increased bladder cancer in patients treated with pioglitazone has been reported [232]. As a precaution, The FDA has recommended that pioglitazone should not be used in patients with active bladder cancer. It is also recommended that caution should be exercised in prescribing pioglitazone to patients with a history of bladder cancer, and that patients on a pioglitazone regimen should be informed of the signs and symptoms of bladder cancer [232].

Pioglitazone has also been associated with increased bone fracture risk, but to a lesser extent than rosiglitazone. Thus, despite the lack of guidelines limiting pioglitazone use as a result of this effect, restricting the use of pioglitazone in patients with low bone density has been suggested [232].

Although data from clinical trials have not shown liver toxicity in patients using pioglitazone, some cases of liver failure associated with the use of this drug have been reported [232]. Consequently and as a precaution, the pioglitazone package contains a recommendation to examine hepatic functions prior to the initiation of treatment [232].

Pioglitazone may also contribute to increased diabetic macular edema probably due to fluid overload [245]. In addition, mild but statistically significant decreases in hemoglobin have been observed after extended treatment with pioglitazone [246]. The decreases in hematologic parameters were not sufficient, however, to impose a limitation on the use of this drug [232].

PPARα/γ dual agonists, muraglitazar, ragaglitazar, and tesaglitazar, were initially considered promising, but alarming side effects observed during their development have diminished enthusiasm for these drugs [247]. In addition, a meta-analysis of phase II and phase III clinical trials has shown that muraglitazar increased the composite risk of nonfatal myocardial infarction, nonfatal stroke, or all-cause mortality in diabetic patients compared with pioglitazone [248]. Furthermore, ragaglitazar showed significant carcinogenic effects in rodent bladders and is no longer under development for human use [249]. Similarly, tesaglitazar's development was discontinued because it severely increased serum creatinine in diabetic patients [250].

5.1.3. PPARδ. Preclinical and short-term clinical studies have demonstrated that PPARβ/δ agonists were benefecial in the treatment of type 2 diabetes mellitus and other conditions. However, issues concerning the connection between PPARβ/δ agonists and carcinogenesis, observed in animal models, necessitate further preclinical and when deemed appropriate, long-term clinical trials to determine the suitability of these agonists for human use [251].

Based on the above findings, it is feasible to conclude that drugs modulating PPAR activity require careful examination, through extensive preclinical and clinical studies, in order to determine benefit to risk ratios that are expected as a result of using these drugs in disease management.

5.2. The promise of PPAR modulators. PPARs have been identified as key regulators in a number of important diseases, physiological and pathological conditions such as diabetes [253, 254], inflammation [254–256], immunity [257–259], pain [260], regulation of male and female fertility [261, 262], obesity [263–265], senescence and senescence-related diseases [266–269], as well as various types of cancer [270–272]. Furthermore, novel PPAR functions are still being discovered and significant new elements in their signal transduction pathways continue to be identified. Consequently, these receptors remain as important potential pharmacological targets for the treatment of a variety of diseases and conditions such as epilepsy [273], drug addiction [274] and Alzheimer's disease [275].

5.2.1. Selective PPAR modulators (SPPARMs). There are efforts aimed at identifying selective PPAR modulators (SPPARMs) to optimize benefit and minimize the toxic effects imparted by full PPAR agonists [276]. Since adverse effects encountered in patients treated with full PPAR agonists may be attributed to the wide spectrum of affected genes, the use of partial PPAR agonism may be a plausible approach to provide a desirable therapeutic outcome [276]. It is reported that a new generation of highly potent and selective PPAR modulators is being developed with the goal of separating their benefits from their unwanted side effects. Among these modulators is aleglitazar [277].

Aleglitazar is a dual PPARα/γ agonist (Figure 5); thus possesses the potential to treat diabetes and dyslipidemia simultaneously. Although preliminary data had shown improvement in hyperglycemia, dyslipidemia and blood pressure in type 2 diabetic patients treated with this drug [247], it is unfortunate that a large study, *AleCardio*, has recently concluded that this drug did not reduce cardiovascular risk in patients suffering from type 2 diabetes and acute coronary syndrome [278]. Additional studies are needed to ascertain the clinical promise as well as safety of similar drugs [279].

In addition to aleglitazar, a short-term study has shown that INT131, a SPPARγM, did not cause fluid retention or weight gain, but reduced fasting plasma glucose to level comparable to that reached with rosiglitazone [277]. Furthermore, GFT505, a dual PPARα/δ agonist, has also recently entered late-phase development [277]. In experimental studies, PPARγ/δ agonists have shown beneficial effects in managing dyslipidemia. These agonists may also cause less weight gain than rosiglitazone [280].

Balaglitazone, a PPARγ partial agonist developed in India, is reported to currently be undergoing a phase III clinical trial [281]. In comparison to full PPARγ agonists, preclinical studies have shown that balaglitazone caused no reduction in bone density and caused less fluid retention and heart enlargement [281, 282]. While these findings are an encouraging indicator of a better safety profile for balaglitazone, further testing is required before ascertaining risks associated with long-term use of this drug.

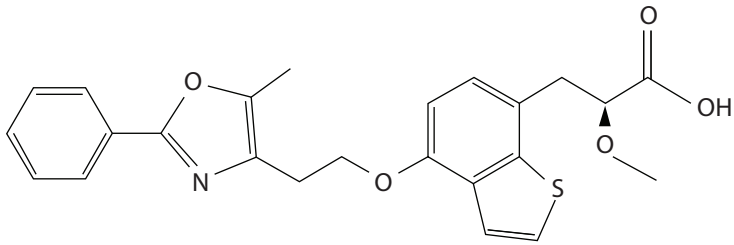
Recently, two selective PPARγ ligands, INT131, and F12016, have been identified [283, 284]. While INT131 has been found to possess an improved hemodynamic and less cardiovascular adverse effects, F12016 exhibited a suppressed ability to cause weight gain, compared to the full agonist rosiglitazone [283, 284]. Both of these ligands induce a distinct pattern of coregulator recruitment by the receptor, and their binding to the PPARγ receptor does not involve Tyr473; a characteristic which is essential for the rosiglitazone-induced receptor activation [283, 284].

Further clinical studies are still needed before these drugs can gain approval for the treatment of diabetes associated with vascular complications.

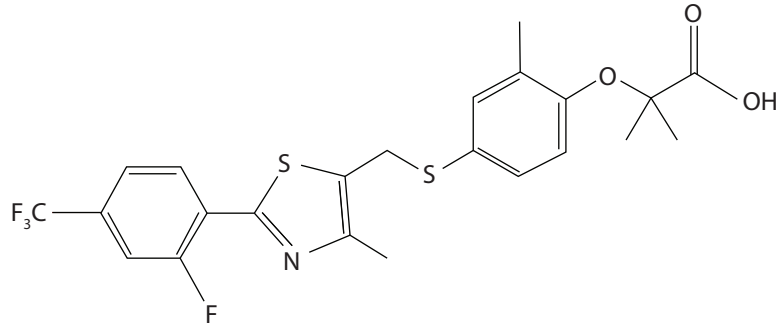
With the advent of the relatively recent discovery of PPAR receptor allostery and allosteric ligands, the field is now poised for a renewed surge in enthusiasm and effort to develop novel PPAR-centered therapies for many diseases. This discovery is hoped to lead to the development of a new class of PPAR modulators, allosteric ligands, which possess more targeted pharmacological effects, combined with less toxicity, compared with the canonical ligands

5.2.2. Other potential therapeutic values of PPAR agonists. The wide spectrum and large number of proposed beneficial uses and various clinical trials utilizing PPAR modulators provide a strong evidence in support of the promise these receptors hold as crucial targets of future novel effective therapies against numerous diseases. For example, it has been shown that endurance exercise training increases the proportion of oxidative fibers in the muscle and enhances the capacity for exercise [285]. While this effect is reported to be mediated by PPARβ/δ through enhanced receptor expression in response to exercise [286–288], studies have also demonstrated that activation of PPARβ/δ can reprogram muscle metabolism and increase endurance in sedentary animals, leading to the suggestion that PPARβ/δ agonists as potential exercise mimetic drugs [289]. However, while the use of PPARβ/δ agonists may provide some benefits in treating certain muscle as well as metabolic diseases, when physical exercise is not an option, caution must be practiced before using these drugs as a routine alternative to exercise in light of their potential other known undesirable effects.

In addition, there are several clinical trials looking into expanding the utilization of PPAR agonists in treating more diseases and conditions. For example, current trials are examining the outcome of treatment with various PPAR agonists on dementia, mental disorders, and cognition [290]. In addition, there is a clinical trial examining the effect of CS7017, an experimental PPARγ agonist, in subjects with



Aleglitazar, a dual PPARα and PPARγ agonist



Sodelglitazar, a pan PPAR agonist

Figure 5: Representative Dual and Pan PPAR Agonists.

stage IIIb/IV non-small cell lung cancer [290]. Another trial, currently in phase II, is investigating the impact of the same agonist in subjects with advanced anaplastic thyroid cancer [290].

Beyond the aforementioned, there are numerous trials evaluating the potential therapeutic benefits of the antidiabetic, PPARγ agonist pioglitazone, in diseases other than diabetes. For example, there is a phase III clinical trial evaluating the benefit of this PPARγ agonist in the treatment of Alzheimer's disease [275]. It has been recently reported that pioglitazone restored memory deficit and brain BDNF levels in animals treated with β-amyloid [291], suggesting an antioxidant, anti-inflammatory, ant apoptotic, as well as a neurogenesis-like effect by this agonist.

Another trial is looking also into the effect of pioglitazone in rheumatoid arthritis [290]. In another trial, the effect of the same PPARγ agonist is being evaluated against asthma [292], while in a fourth trial it is being evaluated in patients addicted to heroin and nicotine [290]. Additionally, the effects and safety of pioglitazone on non-alcoholic fatty liver disease are currently undergoing evaluation in patients with impaired glucose regulation or type 2 diabetes mellitus [283]. Furthermore, a phase III trial is exploring the effects of pioglitazone on neurological functions in Friedreich's ataxia patients [290], and the effect of this PPARγ agonist on insulin and glucose metabolism in women with polycystic ovary syndrome is also under evaluation [290].

5.2.3. Beyond diabetes control: *Endosalicylates*: a hypothesis to explain PPAR-mediated anti-inflammatory effects. Aside from the well-established clinical benefit of PPAR agonists as hypolipidemics and insulin sensitizers in treating type II diabetes, there are numerous trials exploring the promise of these drugs in treating a myriad of additional diseases and conditions. For example, experimental and clinical findings over the last decade have provided evidence demonstrating that PPARs modulate both acute and chronic inflammation [292]. However, the mechanism through which PPARs control inflammatory events remains unclear. In an attempt to evoke a conversation among interested scientists to ultimately reach a rational, scientifically sound understanding, we present below a hypothesis of how these receptors may control a myriad of inflammatory diseases.

