



Review

# Mechanisms Mediating the Regulation of Peroxisomal Fatty Acid Beta-Oxidation by PPAR $\alpha$

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**Abstract:** In mammalian cells, two cellular organelles, mitochondria and peroxisomes, share the ability to degrade fatty acid chains. Although each organelle harbors its own fatty acid  $\beta$ -oxidation pathway, a distinct mitochondrial system feeds the oxidative phosphorylation pathway for ATP synthesis. At the same time, the peroxisomal  $\beta$ -oxidation pathway participates in cellular thermogenesis. A scientific milestone in 1965 helped discover the hepatomegaly effect in rat liver by clofibrate, subsequently identified as a peroxisome proliferator in rodents and an activator of the peroxisomal fatty acid  $\beta$ -oxidation pathway. These peroxisome proliferators were later identified as activating ligands of Peroxisome Proliferator-Activated Receptor  $\alpha$  (PPAR $\alpha$ ), cloned in 1990. The ligand-activated heterodimer PPAR $\alpha$ /RXR $\alpha$  recognizes a DNA sequence, called PPRE (Peroxisome Proliferator Response Element), corresponding to two half-consensus hexanucleotide motifs, AGGTCA, separated by one nucleotide. Accordingly, the assembled complex containing PPRE/PPAR $\alpha$ /RXR $\alpha$ /ligands/Coregulators controls the expression of the genes involved in liver peroxisomal fatty acid  $\beta$ -oxidation. This review mobilizes a considerable number of findings that discuss miscellaneous axes, covering the detailed expression pattern of PPAR $\alpha$  in species and tissues, the lessons from several PPAR $\alpha$  KO mouse models and the modulation of PPAR $\alpha$  function by dietary micronutrients.

**Keywords:** PPAR $\alpha$ ; peroxisome;  $\beta$ -oxidation; PPRE; ligand; coregulator; micronutrients; PPAR $\alpha$  knockout

## 1. Introduction

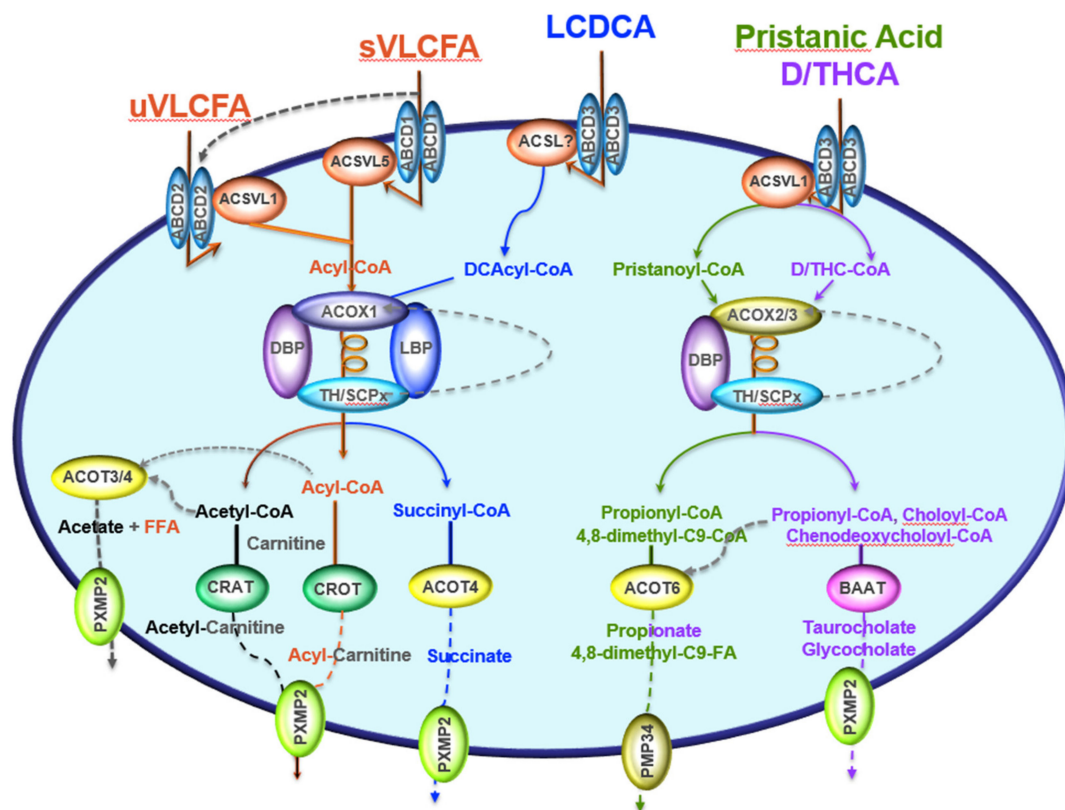
As reported in the review by Latruffe and Vamecq [1], peroxisomes are ubiquitous, single membrane-bound organelles. They belong to the fundamental class of intracellular compartments named microbodies. According to the evolutionists, microbodies and eukaryotic cells appeared on Earth around 1.5 billion years ago. Based on their related cell origin, these organelles are defined as glycosomes, glyoxysomes, hydrogenosomes or peroxisomes. Peroxisomes are found in higher vertebrates; glycosomes exist only in trypanosomes; glyoxysomes are found in leaves and seeds; hydrogenosomes are found in anaerobic unicellular ciliates, flagellates, and fungi. The latter two microbody structures belong to lower eukaryotic species, and all these compartments metabolize hydrogen peroxide. According to the endosymbiotic theory, peroxisomes, mitochondria, and chloroplasts may have derived from free-living prokaryotic ancestors. Only mitochondria and chloroplasts are semi-autonomous organelles, containing a DNA genome, which encodes for just some of their proteins.

In the mammalian liver, very-long-chain-fatty acids (VLCFA) are exclusively shortened in peroxisome through a specific  $\beta$ -oxidation system. Then, shortened fatty acids are metabolized by mitochondrial  $\beta$ -oxidation. Peroxisomes also contain the first enzymatic steps of plasmalogen synthesis [1]. In addition, they are involved in maintaining a redox state through the  $\text{NAD}^+/\text{NADH}$  balance, linked to the pyruvate/lactate level. In 1965, a milestone was reached by Hess et al. [2] who described, for the first time, hepatomegaly induced by clofibrate (ethyl 2-(4-chlorophenoxy)-2-methylpropanoate) in rats, subsequently established as a peroxisome proliferator in rodents and an activator of the fatty acid peroxisomal  $\beta$ -oxidation [3]. Later, Isseman and Green [4] identified peroxisome proliferators (PPs) as activator ligands of a special class of nuclear receptors termed Peroxisome Proliferator-Activated Receptor  $\alpha$  (PPAR  $\alpha$ ). Afterward, several PPAR isoforms were characterized as members of the superfamily of the nuclear steroid receptors. It is recognized that the phylogenetic origin of PPARs dates back 200 million years to the fish-mammalian divergence period [5]. PPARs evolved three times faster than other members of the hormone nuclear receptor superfamily, and are represented now in three isoforms ( $\alpha$ ,  $\beta/\delta$ , and  $\gamma$ ).

## 2. Peroxisomal $\beta$ -Oxidation Systems

In mammalian cells, both mitochondria and peroxisomes can degrade fatty acid chains. Although each organelle harbors its own fatty acid  $\beta$ -oxidation pathway, only the distinct mitochondrial  $\beta$ -oxidation system feeds the oxidative phosphorylation pathway for ATP synthesis, while the peroxisomal  $\beta$ -oxidation pathway participates in cellular thermogenesis [6]. Historically, we owe the first description of the mammalian peroxisomal fatty acid  $\beta$ -oxidation system to Lazarow and de Duve (1976) [7]. Later, a second peroxisomal  $\beta$ -oxidation system was characterized [6]. However, the very-long-chain fatty acids, part of the long-chain class and long-chain dicarboxylic acids, are exclusively processed by the peroxisomal  $\beta$ -oxidation system, whereas other common long-chain fatty acids are oxidized by mitochondria [6,8]. The entry of fatty acids into peroxisome, and activation as acyl-CoAs, depend on ABC membrane transporters (ABCD subfamily) and very-long-chain acyl-CoA synthetases [9,10]. The first  $\beta$ -oxidation system comprises three enzymes: acyl-CoA oxidase 1 (ACOX1), multifunctional protein (L-bifunctional peroxisomal enzyme (L-PBE, also referred to as EHHADH or MFP-1) [11,12], and 3-ketoacyl-CoA thiolases [13] (Figure 1). These three enzymes catalyze four successive reactions, starting with the  $\alpha,\beta$ -dehydrogenation by ACOX1 of the acyl-CoA into 2-trans-enoyl-CoA. L-PBE catalyzes enoyl-CoA hydration into L-3-hydroxyacyl-CoA, which is dehydrogenated, giving the 3-ketoacyl-CoA. Then, the 3-ketoacyl-CoA is subjected to a thiolytic cleavage by thiolase to produce one acetyl-CoA molecule and a two-carbon-shortened acyl-CoA [13] (Figure 1).

The second peroxisomal  $\beta$ -oxidation system (Figure 1), converting fatty carboxylates with a 2-methyl branch, such as pristanic acid and bile acid intermediates, includes the 2-methylacyl-CoA-specific oxidases (trihydroxycoprostanoyl-CoA oxidase and pristanoyl-CoA oxidase), the second multifunctional protein (named MFP-2) [11,14,15], and a 58 kDa sterol-carrier protein (SCP-2) containing thiolase activity [6,16] (Figure 1). Although both LBP/MFP-1 and DBP/MFP-2 provide hydratase and dehydrogenase activities, these proteins exhibit opposite stereospecificities. While LBP/MFP-1 hydrates 2-trans-enoyl-CoAs into L-3-hydroxyacyl-CoAs, and dehydrogenates the L-isomers [11,12], the DBP/MFP-2 transforms 2-trans-enoyl-CoAs into D-3-hydroxyacyl-CoA and dehydrogenates the D-isomers [6,11,14,15]. Despite the fact that the MFP enzymes are structurally unrelated to each other, both MFPs can hydrate 2-methyl-enoyl-CoAs [14]. The 3-hydroxy isomers formed by MFP-2 have the same (3R, 2R) configuration, or (24R, 25R) configuration in bile acid intermediates, underlining the role of MFP-2 in both pristanic acid degradation and bile acid synthesis [15]. Recently, it was demonstrated that LBP/MFP-1 is indispensable for the  $\beta$ -oxidation of dicarboxylic acids and the production of their medium-chain derivatives [6,15,17,18].



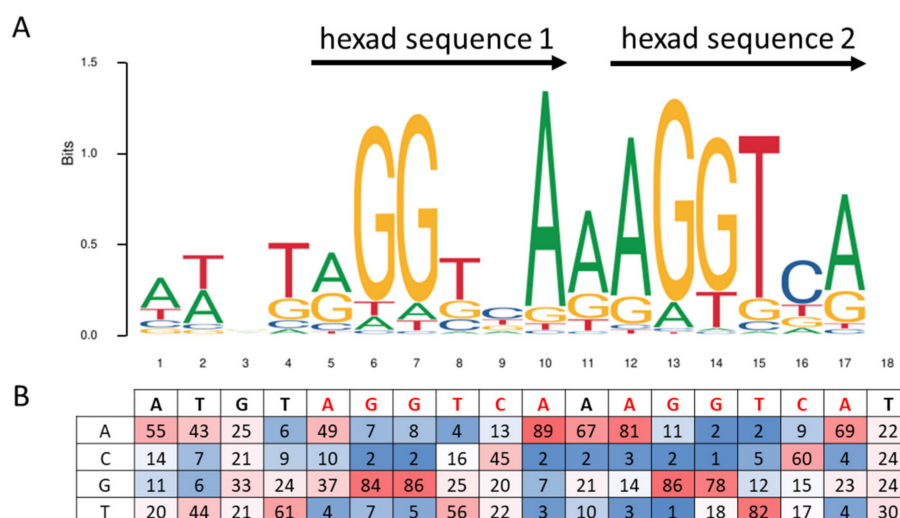
**Figure 1.** Peroxisomal  $\beta$ -oxidation pathways, including different enzymes and transporters. Saturated or unsaturated very-long-chain fatty acids (sVLCFA or uVLCFA) are imported by the solute ABC-transporters ABCD1 and ABCD2, respectively, into peroxisome, where they are transformed into their acyl-CoAs by one of the peroxisomal acyl-CoA synthetases (ACSVL5 for uVLCFA, and ACSVL1 for uVLCFA). The long-chain dicarboxylic acids (LCDCA), originating from the endoplasmic reticulum  $\omega$ -oxidation, are imported by ABCD3 and activated to their acyl-CoA thioesters (DCacyl-CoA) by an unknown acyl-CoA synthetase (ACSL?). The reactions that are catalyzed by ACSVL and ACSL use CoASH and hydrolyze ATP to AMP and pyrophosphate to activate VLCFA or LCDCA molecules, giving acyl-CoA. Acyl-CoA oxidase 1 (ACOX1) is the first flavoenzyme in the straight-chain  $\beta$ -oxidation system, oxidizing sVLCFA, uVLCFA, or LCDCA to their enoyl-CoA derivatives. The second enzyme metabolizing sVLCFA and uVLCFA is the D-bifunctional protein (also called MFP2 or HSD4B17), while the dicarboxylic enoyl-CoA are taken by the L-bifunctional enzyme (also called MFP1 or EHHADH). The thiolytic cleavage is catalyzed by one of the two peroxisomal thiolases (TH: thiolase/ACAA1/2 or SCPx: sterol carrier protein-x). After several rounds of  $\beta$ -oxidation, the peroxisomal system gives shortened acyl-CoA derivatives as hexanoyl- or octanoyl-CoA, and one molecule of acetyl-CoA/round. Both shortened acyl-CoA and acetyl-CoA can be hydrolyzed by acyl-CoA thioesterases 3 or 4 (ACOT3/4) to CoASH, while free fatty acid and acetate are exported by the pore-forming protein PXMP2 (or PMP22) to the cytosol. However, acetyl-CoA and acyl-CoA derivatives can also be transformed to acetyl-carnitine or acyl-carnitine by carnitine acetyl- and carnitine octanoyl transferases (CRAT and CROT), respectively, and then exported by PXMP2 to the cytosol.  $\beta$ -oxidation of DCacyl-CoAs leads to the production of succinyl-CoA, hydrolyzed to succinate and CoASH by ACOT4, and shipped outside by peroxisome PXMP2. Bile acid intermediates, dihydroxycholestanoic acid (DHCA) and trihydroxycholestanoic acid (THCA), imported by ABCD3 transporter, are beta-oxidized by ACOX2, DBP and SCPx enzymes, leading to the formation of choloyl-CoA and chenodeoxycholoyl-CoA, which are conjugated to glycine or taurine by the bile acid-CoA: amino acid N- acyltransferase (BAAT) and then exported by PXMP2. D/THC-CoA indicate DHCA and THCA co-enzyme A thioesters.