When we compared the profile of the anti-inflammatory effect produced by PPARα or PPARγ agonists with those exhibited by dexamethasone or aspirin, only PPAR agonists and aspirin were found to diminish inflammation when given after the inflammatory insult [293]. Furthermore, in contrast to aspirin, only dexamethasone produced an additive anti-inflammatory effect when administered in combination with an agonist of either PPARα or PPARγ [294]. Based on these findings we hypothesize that PPARα and PPARγ regulate inflammation through a mechanism similar to that ascribed to salicylates, while different from that ascribed to steroids.

The literature reveals that while salicylates alleviate peripheral inflammation and hyperalgesia *via* an action in the

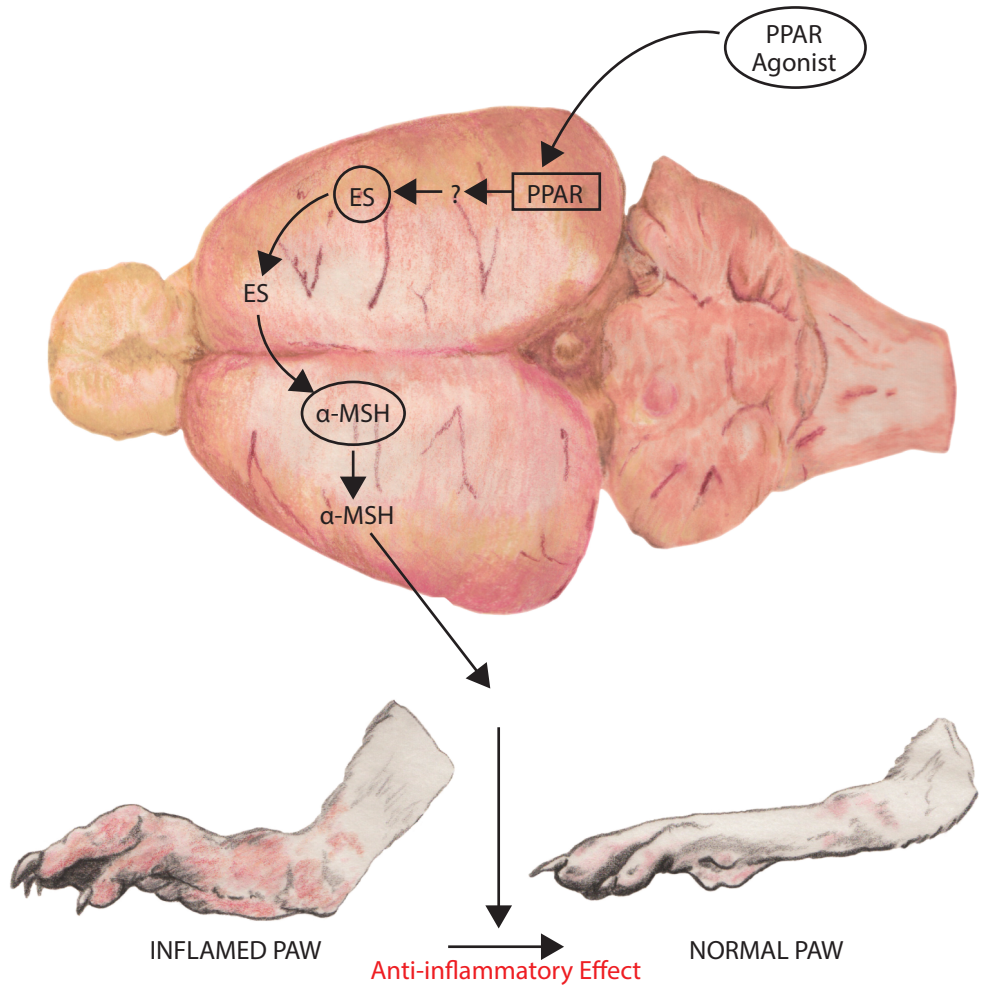


Figure 6: A Schematic Depiction of the *Endosalicylate* Hypothesis.

central nervous system, dexamethasone does not. Considering the fact that PPARs are abundant in the central nervous system [294, 295] and that we have previously documented that, like aspirin, PPAR agonists act centrally to produce their peripheral anti-inflammatory and analgesic effects [293–296], an interplay between salicylates and PPAR-mediated anti-inflammatory effect is hereby postulated. Since salicylates do not activate PPARs [297], the possibility that PPARs may mediate the aspirin effect is thus excluded. Alternatively, a *salicylate-like effect* by PPAR agonists presents itself at the forefront of plausible hypotheses. This *salicylate-like effect* may be through a direct effect on the cyclooxygenase enzyme by PPAR agonists, or through invoking a PPAR-dependent release of a *salicylate-like compound*, an *endosalicylate,* which in turn, would exert the observed anti-inflammatory effect (Figure 6). A direct or indirect role for the cyclooxygenase enzyme is highly unlikely since PPAR agonists failed to affect inflammation when administered at the inflammation site [293]. Thus, since intracerebroventricular administration of salicylates has been reported to elicit the release of physiological anti-inflammatory mediators (e.g., α-melanocyte-stimulating hormone) from the central nervous system, which in turn may exert a peripheral anti-inflammatory effect [298, 299], we hypothesize that: (1) activating PPARs in the central nervous system may elicit the release of a *salicylate-like compound*, an *endosalicylate,* (2) the released *endosalicylate compound* may subsequently cause the release of a physiological anti-inflammatory substance, e.g., α-melanocyte-stimulating hormone, or other substances, in the central nervous system and (3) The *central* anti-inflammatory

mediator may then reach the peripheral inflammation site where it would act to resolve inflammation (Figure 6). Validation of this hypothesis, including the identification of the proposed *endosalicylate* as well as localizing its exact site in the central nervous system, obviously requires extensive experimental testing.

6. Concluding Remarks

In this review, we attempted to give the reader a quick glance at the field of PPAR research, starting with a historic perspective looking at the events that lead to their discovery. Also, we briefly sketched the structural traits of these receptors and how they exert their multifaceted functions. In addition, we presented a summary of the known receptor endogenous as well as exogenous ligands and coregulators. Finally, we shared a provocative hypothesis stipulating that PPAR agonists cause a PPAR-mediated release of putative substance we termed *endosalicylates*, which is responsible for the known anti-inflammatory effects of these agonists.

References

[1] I. Issemann and S. Green, Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators, *Nature*, **347**, 645–650, (1990).

[2] J. Berger and D. E. Moller, The mechanisms of action of PPARs, *Annu Rev Med*, **53**, 409–435, (2002).

[3] S. A. Kliewer, H. E. Xu, M. H. Lambert, and T. M. Willson, PPAR from gene to Physiology, *Recent Prog Horm Res*, **56**, 239–263, (2001).

[4] A. Bugge and S. Mandrup, Molecular Mechanisms and Genome-Wide Aspects of PPAR Subtype Specific Transactivation, *PPAR Res*, **2010**, Article ID 169506, 1–12, (2010).

[5] G. Cantini, A. Lombardi, E. Borgogni, et al., Peroxisome-proliferator-activated receptor gamma (PPARgamma) is required for modulating endothelial inflammatory response through a nongenomic mechanism, *Eur J Cell Biol*, **89**, 645–653, (2010).

[6] M. Luconi, G. Cantini, and M. Serio, Peroxisome proliferator-activated receptor gamma (PPARgamma): is the genomic activity the only answer? *Steroids*, **75**, 585–594, (2010).

[7] J. K. Reddy and T. P. Krishnakantha, Hepatic peroxisome proliferation: induction by two novel compounds structurally unrelated to clofibrate, *Science*, **190**, 787–789, (1975).

[8] N. D. Lalwani, W. E. Fahl, and J. K. Reddy, Detection of a nafenopin-binding protein in rat liver cytosol associated with the induction of peroxisome proliferation by hypolipidemic compounds, *Biochem Biophys Res Commun*, **116**, 388–393, (1983).

[9] N. D. Lalwani, K. Alvares, M. K. Reddy, M. N. Reddy, I. Parikh, and J. K. Reddy, Peroxisome proliferator-binding protein: identification and partial characterization of nafenopin-, clofibric acid-, and ciprofibrate-binding proteins from rat liver, *Proc Natl Acad Sci USA*, **84**, 5242–5246, (1987).

[10] K. Alvares, A. Carrillo, P. M. Yuan, H. Kawano, R. I. Morimoto, and J. K. Reddy, Identification of cytosolic peroxisome proliferator binding protein as a member of the heat shock protein HSP70 family, *Proc Natl Acad Sci USA*, **87**, 5293–5297, (1990).

[11] Q. Huang, K. Alvares, R. Chu, C. A. Bradfield, and J. K. Reddy, Association of peroxisome proliferator-activated receptor and Hsp72, *J Biol Chem*, **269**, 8493–8497, (1994).

[12] M. Göttlicher, E. Widmark, Q. Li, and J. A. Gustafsson, Fatty acids activate a chimera of the clofibric acid-activated receptor and the glucocorticoid receptor, *Proc Natl Acad Sci USA*, **89**, 4653–4657, (1992).

[13] A. Schmidt, N. Endo, S. J. Rutledge, R. Vogel, D. Shinar, and G. A. Rodan, Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids, *Mol Endocrinol*, **6**, 1634–1641, (1992).

[14] C. Dreyer, G. Krey, H. Keller, F. Givel, G. Helftenbein, and W. Wahli, Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors, *Cell*, **68**, 879–887, (1992).

[15] S. A. Kliewer, S. S. Sundseth, S. A. Jones, et al., Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ, *Proc Natl Acad Sci USA*, **94**, 4318–4323, (1997).

[16] B. M. Forman, J. Chen, and R. M. Evans, Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta, *Proc Natl Acad Sci USA*, **94**, 4312–4317, (1997).

[17] F. Lalloyer and B. Staels, Fibrates, glitazones, and peroxisome proliferator-activated receptors, *Arterioscler Thromb Vasc Biol*, **30**, 894–899, (2010).

[18] P. Gervois, I. P. Torra, G. Chinetti, et al., A truncated human peroxisome proliferator-activated receptor alpha splice variant with dominant negative activity, *Mol Endocrinol*, **13**, 1535–1549, (1999).

[19] C. N. Palmer, M. H. Hsu, K. J. Griffin, J. L. Raucy, and E. F. Johnson, Peroxisome proliferator activated receptor-alpha expression in human liver, *Mol Pharmacol*, **53**, 14–22, (1998).

[20] A. Sapone, J. M. Peters, S. Sakai, et al., The human peroxisome proliferator-activated receptor alpha gene: identification and functional characterization of two natural allelic variants, *Pharmacogenetics*, **10**, 321–333, (2000).

[21] D. M. Flavell, I. Pineda Torra, Y. Jamshidi, et al., Variation in the PPARalpha gene is associated with altered function in vitro and plasma lipid concentrations in Type II diabetic subjects, *Diabetologia*, **43**, 673–680, (2000).

[22] E. S. Koytak, D. Mizrak, M. Bektaş, et al., PPAR-alpha L162V polymorphism in human hepatocellular carcinoma, *Turk J Gastroenterol*, **19**, 245–249, (2008).

[23] H. Naito, O. Yamanoshita, M. Kamijima, et al., Association of V227A PPARalpha polymorphism with altered serum biochemistry and alcohol drinking in Japanese men, *Pharmacogenet Genomics*, **16**, 569–577, (2006).

[24] S. Chen, Y. Li, S. Li, and C. Yu, A Val227Ala substitution in the peroxisome proliferator activated receptor alpha (PPAR alpha) gene associated with non-alcoholic fatty liver disease and decreased waist circumference and waist-to-hip ratio, *J Gastroenterol Hepatol*, **23**, 1415–1418, (2008).

[25] K. Lundell, P. Thulin, A. Hamsten, and E. Ehrenborg, Alternative splicing of human peroxisome proliferator-activated receptor delta (PPAR delta): effects on translation efficiency and trans-activation ability, *BMC Mol Biol*, **8**, p. 70, (2007).

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

[27] I. Jguirim-Souissi, A. Jelassi, Y. Hrira, et al., +294T/C polymorphism in the PPAR-delta gene is associated with risk of coronary artery disease in normolipidemic Tunisians, *Genet Mol Res*, **9**, 1326–1333, (2010).

[28] J. Skogsberg, A. D. McMahon, F. Karpe, A. Hamsten, C. J. Packard, and E. Ehrenborg, Peroxisome proliferator activated receptor delta genotype in relation to cardiovascular risk factors and risk of coronary heart disease in hypercholesterolaemic men, *J Intern Med*, **254**, 597–604, (2003).

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

[30] P. Christopoulos, G. Mastorakos, M. Gazouli, et al., Peroxisome proliferator-activated receptor-γ and -δ polymorphisms in women with polycystic ovary syndrome, *Ann NY Acad Sci*, **1205**, 185–191, (2010).

[31] P. Tontonoz, E. Hu, R. A. Graves, A. I. Budavari, and B. M. Spiegelman, mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer, *Genes Dev*, **8**, 1224–1234, (1994).

[32] A. Meirhaeghe, L. Fajas, F. Gouilleux, et al., A functional polymorphism in a STAT5B site of the human PPAR gamma 3 gene promoter affects height and lipid metabolism in a French population, *Arterioscler Thromb Vasc Biol*, **23**, 289–294, (2003).

[33] C. J. Yen, B. A. Beamer, C. Negri, et al., Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation, *Biochem Biophys Res Commun*, **241**, 270–274, (1997).

[34] B. A. Beamer, C. J. Yen, R. E. Andersen, et al., Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma2 gene with obesity in two Caucasian populations, *Diabetes*, **47**, 1806–1808, (1998).

[35] M. M. Swarbrick, C. M. Chapman, B. M. McQuillan, J. Hung, P. L. Thompson, and J. P. Beilby, A Pro12Ala polymorphism in the human peroxisome proliferator-activated receptor-gamma 2 is associated with combined hyperlipidaemia in obesity, *Eur J Endocrinol*, **144**, 277–282, (2001).

[36] D. Evans, J. de Heer, C. Hagemann, et al., Association between the P12A and c1431t polymorphisms in the peroxisome proliferator activated receptor γ (PPARγ) gene and type 2 diabetes, *Exp Clin Endocrinol Diabetes*, **109**, 151–154, (2001).

[37] C. W. Danawati, M. Nagata, H. Moriyama, et al., A possible association of Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma2 gene with obesity in native Javanese in Indonesia, *Diabetes Metab Res Rev*, **21**, 465–469, (2005).

[38] M. B. Mohamed, N. Mtiraoui, I. Ezzidi, M. Chaieb, T. Mahjoub, and W. Y. Almawi, Association of the peroxisome proliferator-activated receptor-gamma2 Pro12Ala but not the C1431T gene variants with lower body mass index in Type 2 diabetes, *J Endocrinol Invest*, **30**, 937–943, (2007).

[39] M. D. Brown, A. R. Shuldiner, R. E. Ferrell, et al., FABP2 genotype is associated with insulin sensitivity in older women, *Metabolism*, **50**, 1102–1105, (2001).

[40] A. S. Doney, B. Fischer, J. E. Cecil, et al., Association of the Pro12Ala and C1431T variants of PPARG and their haplotypes with susceptibility to Type 2 diabetes, *Diabetologia*, **47**, 555–558, (2004).

[41] E. Morini, V. Tassi, D. Capponi, et al., Interaction between PPARγ2 variants and gender on the modulation of body weight, *Obesity*, **16**, 1467–1470, (2008).

[42] G. V. Huguenin and G. Rosa, The Ala allele in the PPAR-gamma2 gene is associated with reduced risk of type 2 diabetes mellitus in Caucasians and improved insulin sensitivity in overweight subjects, *Br J Nutr*, **104**, 488–497, (2010).

[43] W. Johnson, S. E. Harris, J. M. Starr, L. J. Whalley, and I. J. Deary, PPARG Pro12Ala genotype and risk of cognitive decline in elders? Maybe with diabetes, *Neurosci Lett*, **434**, 50–55, (2008).

[44] A. M. Koivisto, S. Helisalmi, J. Pihlajamaki, et al., Association analysis of peroxisome proliferator-activated receptor gamma polymorphisms and late onset Alzheimer's disease in the Finnish population, *Dement Geriatr Cogn Disord*, **22**, 449–453, (2006).

[45] M. Catalano, A. Cortelazzo, R. Santi, et al., The Pro12Ala polymorphism of peroxisome proliferator-activated receptor-gamma2 gene is associated with plasma levels of soluble RAGE (Receptor for Advanced Glycation Endproducts) and the presence of peripheral arterial disease, *Clin Biochem*, **41**, 981–985, (2008).

[46] A. Bazargani, S. S. Khoramrooz, E. Kamali-Sarvestani, S. A. Taghavi, and M. Saberifiroozi, Association between peroxisome proliferator-activated receptor-γ gene polymorphism (Pro12Ala) and Helicobacter pylori infection in gastric carcinogenesis, *Scand J Gastroenterol*, **45**, 1162–1167, (2010).

[47] T. Tahara, T. Arisawa, T. Shibata, et al., Influence of peroxisome proliferator-activated receptor (PPAR)γ Plo12Ala polymorphism as a shared risk marker for both gastric cancer and impaired fasting glucose (IFG) in Japanese, *Digestive Diseases and Sciences*, **53**, 614–621, (2007).

[48] K. N. Prasad, A. Saxena, U. C. Ghoshal, M. R. Bhagat, and N. Krishnani, Analysis of Pro12Ala PPAR gamma polymorphism and Helicobacter pylori infection in gastric adenocarcinoma and peptic ulcer disease, *Ann Oncol*, **19**, 1299–1303, (2008).

[49] K. R. Hwang, Y. M. Choi, J. M. Kim, et al., Association of peroxisome proliferator-activated receptor-gamma 2 Pro12Ala polymorphism with advanced-stage endometriosis, *Am J Reprod Immunol*, **64**, 333–338, (2010).

[50] A. Meirhaeghe, L. Fajas, N. Helbecque, et al., A genetic polymorphism of the peroxisome proliferator-activated receptor gamma gene influences plasma leptin levels in obese humans, *Hum Mol Genet*, **7**, 435–440, (1998).

[51] M. Koch, K. Rett, E. Maerker, et al., The silent PPARγ exon 6 CACHis —> CATHis polymorphism does not affect the plasma leptin levels in a collective of first degree relatives of type 2 diabetes patients from South West Germany, *Exp Clin Endocrinol Diabetes*, **108**, 341–346, (2000).

[52] R. Valve, K. Sivenius, R. Miettinen, et al., Two polymorphisms in the peroxisome proliferator-activated receptor-gamma gene are associated with severe overweight among obese women, *J Clin Endocrinol Metab*, **84**, 3708–3712, (1999).

[53] A. Doney, B. Fischer, D. Frew, et al., Haplotype analysis of the PPARgamma Pro12Ala and C1431T variants reveals opposing associations with body weight, *BMC Genet*, **3**, p. 21, (2002).

[54] E. S. Tai, D. Corella, M. Deurenberg-Yap, et al., Differential effects of the C1431T and Pro12Ala PPARgamma gene variants on plasma lipids and diabetes risk in an Asian population, *J Lipid Res*, **45**, 674–685, (2004).

[55] A. Lüdtke, J. Buettner, W. Wu, et al., Peroxisome proliferator-activated receptor-gamma C190S mutation causes partial lipodystrophy, *J Clin Endocrinol Metab*, **92**, 2248–2255, (2007).

[56] H. Monajemi, L. Zhang, G. Li, et al., Familial partial lipodystrophy phenotype resulting from a single-base mutation in deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-gamma, *J Clin Endocrinol Metab*, **92**, 1606–1612, (2007).

[57] C. E. Juge-Aubry, S. Kuenzli, J. C. Sanchez, D. Hochstrasser, and C. A. Meier, Peroxisomal bifunctional enzyme binds and activates the activation function-1 region of the peroxisome proliferator-activated receptor α, *Biochem J*, **353**, 253–258, (2001).

[58] S. Hummasti and P. Tontonoz, The peroxisome proliferator-activated receptor N-terminal domain controls isotype-selective gene expression and adipogenesis, *Mol Endocrinol*, **20**, 1261–1275, (2006).

[59] C. Tudor, J. N. Feige, H. Pingali, et al., Association with coregulators is the major determinant governing peroxisome proliferator-activated receptor mobility in living cells, *J Biol Chem*, **282**, 4417–4426, (2007).

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

[61] T. Tomaru, T. Satoh, S. Yoshino, et al., Isolation and characterization of a transcriptional cofactor and its novel isoform that bind the deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-gamma, *Endocrinology*, **147**, 377–388, (2006).

[62] D. Genini and C. V. Catapano, Block of nuclear receptor ubiquitination. A mechanism of ligand-dependent control of peroxisome proliferator-activated receptor delta activity, *J Biol Chem*, **282**, 11776–11785, (2007).

[63] J. P. Gray, K. A. Burns, T. L. Leas, G. H. Perdew, and J. P. Vanden Heuvel, Regulation of peroxisome proliferator-activated receptor alpha by protein kinase C, *Biochemistry*, **44**, 10313–10321, (2005).