Distinct carnitine transferases and thioesterase enzymes handle products created from the peroxisomal  $\beta$ -oxidation fatty acyl-CoA derivatives. Carnitine moiety is then transferred to the acyl-CoA or the acetyl-CoA by carnitine octanoyltransferase (CROT) or carnitine acetyltransferase (CRAT). On the other hand, a specific peroxisomal thioesterase can hydrolyze the acyl-CoA or the acetyl-CoA, giving a free fatty acid or acetate that can

be transported to the cytosol by the peroxisomal membrane solute transporters, such as PXMP2 or PMP34 (Figure 1) [19].

### 3. Peroxisome Proliferator Response Element, PPRE

PPAR $\alpha$  is an ultimate lipid sensor [20] that has the potential to orchestrate and prompt the expression of a plethora of target genes implicated in a broad range of fatty acid metabolism processes [21,22], particularly under conditions of fasting-induced lipolysis and a lipid-rich diet [23–25]. Indeed, PPAR $\alpha$  activates many enzymatic pathways involved in fatty acid uptake, intracellular transport [26,27], fatty acid activation and  $\beta$ -oxidation, lipogenesis, ketogenesis and lipoprotein/cholesterol metabolism [28]. As a member of the PPARs family, PPAR $\alpha$  regulates the target gene expression in a transcriptional manner through heterodimerization with another transcription factor, the retinoid X receptor (RXR) encoded by the *NR2B1* gene [29,30]. Once activated by a ligand in the ligand-binding domain (LBD), the dimer binds to a specific DNA sequence element, the peroxisome proliferator response element (PPRE), located in the promoter region of target genes, to modulate their expression [31]. It is noteworthy that this regulation can require the recruitment of coregulators [32–36]. The PPAR $\alpha$  response element is usually composed of a direct repeat 1 type (DR-1), which means two immediate repetitions of the hexanucleotide AGGTCA consensus sequence, spaced by one nucleotide [37] (Figure 2). PPAR $\alpha$  and RXR $\alpha$  bind the first and the second hexamer sequences, respectively. The sequence logo of the PPAR $\alpha$ /RXR $\alpha$  PPRE consensus sequence ATGTAGGTCAAAGGTCA from the MA1148.1 Jaspar matrix [38], and the associated percentage of the four nucleotides at each position, is presented in Figure 2.

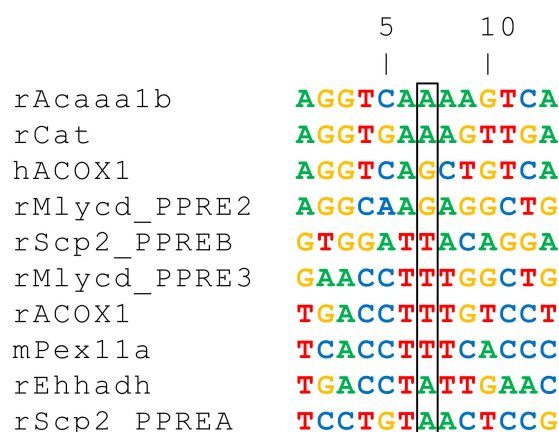


**Figure 2.** Sequence logo and consensus matrix of the PPAR $\alpha$ /RXR $\alpha$  PPRE consensus sequence from MA1148.1 Jaspar matrix [38]. **(A)** Sequence logo of the MA1148.1 Jaspar matrix, presenting the conservation of nucleotides from multiple alignments of 1000 PPAR $\alpha$ /RXR $\alpha$  PPRE sequences. Adenosine (A), cytosine (C), guanosine (G), and thymidine (T) nucleotides are respectively green-, blue-, yellow-, and red-colored, and the relative size of the letters represents their frequency in the consensus. The total height of a logo position corresponds to the degree of conservation in the corresponding multiple sequence alignment. **(B)** A table representing the percentage of the four bases for each position of the consensus. The color gradient code highlights the percentage of conservation of bases from blue to red for the whole table.

Among the hundreds of genes known to be regulated by PPAR $\alpha$ , eight are encoding enzymes that are commonly localized in the peroxisomal compartment (Figure 3), and belong to the three species: human, mouse, and rat. Table 1 presents validated PPREs sequences for functional genes, of which four (*Acox1*, *Ehhadh*, *Acaa1b*, and *Scp2*) are encoding very-long-chain fatty acid  $\beta$ -oxidation enzymes, and the remaining genes are *Cat*, encoding



the catalase enzyme, and *Mlycd* (malonyl-CoA decarboxylase gene), expressing an enzyme with both cytoplasmic and peroxisomal localization. The latter form is believed to be involved in the peroxisomal degradation of malonyl-CoA produced by odd-chain-length dicarboxylic fatty acid  $\beta$ -oxidation [39], and finally, the *Pex11a* gene, which participates particularly in peroxisome biogenesis (Pex11 $\alpha$ ).



**Figure 3.** Multiple alignments of PPRE sequences, identified in peroxisomal gene promoters, and experimentally proved to be regulated through PPAR $\alpha$  binding. Adenosine (A), cytidine (C), guanosine (G) and thymidine (T) nucleotides are respectively green-, blue-, yellow- and red-colored.

**Table 1.** Peroxisomal genes experimentally proved to be regulated through the PPAR $\alpha$  binding to PPREs.

Gene	Protein	Species	PPRE <sup>a</sup>	PPRE Sequence <sup>b</sup>	Reference
<i>Acaa1b</i>	acetyl-coenzyme A acyltransferase 1B	rat	PPRE2	<u>AGGTCAAAGTCA</u>	[40]
<i>ACOX1</i>	acyl-CoA oxidase 1	human	PPRE	<u>AGGTCAAGCTGTCA</u>	[41]
<i>Acox1</i>	acyl-CoA oxidase 1	rat	PPRE	<u>TGACCTTTGTCTT</u>	[36]
<i>Aldh3a2</i>	aldehyde dehydrogenase family 3, subfamily A2	mouse	PPRE	<u>nd</u>	[42]
<i>Cat</i>	catalase	rat	PPRE	<u>AGGTGAAAGTTGA</u>	[43]
<i>Ehhadh</i>	enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase	rat	PPRE	<u>TGACCTATTGAAC</u>	[44]
<i>Mlycd</i>	malonyl-CoA decarboxylase	rat	PPRE-2	<u>AGGCAAGAGGCTG</u>	[45]
<i>Mlycd</i>	malonyl-CoA decarboxylase	rat	PPRE-3	<u>GAACCTTTGGCTG</u>	[45]
<i>Pex11a</i>	peroxisomal biogenesis factor 11 alpha	mouse	PPRE	<u>TCACCTTTCACCC</u>	[46]
<i>Scp2</i>	sterol carrier protein 2	rat	PPRE-A	<u>TCCTGTAACTCCG</u>	[47]
<i>Scp2</i>	sterol carrier protein 2	rat	PPRE-B	<u>GTGGATTACAGGA</u>	[47]

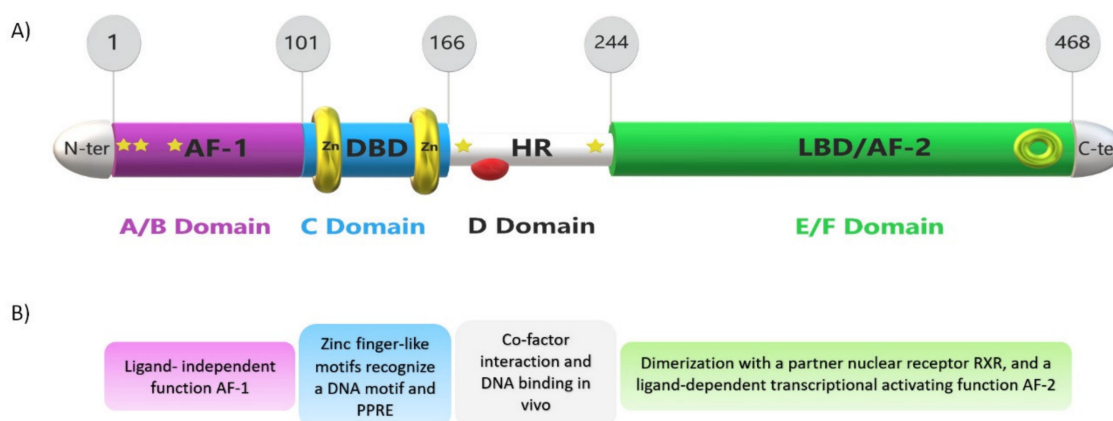
<sup>a</sup> corresponds, for each gene, to the PPRE numbering as stated in the corresponding reference. <sup>b</sup> PPREs sequence: PPAR $\alpha$  DR-1 sequences are shown with hexads underlined and spacing nucleotides in bold.

#### 4. PPARs and PPAR $\alpha$ Structure and Function

Peroxisome proliferator-activated receptors (PPARs) are ligand-regulated transcription factors and belong to a nuclear steroid/thyroid hormone receptor superfamily [48]. Their name originates from their property of peroxisome proliferation [49]. Three PPAR isoforms have been first isolated from the mouse [4], then *Xenopus* [33,50,51], then rat [52] and human [53], including PPAR $\alpha$  (NR1C1), PPAR $\beta/\delta$  (NUC1, NR1C2) and PPAR $\gamma$  (NR1C3). Human PPAR $\alpha$  protein consists of 468 amino acid residues, while PPAR $\beta/\delta$  has 441, and PPAR $\gamma$ , 479 amino acids long [54]. Each is characterized by a distinct tissue expression profile, a definite ligand binding specificity, and a set of functions implicated in

carbohydrate-lipid metabolism, cancer, inflammation, cell proliferation, and differentiation [55–58]. To sustain their protein stability and transcriptional activity, PPARs are subjected to post-translational modifications, such as phosphorylation [59], SUMOylation [60], and ubiquitylation [61]. PPARs act altogether in harmony, to maintain and control cellular and whole-body energy homeostasis by modulating the expression of their specific target genes [57].

The focus here will be on the PPAR $\alpha$  isoform. PPAR $\alpha$  is a type-II non-steroid ligand-regulated nuclear hormone receptor [4,32,62] transcribed from the human PPARA gene, which spans ~93.2 kb [53] and consists of eight exons [63]. It has been mapped to chromosome 15 in the mouse DNA and to chromosome 22 in humans [31]. The PPAR $\alpha$  protein possesses five main functional domains (A–F) embodied in a modular canonical structure [64] (Figure 4). The N-amino terminal end harbors the activation function-1 (AF-1) or A/B domain, which operates autonomously in a ligand-independent manner. The 65 amino acid-long DNA-binding domain (DBD), or C domain, consists of 2 highly conserved zinc finger-like motifs that promote the receptor's binding to the PPRE sequence of the target genes. The D domain or hinge region that bridges the DBD to the ligand-binding domain (LBD) acts as a docking site for cofactors. In the C-terminal region, the LBD, or E/F domain, is responsible for ligand specificity and contains the activation function 2 (AF-2) [28,65]. This latter contains a tyrosine residue on the helix 12, which plays an ultimate role in interacting with the carboxyl group of the ligands [66]. When a ligand enters the LBD pocket of PPAR $\alpha$ , the interface of AF-2 stabilizes and facilitates so that PPAR $\alpha$  can recruit coactivators [67]. The LBD is still a center of interest in numerous pharmaceutical investigations. Recent publications to date on studies based on X-ray crystallography, referenced in the protein data bank website (PDB; <http://www.pdb.org/>, accessed on 1 July 2021), provide fascinating, detailed insight into the LBD domain structure, albeit limited to comparing it with other PPAR receptors. It describes a relatively large Y-shaped hydrophobic cavity in the PPAR $\alpha$ -LBD pocket volume of 1400 Å<sup>3</sup> [68], which allows PPAR $\alpha$  to interact with a broad range of structurally distinct natural and synthetic ligands [67,69].