[64] C. K. Sung, H. She, S. Xiong, and H. Tsukamoto, Tumor necrosis factor-alpha inhibits peroxisome proliferator-activated receptor gamma activity at a posttranslational level in hepatic stellate cells, *Am J Physiol Gastrointest Liver Physiol*, **286**, G722–G729, (2004).

[65] P. Puigserver, Z. Wu, C. W. Park, R. Graves, M. Wright, and B. M. Spiegelman, A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis, *Cell*, **92**, 829–839, (1998).

[66] D. Li, Q. Kang, and D. M. Wang, Constitutive coactivator of peroxisome proliferator-activated receptor (PPARγ), a novel coactivator of PPARγ that promotes adipogenesis, *Mol Endocrinol*, **21**, 2320–2333, (2007).

[67] J. P. Gray, J. W. Davis II, L. Gopinathan, T. L. Leas, C. A. Nugent, and J. P. Vanden Heuvel, The ribosomal protein rpL11 associates with and inhibits the transcriptional activity of peroxisome proliferator-activated receptor-α, *Toxicol Sci*, **89**, 535–546, (2006).

[68] C. B. Li, X. X. Li, Y. G. Chen, et al., Effects and mechanisms of PPARalpha activator fenofibrate on myocardial remodelling in hypertension, *J Cell Mol Med*, **13**, 4444–4452, (2009).

[69] W. K. Sumanasekera, E. S. Tien, J. W. Davis II, R. Turpey, G. H. Perdew, and J. P. Vanden Heuvel, Heat shock protein-90 (Hsp90) acts as a repressor of peroxisome proliferator-activated receptor-alpha (PPARalpha) and PPARbeta activity, *Biochemistry*, **42**, 10726–10735, (2003).

[70] H. E. Xu, M. H. Lambert, V. G. Montana, et al., Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors, *Proc Natl Acad Sci USA*, **98**, 13919–13924, (2001).

[71] R. T. Nolte, G. B. Wisely, S. Westin, et al., Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma, *Nature*, **395**, 137–143, (1998).

[72] V. Zoete, A. Grosdidier, and O. Michielin, Peroxisome proliferator-activated receptor structures: ligand specificity, molecular switch and interactions with regulators, *Biochim Biophys Acta*, **1771**, 915–925, (2007).

[73] V. Chandra, P. Huang, Y. Hamuro, et al., Structure of the intact PPAR-gamma-RXR- nuclear receptor complex on DNA, *Nature*, **456**, 350–356, (2008).

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

[75] C. E. Juge-Aubry, A. Gorla-Bajszczak, A. Pernin, et al., Peroxisome proliferator-activated receptor mediates cross-talk with thyroid hormone receptor by competition for retinoid X receptor. Possible role of a leucine zipper-like heptad repeat, *J Biol Chem*, **270**, 18117–18122, (1995).

[76] I. Zamir, J. Zhang, and M. A. Lazar, Stoichiometric and steric principles governing repression by nuclear hormone receptors, *Genes Dev*, **11**, 835–846, (1997).

[77] S. Hauser, G. Adelmant, P. Sarraf, H. M. Wright, E. Mueller, and B. M. Spiegelman, Degradation of the peroxisome proliferator-activated receptor gamma is linked to ligand-dependent activation, *J Biol Chem*, **275**, 18527–18533, (2000).

[78] I. Tasdelen, O. van Beekum, O. Gorbenko, et al., The serine/threonine phosphatase PPM1B (PP2Cβ) selectively modulates PPARγ activity, *Biochem J*, **451**, 45–53, (2013).

[79] J. H. Choi, A. S. Banks, J. L. Estall, et al., Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARγ by Cdk5, *Nature*, **466**, 451–456, (2010).

[80] M. B. Wright, M. Bortolini, M. Tadayyon, and M. Bopst, Minireview: challenges and opportunities in development of PPAR agonists, *Mol Endocrinol*, **28**, 1756–1768, (2014).

[81] D. M. Lonard and B. W. O'malley, Nuclear receptor coregulators: judges, juries, and executioners of cellular regulation, *Mol Cell*, **27**, 691–700, (2007).

[82] J. N. Feige, L. Gelman, L. Michalik, B. Desvergne, and W. Wahli, From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions, *Prog Lipid Res*, **45**, 120–159, (2006).

[83] N. Mitro, C. Godio, and M. Crestani, Fluorescence resonance energy transfer techniques to study ligand-mediated interactions of PPARs with coregulators, *Methods Mol Biol*, **952**, 219–227, (2013).

[84] R. G. Roeder, Transcriptional regulation and the role of diverse coactivators in animal cells, *FEBS Lett*, **579**, 909–915, (2005).

[85] E. S. Tien, D. B. Hannon, J. T. Thompson, and J. P. Vanden Heuvel, Examination of Ligand-Dependent Coactivator Recruitment by Peroxisome Proliferator-Activated Receptor-α (PPARα), *PPAR Res*, **2006**, Article ID 69612, 1–9, (2006).

[86] J. Lin, C. Handschin, and B. M. Spiegelman, Metabolic control through the PGC-1 family of transcription coactivators, *Cell Metab*, **1**, 361–370, (2005).

[87] J. Lin, P. Puigserver, J. Donovan, P. Tarr, and B. M. Spiegelman, Peroxisome proliferator-activated receptor gamma coactivator 1beta (PGC-1beta), a novel PGC-1-related transcription coactivator associated with host cell factor, *J Biol Chem*, **277**, 1645–1648, (2002).

[88] P. Puigserver, Z. Wu, C. W. Park, R. Graves, M. Wright, and B. M. Spiegelman, A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis, *Cell*, **92**, 829–839, (1998).

[89] Y. -X. Wang, C. -H. Lee, S. Tiep, et al., Peroxisome-proliferator-activated receptor δ activates fat metabolism to prevent obesity, *Cell*, **113**, 159–170, (2003).

[90] Z. Qi and S. Ding, Transcriptional regulation by nuclear corepressors and PGC-1?: implications for mitochondrial quality control and insulin sensitivity, *PPAR Res*, **2012**, Article ID 348245, 1–12, (2012).

[91] T. C. Leone, J. J. Lehman, B. N. Finck, et al., PGC-1α deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis, *PLoS Biol*, **3**, Article ID e101, 672–678, (2005).

[92] J. Sonoda, I. R. Mehl, L. W. Chong, R. R. Nofsinger, and R. M. Evans, PGC-1beta controls mitochondrial metabolism to modulate circadian activity, adaptive thermogenesis, and hepatic steatosis, *Proc Natl Acad Sci USA*, **104**, 5223–5228, (2007).

[93] R. B. Vega, J. M. Huss, and D. P. Kelly, The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes, *Mol Cell Biol*, **20**, 1868–1876, (2000).

[94] C. J. Lelliott, A. Ljungberg, A. Ahnmark, et al., Hepatic PGC-1beta overexpression induces combined hyperlipidemia and modulates the response to PPARalpha activation, *Arterioscler Thromb Vasc Biol*, **27**, 2707–2713, (2007).

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

[96] Y. Li, A. Kovach, K. Suino-Powell, D. Martynowski, and H. E. Xu, Structural and biochemical basis for the binding selectivity of peroxisome proliferator-activated receptor γ to PGC-1α, *J Biol Chem*, **283**, 19132–19139, (2008).

[97] N. Viswakarma, Y. Jia, L. Bai, et al., Coactivators in PPAR-Regulated Gene Expression, *PPAR Res*, **2010**, Article ID 250126, 1–21, (2010).

[98] S. Yu and J. K. Reddy, Transcription coactivators for peroxisome proliferator-activated receptors, *Biochim Biophys Acta*, **1771**, 936–951, (2007).

[99] S. A. Oñate, S. Y. Tsai, M. J. Tsai, and B. W. O'Malley, Sequence and characterization of a coactivator for the steroid hormone receptor superfamily, *Science*, **270**, 1354–1357, (1995).

[100] Y. Zhu, C. Qi, C. Calandra, M. S. Rao, and J. K. Reddy, Cloning and identification of mouse steroid receptor coactivator-1 (mSRC-1), as a coactivator of peroxisome proliferator-activated receptor gamma, *Gene Expr*, **6**, 185–195, (1996).

[101] J. DiRenzo, M. Söderstrom, R. Kurokawa, et al., Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors, *Mol Cell Biol*, **17**, 2166–2176, (1997).

[102] F. Picard, M. Géhin, J. Annicotte, et al., SRC-1 and TIF2 control energy balance between white and brown adipose tissues, *Cell*, **111**, 931–941, (2002).

[103] A. Koppen and E. Kalkhoven, Brown vs white adipocytes: the PPARgamma coregulator story, *FEBS Lett*, **584**, 3250–3259, (2010).

[104] A. Koppen, R. Houtman, D. Pijnenburg, E. H. Jeninga, R. Ruijtenbeek, and E. Kalkhoven, Nuclear receptor-coregulator interaction profiling identifies TRIP3 as a novel peroxisome proliferator-activated receptor gamma cofactor, *Mol Cell Proteomics*, **8**, 2212–2226, (2009).

[105] J. F. Louet, A. Coste, L. Amazit, et al., Oncogenic steroid receptor coactivator-3 is a key regulator of the white adipogenic program, *Proc Natl Acad Sci USA*, **103**, 17868–17873, (2006).

[106] Z. Wang, C. Qi, A. Krones, et al., Critical roles of the p160 transcriptional coactivators p/CIP and SRC-1 in energy balance, *Cell Metab*, **3**, 111–122, (2006).

[107] S. M. Hartig, B. He, W. Long, B. M. Buehrer, and M. A. Mancini, Homeostatic levels of SRC-2 and SRC-3 promote early human adipogenesis, *J Cell Biol*, **192**, 55–67, (2011).

[108] Z. Arany, W. R. Sellers, D. M. Livingston, and R. Eckner, E1A-associated p300 and CREB-associated CBP belong to a conserved family of coactivators, *Cell*, **77**, 799–800, (1994).

[109] S. Surapureddi, S. Yu, H. Bu, et al., Identification of a transcriptionally active peroxisome proliferator-activated receptor alpha -interacting cofactor complex in rat liver and characterization of PRIC285 as a coactivator, *Proc Natl Acad Sci USA*, **99**, 11836–11841, (2002).

[110] M. J. Barberá, A. Schlüter, N. Pedraza, R. Iglesias, F. Villarroya, and M. Giralt, Peroxisome proliferator-activated receptor alpha activates transcription of the brown fat uncoupling protein-1 gene. A link between regulation of the thermogenic and lipid oxidation pathways in the brown fat cell, *J Biol Chem*, **276**, 1486–1493, (2001).