**Figure 4.** Schematic view of PPAR $\alpha$  structure and domain function, with phosphorylation and cofactor binding sites. From the left N-terminus to the right C-terminus of the PPAR $\alpha$  protein, (A) domain structure of the PPAR $\alpha$  protein with the ligand-independent activation function-1 (AF-1) domain or A/B domain shown in purple, the DNA-binding domain (DBD) or C domain shown in blue with two zinc finger-like motifs, the hinge region (HR) or D domain shown in white, and the ligand-binding domain (LBD) or E domain together with the activation function 2 (AF-2) or F domain shown in green. Phosphorylation sites are labeled with yellow stars (6, 12, 21, 179, 230) amino acids, the corepressor site is marked with a red half-sphere, and the coactivator binding site is shown with a green ring. The panels on top show the number of amino acid residues. (B) Structural function of A/B, C, D, and E/F domains, respectively.

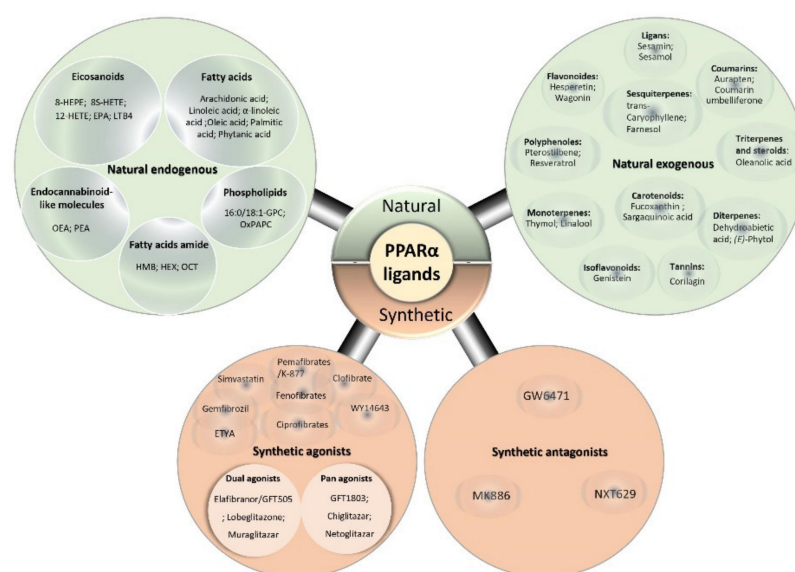
## 5. PPAR $\alpha$ Ligands

Recently, PPAR $\alpha$ -ligands have gained consistent interest in several complex metabolic disease investigations [60,67], such as lipid metabolism disorders. Due to their engagement in physiological and pathophysiological metabolic processes, and their role in activating transcriptional regulatory networks, these ligands are becoming intriguing bona fide treatment opportunities and present a way to unveil many relevant potential roles of PPAR $\alpha$ , also known as promising versatile drug targets.

Evidence indicates that a wide variety of lipophilic molecules, the so-called ligands, can activate PPAR $\alpha$ , encompassing natural saturated, unsaturated, and polyunsaturated fatty acids (PUFAs) [70,71], and synthetic ligands that are collectively referred to as PPAR $\alpha$ -activators [72].

### 5.1. PPAR $\alpha$ Natural Ligands

Natural ligands include endogenous metabolites products derived from the lipid metabolism, such as acyl CoAs [73,74], oxidized fatty acids [63], phospholipids [75], certain nitrated derivatives of fatty acids, eicosanoids [76], endocannabinoid-like molecules [77], and lipoprotein lipolytic products [78]. PPAR $\alpha$  natural activators could also originate from an exogenous source that is either found in dietary constituents [65], e.g., dietary  $\omega$ -3 polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid) or issuing from traditionally used medicinal plants (reviewed by Rigano et al. [79]) (Figure 5).



**Figure 5.** Diagram of different types and classes of PPAR $\alpha$  ligands. The natural ligands type encompasses endogenous natural ligands (fatty acids [28,80–82], eicosanoids [31,83–85], phospholipids [75,86], fatty-acid amide [87] and endocannabinoid-like molecules [77], and exogenous natural ligands [30,88] (polyphenol flavonoids, isoflavonoids, monoterpenes, sesquiterpenes, diterpenes, triterpenes and steroids, carotenoids, coumarins, ligands, and tannins). The synthetic ligands type includes various classes of synthetic agonists [28,31,62,67,69,88–91] with various activation and binding modes (single [88,92], dual [28,91,93,94] and pan agonists [28,92]), and synthetic antagonists [89,90,95]. Abbreviations: 8-HEPE: 8-hydroxyeicosapentaenoic acid, 12-HETE: 12-hydroxyeicosatetraenoic acid, 8S-HETE: 8 (S)-hydroxyeicosatetraenoic acids, 16:0/18:1-GPC: phosphatidylcholine(1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine), EPA: eicosapentaenoic acid (20:5), ETYA: eicosatetraenoic acid, HEX: hexadecanamide, HMB: 3-hydroxy-(2,2)-dimethyl butyrate, OCT:9-octadecenamide, OEA: oleoyl-ethanolamide, OxPAPC: oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine, PEA: palmitoyl-ethanolamine.

Numerous findings provide evidence that natural ligands exhibit different binding affinities, which subsequently impact PPAR $\alpha$  activation potency. Previous reports showed that omega-3 eicosapentaenoic acid (20:5,  $\omega$ 3) and, to a lesser extent, docosahexaenoic acid (22:6,  $\omega$ 3), are potent ligands [96,97] and consistent activators of PPAR $\alpha$  [98–100], while omega-3 PUFA like linolenic acid (C18:3,  $\omega$ 3) and docosapentaenoic (22:5,  $\omega$ 3) acids, and omega-6 PUFA such as linoleic (C18:2,  $\omega$ 6) and arachidonic (C20:4,  $\omega$ 6) acids are weaker PPAR $\alpha$  activators [74,99,100]. In addition, experiments performed by Ellinghaus et al. and Zomer et al. [101,102] revealed that phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) is a strong natural physiological ligand for PPAR $\alpha$ . These assumptions were then followed by reports from Hostetler et al. [103], showing that PPAR $\alpha$  binds the fatty acyl-CoAs (3–20 nM Kds) and branched-chain fatty acyl-CoA (BCFA-CoAs, phytanoyl-CoA, pristanoyl-CoA; Kds near 11 nM) with the highest affinities (i.e., Kd at nM range).