[111] K. Mochizuki, K. Suruga, N. Sakaguchi, S. Takase, and T. Goda, Major intestinal coactivator p300 strongly activates peroxisome proliferator-activated receptor in intestinal cell line, Caco-2, *Gene*, **291**, 271–277, (2002).

[112] L. Gelman, G. Zhou, L. Fajas, E. Raspé, J. C. Fruchart, and J. Auwerx, p300 interacts with the N- and C-terminal part of PPARgamma2 in a ligand-independent and -dependent manner, respectively, *J Biol Chem*, **274**, 7681–7688, (1999).

[113] R. C. Conaway, S. Sato, C. Tomomori-Sato, T. Yao, and J. W. Conaway, The mammalian Mediator complex and its role in transcriptional regulation, *Trends Biochem Sci*, **30**, 250–255, (2005).

[114] R. D. Kornberg, The molecular basis of eukaryotic transcription, *Proc Natl Acad Sci USA*, **104**, 12955–12961, (2007).

[115] K. Ge, Y. W. Cho, H. Guo, et al., Alternative mechanisms by which mediator subunit MED1/TRAP220 regulates peroxisome proliferator-activated receptor gamma-stimulated adipogenesis and target gene expression, *Mol Cell Biol*, **28**, 1081–1091, (2008).

[116] K. Matsumoto, S. Yu, Y. Jia, et al., Critical role for transcription coactivator peroxisome proliferator-activated receptor (PPAR)-binding protein/TRAP220 in liver regeneration and PPARalpha ligand-induced liver tumor development, *J Biol Chem*, **282**, 17053–17060, (2007).

[117] L. Grøntved, M. S. Madsen, M. Boergesen, R. G. Roeder, and S. Mandrup, MED14 tethers mediator to the N-terminal domain of peroxisome proliferator-activated receptor gamma and is required for full transcriptional activity and adipogenesis, *Mol Cell Biol*, **30**, 2155–2169, (2010).

[118] Y. Zhu, L. Kan, C. Qi, et al., Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR, *J Biol Chem*, **275**, 13510–13516, (2000).

[119] J. Sarkar, C. Qi, D. Guo, et al., Transcription coactivator PRIP, the peroxisome proliferator-activated receptor (PPAR)-interacting protein, is redundant for the function of nuclear receptors PParalpha and CAR, the constitutive androstane receptor, in mouse liver, *Gene Expr*, **13**, 255–269, (2007).

[120] C. Qi, S. Surapureddi, Y. J. Zhu, et al., Transcriptional coactivator PRIP, the peroxisome proliferator-activated receptor gamma (PPARgamma)-interacting protein, is required for PPARgamma-mediated adipogenesis, *J Biol Chem*, **278**, 25281–25284, (2003).

[121] T. Tomaru, T. Satoh, S. Yoshino, et al., Isolation and characterization of a transcriptional cofactor and its novel isoform that bind the deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-gamma, *Endocrinology*, **147**, 377–388, (2006).

[122] J. A. Hall and P. T. Georgel, CHD proteins: a diverse family with strong ties, *Biochem Cell Biol*, **85**, 463–476, (2007).

[123] S. Surapureddi, N. Viswakarma, S. Yu, D. Guo, M. S. Rao, and J. K. Reddy, PRIC320, a transcription coactivator, isolated from peroxisome proliferator-binding protein complex, *Biochem Biophys Res Commun*, **343**, 535–543, (2006).

[124] S. R. Pyper, N. Viswakarma, Y. Jia, Y. J. Zhu, J. D. Fondell, and J. K. Reddy, PRIC295, a nuclear receptor coactivator, identified from PPARα-interacting cofactor complex, *PPAR Res*, **2010**, Article ID 173907, 1–16, (2010).

[125] A. Mehrotra, G. Mehta, S. Aras, A. Trivedi, and I. L. de la Serna, SWI/SNF chromatin remodeling enzymes in melanocyte differentiation and melanoma, *Crit Rev Eukaryot Gene Expr*, **24**, 151–161, (2014).

[126] W. Wang, Y. Xue, S. Zhou, A. Kuo, B. R. Cairns, and G. R. Crabtree, Diversity and specialization of mammalian SWI/SNF complexes, *Genes Dev*, **10**, 2117–2130, (1996).

[127] S. Li, C. Liu, N. Li, et al., Genome-wide coactivation analysis of PGC-1alpha identifies BAF60a as a regulator of hepatic lipid metabolism, *Cell Metab*, **8**, 105–117, (2008).

[128] N. Salma, H. Xiao, E. Mueller, and A. N. Imbalzano, Temporal recruitment of transcription factors and SWI/SNF chromatin-remodeling enzymes during adipogenic induction of the peroxisome proliferator-activated receptor gamma nuclear hormone receptor, *Mol Cell Biol*, **24**, 4651–4663, (2004).

[129] M. B. Debril, L. Gelman, E. Fayard, J. S. Annicotte, S. Rocchi, and J. Auwerx, Transcription factors and nuclear receptors interact with the SWI/SNF complex through the BAF60c subunit, *J Biol Chem*, **279**, 16677–16686, (2004).

[130] Y. Jia, N. Viswakarma, S. E. Crawford, et al., Early embryonic lethality of mice with disrupted transcription cofactor PIMT/NCOA6IP/Tgs1 gene, *Mech Dev*, **129**, 193–207, (2012).

[131] P. Misra, C. Qi, S. Yu, et al., Interaction of PIMT with transcriptional coactivators CBP, p300, and PBP differential role in transcriptional regulation, *J Biol Chem*, **277**, 20011–20019, (2002).

[132] N. Yadav, D. Cheng, S. Richard, et al., CARM1 promotes adipocyte differentiation by coactivating PPARgamma, *EMBO Rep*, **9**, 193–198, (2008).

[133] C. A. Heinlein and C. Chang, Induction and repression of peroxisome proliferator-activated receptor alpha transcription by coregulator ARA70, *Endocrine*, **21**, 139–146, (2003).

[134] C. A. Heinlein, H. J. Ting, S. Yeh, and C. Chang, Identification of ARA70 as a ligand-enhanced coactivator for the peroxisome proliferator-activated receptor gamma, *J Biol Chem*, **274**, 16147–16152, (1999).

[135] M. Viladomiu, R. Hontecillas, M. Pedragosa, et al., Modeling the role of peroxisome proliferator-activated receptor γ and microRNA-146 in mucosal immune responses to Clostridium difficile, *PLoS One*, **7**, Article ID e47525, 1–10, (2012).

[136] M. J. Harms, J. Ishibashi, W. Wang, et al., Prdm16 is required for the maintenance of brown adipocyte identity and function in adult mice, *Cell Metab*, **19**, 593–604, (2014).

[137] T. Urano, M. Shiraki, N. Sasaki, Y. Ouchi, and S. Inoue, Large-scale analysis reveals a functional single-nucleotide polymorphism in the 5′-flanking region of PRDM16 gene associated with lean body mass, *Aging Cell*, **13**, 739–743, (2014).

[138] P. Seale, B. Bjork, W. Yang, et al., PRDM16 controls a brown fat/skeletal muscle switch, *Nature*, **454**, 961–967, (2008).

[139] H. Ohno, K. Shinoda, B. M. Spiegelman, and S. Kajimura, PPARγ agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein, *Cell Metab*, **15**, 395–404, (2012).

[140] S. Kajimura, P. Seale, T. Tomaru, et al., Regulation of the brown and white fat gene programs through a PRDM16/CtBP transcriptional complex, *Genes Dev*, **22**, 1397–1409, (2008).

[141] Y. Zhou, J. Yang, J. Huang, et al., The formation of brown adipose tissue induced by transgenic over-expression of PPARγ2, *Biochem Biophys Res Commun*, **446**, 959–964, (2014).

[142] S. Kokabu, T. Nguyen, S. Ohte, et al., TLE3, transducing-like enhancer of split 3, suppresses osteoblast differentiation of bone marrow stromal cells, *Biochem Biophys Res Commun*, **438**, 205–210, (2013).

[143] C. J. Villanueva, H. Waki, C. Godio, et al., TLE3 is a dual-function transcriptional coregulator of adipogenesis, *Cell Metab*, **13**, 413–427, (2011).

[144] C. J. Villanueva, L. Vergnes, J. Wang, et al., Adipose subtype-selective recruitment of TLE3 or Prdm16 by PPARγ specifies lipid storage versus thermogenic gene programs, *Cell Metab*, **17**, 423–435, (2013).

[145] D. Li, Q. Kang, and D. M. Wang, Constitutive coactivator of peroxisome proliferator-activated receptor (PPARgamma), a novel coactivator of PPARgamma that promotes adipogenesis, *Mol Endocrinol*, **21**, 2320–2333, (2007).

[146] H. P. Guan, T. Ishizuka, P. C. Chui, M. Lehrke, and M. A. Lazar, Corepressors selectively control the transcriptional activity of PPARγ in adipocytes, *Genes Dev*, **19**, 453–461, (2005).

[147] X. Hu and M. A. Lazar, The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors, *Nature*, **402**, 93–96, (1999).

[148] I. Gurevich, A. M. Flores, and B. J. Aneskievich, Corepressors of agonist-bound nuclear receptors, *Toxicol Appl Pharmacol*, **223**, 288–298, (2007).

[149] V. Perissi, K. Jepsen, C. K. Glass, and M. G. Rosenfeld, Deconstructing repression: evolving models of co-repressor action, *Nat Rev Genet*, **11**, 109–123, (2010).

[150] P. Karagianni and J. Wong, HDAC3: taking the SMRT-NCoRrect road to repression, *Oncogene*, **26**, 5439–5449, (2007).

[151] B. Pourcet, I. Pineda-Torra, B. Derudas, B. Staels, and C. Glineur, SUMOylation of human peroxisome proliferator-activated receptor alpha inhibits its trans-activity through the recruitment of the nuclear corepressor NCoR, *J Biol Chem*, **285**, 5983–5992, (2010).

[152] H. Yamamoto, E. G. Williams, L. Mouchiroud, et al., NCoR1 is a conserved physiological modulator of muscle mass and oxidative function, *Cell*, **147**, 827–839, (2011).

[153] C. Yu, K. Markan, K. A. Temple, D. Deplewski, M. J. Brady, and R. N. Cohen, The nuclear receptor corepressors NCoR and SMRT decrease peroxisome proliferator-activated receptor gamma transcriptional activity and repress 3T3-L1 adipogenesis, *J Biol Chem*, **280**, 13600–13605, (2005).

[154] P. Li, W. Fan, J. Xu, et al., Adipocyte NCoR knockout decreases PPARγ phosphorylation and enhances PPARγ activity and insulin sensitivity, *Cell*, **147**, 815–826, (2011).