Natural PPAR $\alpha$  ligands description studies, using full-length- or chimeric LBD-PPAR $\alpha$  constructs, revealed the ability of many saturated and unsaturated fatty acids to activate target gene expression through PPAR $\alpha$  modulation. Several PPAR $\alpha$ -responsive genes are involved in fatty acid oxidation: (i) mitochondrial  $\beta$ -oxidation pathway (i.e., carnitine palmitoyltransferase 1A) [104]; (ii) microsomal  $\omega$ -hydroxylation (i.e., CYP4A1-subclass of cytochrome P450 enzymes); and (iii) peroxisomal  $\beta$ -oxidation pathway (i.e., ACOX1; enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase [105], 3-ketoacyl-CoA Thiolase and SCPx) [7,106,107].

The abovementioned results were recently supported by Chen et al. [108], reporting that feeding animals a diet high in rapeseed oil (rich in erucic acid, a very-long-chain fatty acid) leads to PPAR $\alpha$  activation with an adaptive elevation in peroxisomal  $\beta$ -oxidation capacity, which suggested that erucic acid might act as a potential ligand for PPAR $\alpha$ . In line with prior communicated data, Maheshwari et al. [109] reported that treating rat Fao cells with a fungal lipid extract rich in monomethyl BCFAs (*Conidiobolus heterosporus*) increases mRNA levels of the PPAR $\alpha$  target genes *Acox1*, *Cyp4a1*, *Cpt1A*, and *Slc22A5*, strongly suggesting that BCFAs are similarly potent PPAR $\alpha$  activators [109]. Taken together, these relevant results from our laboratory and from others all affirm that the peroxisomal  $\beta$ -oxidation substrates are potent PPAR $\alpha$  ligands that modulate the expression of a battery of lipid-metabolizing enzymes to maintain lipid homeostasis and to alleviate the toxic effect of VLCFA and BCFA overload [57].

## 5.2. PPAR $\alpha$ Synthetic Ligands

In the same way, PPAR $\alpha$  binds to synthetic ligands termed PPAR $\alpha$  activators. Interestingly, PPAR $\alpha$ -activators exhibit structural features like a carboxylic acid head and a hydrophobic tail, connected via an aliphatic chain and a central aromatic ring [101]. This group of compounds includes various insecticides (2,4-dichlorophenoxyacetic acid); herbicides (phenoxyacetate derivatives) [110]; surfactants (perfluorooctanoic acid-PFOA); organic chlorinated hydrocarbons solvents such as perchloroethylene and trichloroethylene [111]; food flavors [112]; leukotriene D4 receptor antagonists [113]; phthalate plasticizers, such as di-(2-ethylhexyl)-phthalate and di-(2-ethylhexyl) adipate [114]; and amphipathic carboxylic acids [98]. The latter form the hypolipidemic fibrate class of drugs, acknowledged as the archetypal PPAR $\alpha$  agonists, including clofibrates [88,89]; pemafibrates [67,69]; fenofibrates [67], and ciprofibrates [115]. It is notable that certain synthetic ligands are designed to act as dual agonists, like muraglitazar [93], that target both PPAR $\alpha$  and PPAR $\gamma$  isotypes; others act as pan-agonists that activate all PPAR receptors like bezafibrates [92]; or as a PPAR $\alpha$  partial agonist such as GW9662 [69], known as a PPAR $\gamma$ -selective antagonist (Figure 5). Interestingly, GW9662 displays dual effects by acting as agonist and antagonist against PPAR $\alpha$  and also has the ability to enhance agonistic activities of certain less potent fibrates [69], whereas PPAR $\alpha$  antagonists like GW6471 [89], MK886 [90], and NXT629 [95] represent the rare range of synthetic ligands that prevent other molecules from binding to this nuclear receptor.



To date, various synthetic single, dual and pan agonists, respectively, are in clinical use as medications to treat dyslipidemia, hyperglycemia in patients with Type 2 diabetes mellitus, hypertriglyceridemia, and cardiovascular disease [28,72,91]. Indeed, potent synthetic ligands could elicit both desirable and undesirable side effects. Studies conducted by Preiss et al. [116] proved that the chronic administration of peroxisome proliferators to rodents causes hepatocellular carcinoma, and it may also increase the risk of gallstones and cause anemia and leukopenia [117]. Much of what we know about PPAR $\alpha$ -ligands comes from a collective knowledge primarily derived from rodent studies, via the treatment of mice or rats with synthetic PPAR $\alpha$  peroxisome proliferators or by using PPAR $\alpha$  null mice [98]. It has been reported that human and mouse PPAR $\alpha$  have different binding affinities and physiological effects [118] and are diversely activated by specific ligands, including phthalates and fibrates [119]. Nevertheless, these differences are negligible and do not call into question the tenet of the ultimate role that PPAR $\alpha$  plays as a general lipid sensor in both species [98].

To date, tremendous efforts are in progress to develop new, highly PPAR $\alpha$ -specific ligands with different activation and binding modes that could more selectively activate PPAR $\alpha$ -RXR $\alpha$  transcriptional complex assembly, with tissue-selective and gene-selective activities, to reduce unwanted side effects and assure reasonable safety. In parallel, the “micronutrients” found in food that activate PPAR receptors are gaining increasing interest, as nutritional therapy becomes an unstoppable trend for treating lipid disorders [79].