[155] R. R. Nofsinger, P. Li, S. H. Hong, et al., SMRT repression of nuclear receptors controls the adipogenic set point and metabolic homeostasis, *Proc Natl Acad Sci USA*, **105**, 20021–20026, (2008).

[156] R. Hock, T. Furusawa, T. Ueda, and M. Bustin, HMG chromosomal proteins in development and disease, *Trends Cell Biol*, **17**, 72–79, (2007).

[157] M. Bloch, A. Prock, F. Paonessa, et al., High-mobility group A1 protein: a new coregulator of peroxisome proliferator-activated receptor-γ-mediated transrepression in the vasculature, *Circ Res*, **110**, 394–405, (2012).

[158] Y. Takahashi, N. Ohoka, H. Hayashi, and R. Sato, TRB3 suppresses adipocyte differentiation by negatively regulating PPARgamma transcriptional activity, *J Lipid Res*, **49**, 880–892, (2008).

[159] I. Fernandes, Y. Bastien, T. Wai, et al., Ligand-dependent nuclear receptor corepressor LCoR functions by histone deacetylase-dependent and -independent mechanisms, *Mol Cell*, **11**, 139–150, (2003).

[160] J. H. White, I. Fernandes, S. Mader, and X. J. Yang, Corepressor recruitment by agonist-bound nuclear receptors, *Vitam Horm*, **68**, 123–143, (2004).

[161] A. Jiang, S. Zhang, Z. Li, et al., miR-615-3p promotes the phagocytic capacity of splenic macrophages by targeting ligand-dependent nuclear receptor corepressor in cirrhosis-related portal hypertension, *Exp Biol Med (Maywood)*, **236**, 672–680, (2011).

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

[163] L. N. Wei, X. Hu, D. Chandra, E. Seto, and M. Farooqui, Receptor-interacting protein 140 directly recruits histone deacetylases for gene silencing, *J Biol Chem*, **275**, 40782–40787, (2000).

[164] M. Hallberg, D. L. Morganstein, E. Kiskinis, et al., A functional interaction between RIP140 and PGC-1alpha regulates the expression of the lipid droplet protein CIDEA, *Mol Cell Biol*, **28**, 6785–6795, (2008).

[165] M. M. Rytinki and J. J. Palvimo, SUMOylation attenuates the function of PGC-1α, *J Biol Chem*, **284**, 26184–26193, (2009).

[166] Y. Chen, Y. Wang, J. Chen, et al., Roles of transcriptional corepressor RIP140 and coactivator PGC-1α in energy state of chronically infarcted rat hearts and mitochondrial function of cardiomyocytes, *Mol Cell Endocrinol*, **362**, 11–18, (2012).

[167] S. Cohen, A. Ciechanover, Y. Kravtsova-Ivantsiv, D. Lapid, and S. Lahav-Baratz, ABIN-1 negatively regulates NF-kappaB by inhibiting processing of the p105 precursor, *Biochem Biophys Res Commun*, **389**, 205–210, (2009).

[168] I. Gurevich and B. J. Aneskievich, Liganded RARalpha and RARgamma interact with but are repressed by TNIP1, *Biochem Biophys Res Commun*, **389**, 409–414, (2009).

[169] A. M. Flores, I. Gurevich, C. Zhang, V. P. Ramirez, T. R. Devens, and B. J. Aneskievich, TNIP1 is a corepressor of agonist-bound PPARs, *Arch Biochem Biophys*, **516**, 58–66, (2011).

[170] J. H. Hong, E. S. Hwang, M. T. McManus, et al., TAZ, a transcriptional modulator of mesenchymal stem cell differentiation, *Science*, **309**, 1074–1078, (2005).

[171] H. Jung, M. S. Lee, E. J. Jang, et al., Augmentation of PPARgamma-TAZ interaction contributes to the anti-adipogenic activity of KR62980, *Biochem Pharmacol*, **78**, 1323–1329, (2009).

[172] M. R. Byun, H. Jeong, S. J. Bae, A. R. Kim, E. S. Hwang, and J. H. Hong, TAZ is required for the osteogenic and anti-adipogenic activities of kaempferol, *Bone*, **50**, 364–372, (2012).

[173] E. J. Jang, H. Jeong, J. O. Kang, et al., TM-25659 enhances osteogenic differentiation and suppresses adipogenic differentiation by modulating the transcriptional co-activator TAZ, *Br J Pharmacol*, **165**, 1584–1594, (2012).

[174] A. M. Flores, L. Li, and B. J. Aneskievich, Isolation and functional analysis of a keratinocyte-derived, ligand-regulated nuclear receptor comodulator, *J Invest Dermatol*, **123**, 1092–1101, (2004).

[175] G. V. Denis, Duality in bromodomain-containing protein complexes, *Front Biosci*, **6**, D849–D852, (2001).

[176] F. Wang, H. Liu, W. P. Blanton, A. Belkina, N. K. Lebrasseur, and G. V. Denis, Brd2 disruption in mice causes severe obesity without Type 2 diabetes, *Biochem J*, **425**, 71–83, (2010).

[177] J. H. Lee, J. H. Woo, S. U. Woo, et al., The 15-deoxy-delta 12,14-prostaglandin J2 suppresses monocyte chemoattractant protein-1 expression in IFN-gamma-stimulated astrocytes through induction of MAPK phosphatase-1, *J Immunol*, **181**, 8642–8649, (2008).

[178] G. Cantini, A. Lombardi, E. Borgogni, et al., Peroxisome-proliferator-activated receptor gamma (PPARgamma) is required for modulating endothelial inflammatory response through a nongenomic mechanism, *Eur J Cell Biol*, **89**, 645–653, (2010).

[179] N. Silswal, N. K. Parelkar, M. J. Wacker, M. Badr, and J. Andresen, PPARα-Independent Arterial Smooth Muscle Relaxant Effects of PPARα Agonists, *PPAR Res*, **2012**, Article ID 302495, 1–10, (2012).

[180] R. B. Griggs, R. R. Donahue, J. Morgenweck, et al., Pioglitazone rapidly reduces neuropathic pain through astrocyte and nongenomic PPARγ mechanisms, *Pain*, **156**, 469–482, (2015).

[181] E. Galatou, T. Kelly, and A. Lazou, The PPARβ/δ agonist GW0742 modulates signaling pathways associated with cardiac myocyte growth via a non-genomic redox mechanism, *Mol Cell Biochem*, **395**, 145–154, (2014).

[182] C. Dreyer, H. Keller, A. Mahfoudi, V. Laudet, G. Krey, and W. Wahli, Positive regulation of the peroxisomal beta-oxidation pathway by fatty acids through activation of peroxisome proliferator-activated receptors (PPAR), *Biol Cell*, **77**, 67–76, (1993).

[183] P. A. Grimaldi, Peroxisome proliferator-activated receptors as sensors of fatty acids and derivatives, *Cell Mol Life Sci*, **64**, 2459–2464, (2007).

[184] M. V. Chakravarthy, I. J. Lodhi, L. Yin, et al., Identification of a physiologically relevant endogenous ligand for PPARalpha in liver, *Cell*, **138**, 476–488, (2009).

[185] V. R. Narala, R. K. Adapala, M. V. Suresh, T. G. Brock, M. Peters-Golden, and R. C. Reddy, Leukotriene B4 is a physiologically relevant endogenous peroxisome proliferator-activated receptor-alpha agonist, *J Biol Chem*, **285**, 22067–22074, (2010).

[186] P. Delerive, C. Furman, E. Teissier, J. Fruchart, P. Duriez, and B. Staels, Oxidized phospholipids activate PPARα in a phospholipase A2-dependent manner, *FEBS Lett*, **471**, 34–38, (2000).

[187] S. E. O'Sullivan and D. A. Kendall, Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease, *Immunobiology*, **215**, 611–616, (2010).

[188] M. Schupp and M. A. Lazar, Endogenous ligands for nuclear receptors: digging deeper, *J Biol Chem*, **285**, 40409–40415, (2010).

[189] M. D. Leibowitz, C. Fiévet, N. Hennuyer, et al., Activation of PPARdelta alters lipid metabolism in db/db mice, *FEBS Lett*, **473**, 333–336, (2000).

[190] R. A. Gupta, J. Tan, W. F. Krause, et al., Prostacyclin-mediated activation of peroxisome proliferator-activated receptor delta in colorectal cancer, *Proc Natl Acad Sci USA*, **97**, 13275–13280, (2000).

[191] M. Ghosh, H. Wang, Y. Ai, et al., COX-2 suppresses tissue factor expression via endocannabinoid-directed PPARdelta activation, *J Exp Med*, **204**, 2053–2061, (2007).

[192] N. Shaw, M. Elholm, and N. Noy, Retinoic acid is a high affinity selective ligand for the peroxisome proliferator-activated receptor beta/delta, *J Biol Chem*, **278**, 41589–41592, (2003).

[193] S. A. Fyffe, M. S. Alphey, L. Buetow, et al., Recombinant human PPAR-beta/delta ligand-binding domain is locked in an activated conformation by endogenous fatty acids, *J Mol Biol*, **356**, 1005–1013, (2006).

[194] J. D. Coleman, K. S. Prabhu, J. T. Thompson, et al., The oxidative stress mediator 4-hydroxynonenal is an intracellular agonist of the nuclear receptor peroxisome proliferator-activated receptor-beta/delta (PPARbeta/delta), *Free Radic Biol Med*, **42**, 1155–1164, (2007).

[195] F. J. Schopfer, M. P. Cole, A. L. Groeger, et al., Covalent peroxisome proliferator-activated receptor gamma adduction by nitro-fatty acids: selective ligand activity and anti-diabetic signaling actions, *J Biol Chem*, **285**, 12321–12333, (2010).

[196] T. Waku, T. Shiraki, T. Oyama, K. Maebara, R. Nakamori, and K. Morikawa, The nuclear receptor PPARγ individually responds to serotonin- and fatty acid-metabolites, *EMBO J*, **29**, 3395–3407, (2010).

[197] T. Goto, H. Nagai, K. Egawa, et al., Farnesyl pyrophosphate regulates adipocyte functions as an endogenous PPARγ agonist, *Biochem J*, **438**, 111–119, (2011).

[198] T. Tsukahara, R. Tsukahara, Y. Fujiwara, et al., Phospholipase D2-dependent inhibition of the nuclear hormone receptor PPARγ by cyclic phosphatidic acid, *Mol Cell*, **39**, 421–432, (2010).

[199] D. Barnett, J. G. Craig, D. S. Robinson, and M. P. Rogers, Effect of clofibrate on glucose tolerance in maturity onset diabetes, *Br J Clin Pharmacol*, **4**, 455–458, (1977).