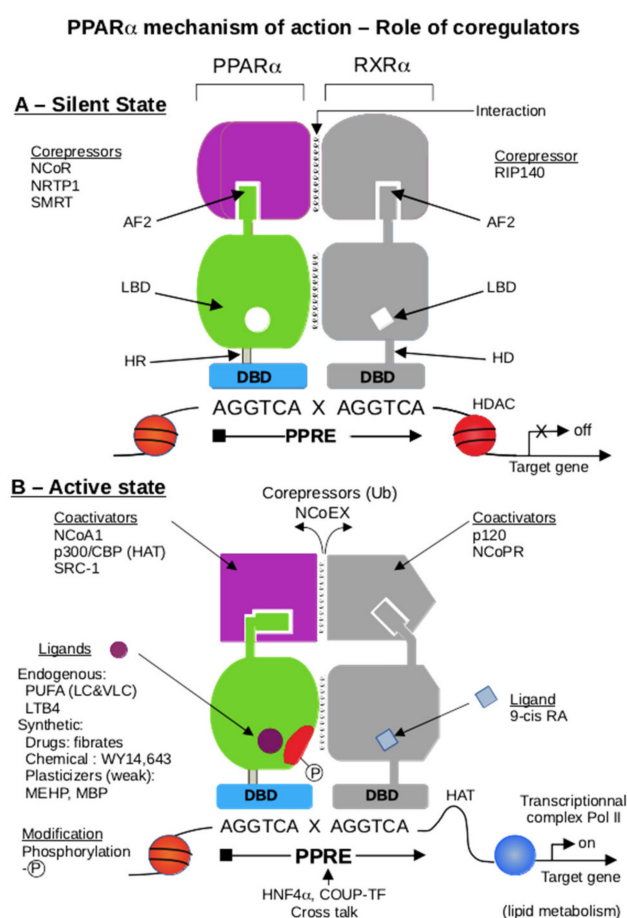
## 6. PPAR $\alpha$ and Coregulators

The identification of PPAR in the 1990s heralded a new era of biotic and xenobiotic sensing by the liver [4]. The PPAR subfamily of nuclear receptors functions as sensors for fatty acids and fatty acid derivatives and controls critical metabolic pathways involved in lipid and energy metabolism [120,121] and catabolism [122–125]. The transcriptional activation of genes is a complex process that involves the participation of many transcription factors [126]. While the nuclear receptors (NRs) mediated gene-regulation provide the backbone for the transcription factor-specific gene regulation, coregulators provide the much-needed tissue-, cell-, and species-specific differences in the peroxisome proliferator-induced pleiotropic responses of PPAR $\alpha$  [127,128]. However, we would like to focus this review section on the role of PPAR $\alpha$  and its associated proteins in regulating peroxisomal beta-oxidation genes/pathways. Coregulators are proteins that bind to the nuclear receptor by a specific domain LXXLL, a hallmark for all coregulators [129]. Most coregulators have more than one LXXLL domain and are essential for protein–protein interactions between the nuclear receptor and the coregulator [130] (Figure 6). Moreover, each LXXLL could function in a specific nuclear interaction, suggesting that the coregulators are shared between different NRs.

Coregulators can be broadly classified into subgroups, such as essential vs. non-essential, repressors vs. activators, and DNA binding region (DBD) vs. ligand binding-region (LBD) interacting coregulators [127]. Essential coregulators are proteins deemed critical for the survival of the offspring, and their absence results in embryonic lethality: cAMP-response element-binding protein (CBP); PPAR-interacting protein/activating signal cointegrator 2 (PRIP/ASC2); PPAR-binding protein/mediator complex subunit 1 (PBP/Med1); mediator complex subunit 25 (Med25) [131–133]. Non-essential coregulators are proteins with such critical functional responsibilities that they are usually represented by more than one isoform—steroid receptor coactivators (SRCs) [131,132,134], Asp-Glu-Ala-Asp (DEAD)-box helicases [135–137], sirtuins (SIRT) [96,97], PPAR $\gamma$  coactivators (PGCs) [138–141]—and the loss of one isoform is compensated by others. Repressors that bind to the nuclear receptor PPAR $\alpha$  in the absence of/or independent of ligands prevent it from binding to the peroxisomal proliferator response elements (PPRE) of the target genes as nuclear corepressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone (SMRT) [96] (Figure 7A). This group of proteins usually bind to the AF-1 domain of the DNA binding region of the receptor. The ligand-independent coregulators (heat-

shock protein-70) could also prevent the PPAR $\alpha$  from proteolytic degradation in the cytosol before PPAR $\alpha$  could translocate to the nucleus in the activated state [131] and, typically, these proteins bind to the hinge region of the nuclear receptor that interconnects the DNA binding region to the ligand-binding region of the receptor [127]. The activators, on the other hand, could help PPAR $\alpha$  zero in onto the specific PPREs of the target genomic region, help attach it to the PPREs with the assistance of nucleosomal-specific functions such as histone methylases (SRC proteins) [142], histone acetyltransferases (CBP/p300) [143,144], DNA-helicases [145], PRIC285 [124], and PRIC320 [146]. The activators would also function by stabilizing the transcriptional complex (PRIP/ASC2 [147]) and potentiate the recruitment of RNA-polymerase complex proteins to the transitional complex (mediator complex, PBP [148,149] (Figure 7B). Additionally, the activators would consist of proteins responsible for separating the transcribed mRNA from the genomic region (protein-L-isoaspartate (D-aspartate) O-methyltransferase (PIMT) [147]. These proteins activate the AF-2 domain of the nuclear receptor and enhance transcription by linking the liganded nuclear receptor to the basal transcription machinery. We have identified almost all these groups of coregulators using either a direct protein–protein interaction assay, such as a yeast two-hybrid assay [150], GST-pull downs [124], and ligand affinity chromatography [141] to identify the PPAR $\alpha$ -interacting proteins and a functional transcriptional activation complex [131]. PPARs, like other nuclear receptors, interact with coactivators such as SRC-1 (steroid receptor coactivator-1) or corepressors such as NCoR and SMRT. PPAR $\alpha$ -interacting coactivators and corepressors augment or repress, respectively, the PPAR $\alpha$  transactivation activity. Since the cloning of SRC-1 twenty-five years ago, over 300 coactivators/coregulators have been identified, with new members still being added to this expanding spectrum. PPAR $\alpha$  is known to interact with some of these coregulators [151]. These include CBP/p300-dependent binding complex [152], members of the SRC/p160 superfamily, members of PBP/MED1 complex (PBP/TRAP220/DRIP205/MED1 [133,149,153], members of PRIP/NCoA6 (ASC2/RAP250/TRBP/NRC), members of PRIC complex PRIC285 [124], PRIC295 [141], PRIC320 [146], PPAR gamma-binding proteins, PGC-1 $\alpha$  [147,154], and PGC-1 $\beta$  [155,156], as well as coactivator-associated proteins PIMT [131] (NCoA6IP) and coactivator-associated arginine methyltransferase 1 (CARM-1) [157,158]. The PPAR $\alpha$ -interacting coregulator (PRIC) complex isolated from rat liver nuclear extracts reveals many coregulators, presumably forming one mega-complex. An almost similar complex was isolated with ciprofibrate as the ligand in affinity chromatography. This diversity raises several issues about the evolutionary importance of the versatility and complexity of coregulatory molecules, their relative abundance in various cell types, and their affinity for a given nuclear receptor in orchestrating transcription in gene-, cell-, and developmental stage-specific transcription. In the absence of a specific ligand, PPAR $\alpha$  interacts with the corepressors NCoR and SMRT, but the importance of PPAR $\alpha$  action is not well documented, as endogenous ligands could potentially activate PPAR $\alpha$  [159]. The homozygous deletion of NCoR or SMRT in mice is embryonically lethal, indicating that they cannot fully compensate for each other during development [160–162]. Furthermore, another corepressor, the receptor-interacting protein 140 (RIP140), which can interact with PPAR $\alpha$ , is known to repress the activity of NRs by competing with coactivators and by recruiting downstream effectors such as histone deacetylases (HDACs) [163]. Interestingly, the phenotype of RIP140 knockout mice suggests a role for this corepressor in PPAR $\alpha$  signaling, as these mice exhibit resistance to high-fat diet-induced obesity, resulting from the upregulation of genes involved in energy dissipation [163]. Interestingly, hepatic sirtuin 1 (SIRT1) regulates lipid homeostasis by positively regulating PPAR $\alpha$  [164,165]. On the other hand, SIRT1 interacts with PPAR $\gamma$  and is regulated by PPAR $\gamma$  in a negative feedback mechanism [166]. SIRT6 binds NCOA2, a PPAR $\alpha$  coactivator and part of the SRC family of coactivators; the binding results in the decrease of the acetylation of SRC2/NCOA2 K780 in the liver, thus, interaction with SIRT6 mediates the activation of PPAR $\alpha$  and thus the inhibition of SREBP-dependent cholesterol and triglyceride synthesis [167]. The ligand binding to a nuclear receptor triggers a molecular switch that releases corepressors and begins the