[200] F. Matzkies, D. Schulzky, and G. Berg, Procetofen, a new lipid- and urine-acid-reducing substance, *Fortschr Med*, **96**, 1939–1941, (1978).

[201] T. Sohda, K. Mizuno, H. Tawada, Y. Sugiyama, T. Fujita, and Y. Kawamatsu, Studies on antidiabetic agents. I. Synthesis of 5-[4-(2-methyl-2-phenylpropoxy)-benzyl]thiazolidine-2,4-dione (AL-321) and related compounds, *Chem Pharm Bull (Tokyo)*, **30**, 3563–3573, (1982).

[202] T. Sohda, K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita, and Y. Kawamatsu, Studies on antidiabetic agents. II. Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives, *Chem Pharm Bull (Tokyo)*, **30**, 3580–3600, (1982).

[203] T. Fujita, Y. Sugiyama, S. Taketomi, et al., Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63,287, ciglitazone), a new antidiabetic agent, *Diabetes*, **32**, 804–810, (1983).

[204] A. Y. Chang, B. M. Wyse, B. J. Gilchrist, T. Peterson, and A. R. Diani, Ciglitazone, a new hypoglycemic agent. I. Studies in ob/ob and db/db mice, diabetic Chinese hamsters, and normal and streptozotocin-diabetic rats, *Diabetes*, **32**, 830–838, (1983).

[205] T. Fujiwara, S. Yoshioka, T. Yoshioka, I. Ushiyama, and H. Horikoshi, Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats, *Diabetes*, **37**, 1549–1558, (1988).

[206] B. C. Cantello, M. A. Cawthorne, G. P. Cottam, et al., [[omega-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents, *J Med Chem*, **37**, 3977–3985, (1994).

[207] P. B. Watkins and R. W. Whitcomb, Hepatic dysfunction associated with troglitazone, *N Engl J Med*, **338**, 916–917, (1998).

[208] N. D. Oakes, C. J. Kennedy, A. B. Jenkins, D. R. Laybutt, D. J. Chisholm, and E. W. Kraegen, A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat, *Diabetes*, **43**, 1203–1210, (1994).

[209] A. Christopoulos, J. P. Changeux, W. A. Catterall, et al., International Union of Basic and Clinical Pharmacology. XC. multisite pharmacology: recommendations for the nomenclature of receptor allosterism and allosteric ligands, *Pharmacol Rev*, **66**, 918–947, (2014).

[210] R. R. Neubig, M. Spedding, T. Kenakin, and A. Christopoulos, International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. XXXVIII. Update on terms and symbols in quantitative pharmacology, *Pharmacol Rev*, **55**, 597–606, (2003).

[211] J. P. Changeux, Allostery and the Monod-Wyman-Changeux model after 50 years, *Annu Rev Biophys*, **41**, 103–133, (2012).

[212] B. J. Melancon, C. R. Hopkins, M. R. Wood, et al., Allosteric modulation of seven transmembrane spanning receptors: theory, practice, and opportunities for central nervous system drug discovery, *J Med Chem*, **55**, 1445–1464, (2012).

[213] D. Wootten, A. Christopoulos, and P. M. Sexton, Emerging paradigms in GPCR allostery: implications for drug discovery, *Nat Rev Drug Discov*, **12**, 630–644, (2013).

[214] H. S. Camp, O. Li, S. C. Wise, et al., Differential activation of peroxisome proliferator-activated receptor-gamma by troglitazone and rosiglitazone, *Diabetes*, **49**, 539–547, (2000).

[215] T. Venäläinen, F. Molnár, C. Oostenbrink, C. Carlberg, and M. Peräkylä, Molecular mechanism of allosteric communication

in the human PPARalpha-RXRalpha heterodimer, *Proteins*, **78**, 873–887, (2010).

[216] T. S. Hughes, P. K. Giri, I. M. de Vera, et al., An alternate binding site for PPARγ ligands, *Nat Commun*, **5**, p. 3571, (2014).

[217] A. Tenenbaum and E. Z. Fisman, Fibrates are an essential part of modern anti-dyslipidemic arsenal: spotlight on atherogenic dyslipidemia and residual risk reduction, *Cardiovasc Diabetol*, **11**, p. 125, (2012).

[218] M. H. Davidson, A. Armani, J. M. McKenney, and T. A. Jacobson, Safety considerations with fibrate therapy, *Am J Cardiol*, **99**, 3C–18C, (2007).

[219] C. Enger, R. Gately, E. E. Ming, S. J. Niemcryk, L. Williams, and A. T. McAfee, Pharmacoepidemiology safety study of fibrate and statin concomitant therapy, *Am J Cardiol*, **106**, 1594–1601, (2010).

[220] S. E. Kahn, S. M. Haffner, M. A. Heise, et al., Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, *N Engl J Med*, **355**, 2427–2443, (2006).

[221] S. E. Nissen and K. Wolski, Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes, *N Engl J Med*, **356**, 2457–2471, (2007).

[222] C. J. Rosen, The rosiglitazone story—lessons from an FDA Advisory Committee meeting, *N Engl J Med*, **357**, 844–846, (2007).

[223] S. Singh, Y. K. Loke, and C. D. Furberg, Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis, *JAMA*, **298**, 1189–1195, (2007).

[224] L. L. Lipscombe, T. Gomes, L. E. Lévesque, J. E. Hux, D. N. Juurlink, and D. A. Alter, Thiazolidinediones and cardiovascular outcomes in older patients with diabetes, *JAMA*, **298**, 2634–2643, (2007).

[225] D. J. Graham, R. Ouellet-Hellstrom, T. E. MaCurdy, et al., Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone, *JAMA*, **304**, 411–418, (2010).

[226] W. C. Winkelmayer, S. Setoguchi, R. Levin, and D. H. Solomon, Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy, *Arch Intern Med*, **168**, 2368–2375, (2008).

[227] D. N. Juurlink, T. Gomes, L. L. Lipscombe, P. C. Austin, J. E. Hux, and M. M. Mamdani, Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study, *BMJ*, **339**, p. b2942, (2009).

[228] J. S. Brownstein, S. N. Murphy, A. B. Goldfine, et al., Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records, *Diabetes Care*, **33**, 526–531, (2010).

[229] C. M. Gerrits, M. Bhattacharya, S. Manthena, R. Baran, A. Perez, and S. Kupfer, A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes, *Pharmacoepidemiol Drug Saf*, **16**, 1065–1071, (2007).

[230] N. Ziyadeh, A. T. McAfee, C. Koro, J. Landon, and K. Arnold Chan, The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: a retrospective cohort study using a US health insurance database, *Clin Ther*, **31**, 2665–2677, (2009).

[231] P. D. Home, S. J. Pocock, H. Beck-Nielsen, et al., Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial, *Lancet*, **373**, 2125–2135, (2009).

[232] J. Kung and R. R. Henry, Thiazolidinedione safety, *Expert Opin Drug Saf*, **11**, 565–579, (2012).

[233] E. Mannucci, M. Monami, M. Di Bari, et al., Cardiac safety profile of rosiglitazone: a comprehensive meta-analysis of randomized clinical trials, *Int J Cardiol*, **143**, 135–140, (2010).

[234] A. T. McAfee, C. Koro, J. Landon, N. Ziyadeh, and A. M. Walker, Coronary heart disease outcomes in patients receiving antidiabetic agents, *Pharmacoepidemiol Drug Saf*, **16**, 711–725, (2007).

[235] D. J. Margolis, O. Hoffstad, and B. L. Strom, Association between serious ischemic cardiac outcomes and medications used to treat diabetes, *Pharmacoepidemiol Drug Saf*, **17**, 753–759, (2008).

[236] S. E. Nissen and K. Wolski, Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality, *Arch Intern Med*, **170**, 1191–1201, (2010).

[237] K. W. Mahaffey, G. Hafley, S. Dickerson, et al., Results of a reevaluation of cardiovascular outcomes in the RECORD trial, *Am Heart J*, **166**, 240–249.e1, (2013).

[238] P. Berhanu, A. Perez, and S. Yu, Effect of pioglitazone in combination with insulin therapy on glycaemic control, insulin dose requirement and lipid profile in patients with type 2 diabetes previously poorly controlled with combination therapy, *Diabetes Obes Metab*, **9**, 512–520, (2007).

[239] G. Schernthaner, D. R. Matthews, B. Charbonnel, M. Hanefeld, and P. Brunetti, Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial, *J Clin Endocrinol Metab*, **89**, 6068–6076, (2004).

[240] V. Mattoo, D. Eckland, M. Widel, et al., Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study, *Clin Ther*, **27**, 554–567, (2005).

[241] Y. Miyazaki, A. Mahankali, M. Matsuda, et al., Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients, *J Clin Endocrinol Metab*, **87**, 2784–2791, (2002).

[242] S. R. Smith, L. De Jonge, J. Volaufova, Y. Li, H. Xie, and G. A. Bray, Effect of pioglitazone on body composition and energy expenditure: a randomized controlled trial, *Metabolism*, **54**, 24–32, (2005).

[243] R. W. Nesto, D. Bell, R. O. Bonow, et al., Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association, *Circulation*, **108**, 2941–2948, (2003).

[244] J. A. Dormandy, B. Charbonnel, D. J. Eckland, et al., Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial, *Lancet*, **366**, 1279–1289, (2005).

[245] D. S. Fong and R. Contreras, Glitazone use associated with diabetic macular edema, *Am J Ophthalmol*, **147**, 583–586.e1, (2009).

[246] R. Berria, L. Glass, A. Mahankali, et al., Reduction in hematocrit and hemoglobin following pioglitazone treatment is not hemodilutional in Type II diabetes mellitus, *Clin Pharmacol Ther*, **82**, 275–281, (2007).

[247] M. Bortolini, M. B. Wright, M. Bopst, and B. Balas, Examining the safety of PPAR agonists - current trends and future prospects, *Expert Opin Drug Saf*, **12**, 65–79, (2013).

[248] S. E. Nissen, K. Wolski, and E. J. Topol, Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus, *JAMA*, **294**, 2581–2586, (2005).

[249] M. B. Oleksiewicz, I. Thorup, H. S. Nielsen, et al., Generalized cellular hypertrophy is induced by a dual-acting PPAR agonist in rat urinary bladder urothelium in vivo, *Toxicol Pathol*, **33**, 552–560, (2005).

[250] R. E. Ratner, S. Parikh, and C. Tou, Efficacy, safety and tolerability of tesaglitazar when added to the therapeutic regimen of poorly controlled insulin-treated patients with type 2 diabetes, *Diab Vasc Dis Res*, **4**, 214–221, (2007).

[251] L. Salvadó, L. Serrano-Marco, E. Barroso, X. Palomer, and M. Vázquez-Carrera, Targeting PPARβ/δ for the treatment of type 2 diabetes mellitus, *Expert Opin Ther Targets*, **16**, 209–223, (2012).

[252] A. M. Lefebvre, I. Chen, P. Desreumaux, et al., Activation of the peroxisome proliferator-activated receptor gamma promotes the development of colon tumors in C57BL/6J-APCMin/+ mice, *Nat Med*, **4**, 1053–1057, (1998).

[253] T. Allen, F. Zhang, S. A. Moodie, et al., Halofenate is a selective peroxisome proliferator-activated receptor gamma modulator with antidiabetic activity, *Diabetes*, **55**, 2523–2533, (2006).

[254] G. Chinetti, J. C. Fruchart, and B. Staels, Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation, *Inflamm Res*, **49**, 497–505, (2000).

[255] P. Delerive, J. C. Fruchart, and B. Staels, Peroxisome proliferator-activated receptors in inflammation control, *J Endocrinol*, **169**, 453–459, (2001).

[256] A. J. Guri, S. K. Mohapatra, W. T. Horne II, R. Hontecillas, and J. Bassaganya-Riera, The role of T cell PPAR gamma in mice with experimental inflammatory bowel disease, *BMC Gastroenterol*, **10**, p. 60, (2010).

[257] B. M. Spiegelman, PPARγ in monocytes: less pain, any gain? *Cell*, **93**, 153–155, (1998).

[258] T. S. Farnesi-de-Assunção, V. Carregaro, C. A. da Silva, A. J. de Pinho Jr, and M. H. Napimoga, The modulatory effect of 15d-PGJ2 in dendritic cells, *Nucl Receptor Res*, **1**, Article ID 101083, 1–7, (2014).

[259] L. Peyrin-Biroulet, J. Beisner, G. Wang, et al., Peroxisome proliferator-activated receptor gamma activation is required for maintenance of innate antimicrobial immunity in the colon, *Proc Natl Acad Sci USA*, **107**, 8772–8777, (2010).

[260] C. M. Freitag and R. J. Miller, Peroxisome proliferator-activated receptor agonists modulate neuropathic pain: a link to chemokines? *Front Cell Neurosci*, **8**, p. 238, (2014).

[261] Y. Barak, D. Liao, W. He, et al., Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer, *Proc Natl Acad Sci USA*, **99**, 303–308, (2002).

[262] P. Froment, PPARs and RXRs in Male and Female Fertility and Reproduction, *PPAR Res*, **2008**, Article ID 637490, 1–2, (2008).

[263] B. M. Spiegelman and J. S. Flier, Adipogenesis and obesity: rounding out the big picture, *Cell*, **87**, 377–389, (1996).

[264] F. M. Gregoire, S. Kersten, and W. Harrington, PPARS and Obesity, *PPAR Res*, **2007**, Article ID 78475, 1–1, (2007).

[265] F. Zhang, B. E. Lavan, and F. M. Gregoire, Selective Modulators of PPAR-γ Activity: Molecular Aspects Related to Obesity and Side-Effects, *PPAR Res*, **2007**, Article ID 32696, 1–7, (2007).

[266] C. J. Masters and D. I. Crane, On the role of the peroxisome in ontogeny, ageing and degenerative disease, *Mech Ageing Dev*, **80**, 69–83, (1995).

[267] J. Youssef and M. Badr, Biology of senescent liver peroxisomes: role in hepatocellular aging and disease, *Environ Health Perspect*, **107**, 791–797, (1999).

[268] J. Youssef and M. Badr. *Peroxisomal alterations in aging and disease. In Interorganellar Signaling in Age-Related Disease*. ed M. Mattson. Advances in Cell Aging and Gerontology, Elsevier Press, 1–28, (2001).

[269] L. Han, R. Zhou, J. Niu, M. A. McNutt, P. Wang, and T. Tong, SIRT1 is regulated by a PPARγ-SIRT1 negative feedback loop associated with senescence, *Nucleic Acids Res*, **38**, 7458–7471, (2010).

[270] M. Badr, Peroxisome proliferator-activated receptor alpha and cancer: friends or foes? *Int J Cancer Prev*, **1**, 77–87, (2004).

[271] D. Panigrahy, A. Kaipainen, M. W. Kieran, and S. Huang, PPARs: A Double-Edged Sword in Cancer Therapy? *PPAR Res*, **2008**, Article ID 350351, 1–2, (2008).

[272] J. Youssef and M. Badr, Peroxisome proliferator-activated receptors and cancer: challenges and opportunities, *Br J Pharmacol*, **164**, 68–82, (2011).

[273] M. Puligheddu, G. Pillolla, M. Melis, et al., PPAR-Alpha Agonists as Novel Antiepileptic Drugs: Preclinical Findings, *PLoS One*, **8**, Article ID e64541, 1–10, (2013).

[274] B. Le Foll, P. Di Ciano, L. V. Panlilio, S. R. Goldberg, and R. Ciccocioppo, Peroxisome proliferator-activated receptor (PPAR) agonists as promising new medications for drug addiction: preclinical evidence, *Curr Drug Targets*, **14**, 768–776, (2013).

[275] S. Mandrekar-Colucci, J. C. Karlo, and G. E. Landreth, Mechanisms underlying the rapid peroxisome proliferator-activated receptor-γ-mediated amyloid clearance and reversal of cognitive deficits in a murine model of Alzheimer's disease, *J Neurosci*, **32**, 10117–10128, (2012).

[276] T. P. Burris, L. A. Solt, Y. Wang, et al., Nuclear receptors and their selective pharmacologic modulators, *Pharmacol Rev*, **65**, 710–778, (2013).

[277] J.-C. Fruchart, Selective peroxisome proliferator-activated receptor α modulators (SPPARMα): the next generation of peroxisome proliferator-activated receptor α-agonists, *Cardiovasc Diabetol*, **12**, p. 82, (2013).

[278] A. M. Lincoff, J. C. Tardif, G. G. Schwartz, et al., Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial, *JAMA*, **311**, 1515–1525, (2014).

[279] L. M. Younk, L. Uhl, and S. N. Davis, Pharmacokinetics, efficacy and safety of aleglitazar for the treatment of type 2 diabetes with high cardiovascular risk, *Expert Opin Drug Metab Toxicol*, **7**, 753–763, (2011).

[280] I. C. Gonzalez, J. Lamar, F. Iradier, et al., Design and synthesis of a novel class of dual PPARgamma/delta agonists, *Bioorg Med Chem Lett*, **17**, 1052–1055, (2007).

[281] R. Agrawal, P. Jain, and S. N. Dikshit, Balaglitazone: a second generation peroxisome proliferator-activated receptor (PPAR) gamma (γ) agonist, *Mini Rev Med Chem*, **12**, 87–97, (2012).

[282] K. Henriksen, I. Byrjalsen, P. Qvist, et al., Efficacy and safety of the PPARγ partial agonist balaglitazone compared with pioglitazone and placebo: a phase III, randomized, parallel-group study in patients with type 2 diabetes on stable insulin therapy, *Diabetes Metab Res Rev*, **27**, 392–401, (2011).

[283] A. Motani, Z. Wang, J. Weiszmann, et al., INT131: a selective modulator of PPARγ, *J Mol Biol*, **386**, 1301–1311, (2009).

[284] C. Liu, T. Feng, N. Zhu, et al., Identification of a novel selective agonist of PPARγ with no promotion of adipogenesis and less inhibition of osteoblastogenesis, *Sci Rep*, **5**, p. 9530, (2015).

[285] Z. Gan, J. Rumsey, B. C. Hazen, et al., Nuclear receptor/microRNA circuitry links muscle fiber type to energy metabolism, *J Clin Invest*, **123**, 2564–2575, (2013).

[286] A. P. Russell, J. Feilchenfeldt, S. Schreiber, et al., Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle, *Diabetes*, **52**, 2874–2881, (2003).

[287] T. Fritz, D. K. Krämer, H. K. Karlsson, et al., Low-intensity exercise increases skeletal muscle protein expression of PPARdelta and UCP3 in type 2 diabetic patients, *Diabetes Metab Res Rev*, **22**, 492–498, (2006).

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

[289] V. A. Narkar, M. Downes, R. T. Yu, et al., AMPK and PPARdelta agonists are exercise mimetics, *Cell*, **134**, 405–415, (2008).

[290] http://www.clinicaltrials.gov.

[291] A. Prakash and A. Kumar, Role of nuclear receptor on regulation of BDNF and neuroinflammation in hippocampus of β-amyloid animal model of Alzheimer's disease, *Neurotox Res*, **25**, 335–347, (2014).

[292] J. C. Fehrenbacher, J. Loverme, W. Clarke, K. M. Hargreaves, D. Piomelli, and B. K. Taylor, Rapid pain modulation with nuclear receptor ligands, *Brain Res Brain Res Rev*, **60**, 114–124, (2009).

[293] B. K. Taylor, C. Kriedt, S. Nagalingam, N. Dadia, and M. Badr, Central administration of perfluorooctanoic acid inhibits cutaneous inflammation, *Inflamm Res*, **54**, 235–242, (2005).

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

[295] T. E. Cullingford, K. Bhakoo, S. Peuchen, C. T. Dolphin, R. Patel, and J. B. Clark, Distribution of mRNAs encoding the peroxisome proliferator-activated receptor alpha, beta, and gamma and the retinoid X receptor alpha, beta, and gamma in rat central nervous system, *J Neurochem*, **70**, 1366–1375, (1998).

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

[297] J. M. Lehmann, J. M. Lenhard, B. B. Oliver, G. M. Ringold, and S. A. Kliewer, Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs, *J Biol Chem*, **272**, 3406–3410, (1997).

[298] A. Catania, J. Arnold, A. Macaluso, M. E. Hiltz, and J. M. Lipton, Inhibition of acute inflammation in the periphery by central action of salicylates, *Proc Natl Acad Sci USA*, **88**, 8544–8547, (1991).

[299] A. B. Gómez-SanMiguel, A. I. Martín, M. P. Nieto-Bona, et al., Systemic α-melanocyte-stimulating hormone administration decreases arthritis-induced anorexia and muscle wasting, *Am J Physiol Regul Integr Comp Physiol*, **304**, R877–R886, (2013).

[300] J. Youssef and M. Badr, *Peroxisome proliferator-activated receptors: discovery and recent advances*, Springer Publishing Company, New York, New York, 2013.

[301] E. Esposito and S. Cuzzocrea, Targeting the peroxisome proliferator-activated receptors (PPARs) in spinal cord injury, *Exp Opin Ther Targets*, **15**, 943–959, (2011).

[302] M. Schupp and M. A. Lazar, Endogenous ligands for nuclear receptors: digging deeper, *J Biol Chem*, **285**, 40409–40415, (2010).