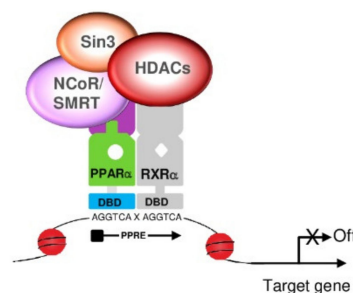
recruitment of coactivator complexes, such as members of the CBP/p300 family, which exhibit the histone acetyltransferase activity required to facilitate chromatin remodeling. The subsequent recruitment of other coregulators, either singly or as preassembled multi-subunit protein complexes, including mediator complex and RNA polymerase machinery, is facilitated by the interaction of the general basal transcription machinery to enhance the transcription of a specific set of genes [97,168]. As discussed previously, coregulators contain an LXXLL motif that forms two turns of the  $\alpha$ -helix and binds to a hydrophobic cleft on the surface of the nuclear receptor. The identification and characterization of coregulators have been derived mostly from *in vitro* experiments, but there is a paucity of information about individual coactivators *in vivo* cell- and gene-specific functional roles [131].



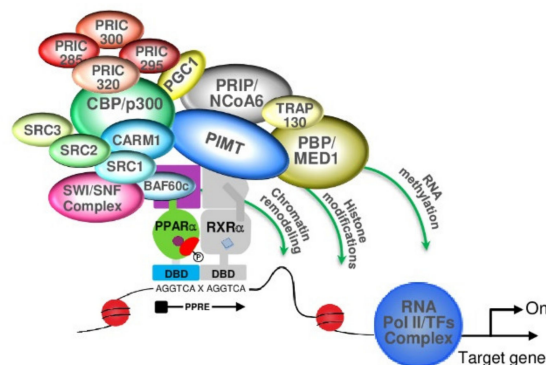
**Figure 6.** Scheme of heterodimer PPAR $\alpha$ /RXR $\alpha$ , located on a PPRE DNA region. The graphic displays two parts: part (A), the silent state, and part (B), the active state. Part (A). In the absence of the ligand, PPAR $\alpha$  interacts with transcriptional corepressors (NCoR, SMRT, NRTP-1) by recognizing the AF2 region. The same process is at the RXR, where AF2 interacts with RIP140 as RXR $\alpha$  corepressor [169]. Due to the chromatin condensed state, the heterodimer cannot bind the PPRE properly. Part (B). In the presence of a PPAR $\alpha$  ligand, either a long-chain or very-long-chain polyunsaturated fatty acid, leukotriene LTB4, fibrate or other chemicals [170], and a 9-cis retinoic acid as RXR $\alpha$  ligand, an exchange corepressor/coactivator is made by NCoEX, which suppresses the repressive of corepressor state by ubiquitinylation-inducing degradation by the proteasome system. The fixation of a ligand induces an allosteric LBD conformational change of AF2, allowing the recruitment of coactivators, either NCoR1, p300/CBP, or SRC1 for PPAR $\alpha$ , and p120 and NCoPR for RXR $\alpha$  [171]. The CBP-dependent HAT activity induces the remodeling of chromatin and allows the PPAR $\alpha$ /RXR $\alpha$  heterodimer to bind to PPRE correctly, then activates the Pol II transcription complex and triggers the transcription of lipid metabolism-encoding genes. Some post-translational

modifications of PPAR $\alpha$  regulate its activity [172,173]. For instance, phosphorylation stimulates PPAR $\alpha$  transcriptional activity [174]. The HNF4 $\alpha$  transcription factor recognizes a similar response element as the PPRE and interplay with PPAR $\alpha$  [175]. A comparable mechanism has been reported with the Coup-TF transcription factor. While several works consider PGC-1 $\alpha$  [176] as an important coregulator of PPAR $\alpha$ , it seems to be more specific for PPAR  $\gamma$ . The 15(S)-HETE, 15-hydroxyicosatetraenoic acid, family of arachidonic acid metabolites; 9-cisRA, retinoic acid cis conformation in carbon 9; AF1, activating domain 1; AF2, activating domain 2; CBP, CREBP binding protein; CoPRs, COPR1 and COPR2 as corepressors of PPAR and RXR, respectively; COUP-TF, chicken ovalbumin upstream promoter transcription factor; CTBP-2, C-terminal binding protein-2; DBD, DNA binding domain; HAT, histone acetyl-transferase; HD, hinge domain; HNF-4 $\alpha$ , hepatic nuclear factor 4  $\alpha$ ; HDAC, histone de-acetyl transferase; LBD, ligand binding domain; LTB4, leukotrien B4; MBP, mono butyl phthalate; MEHP, mono ethyl hexyl phthalate; NCoA1, nuclear receptor coactivator 1; NCoEX, nuclear receptor corepressor Excit; NCoR1, nuclear receptor corepressor 1; NRTP-1, nuclear repressor transcription factor; p120, protein 120 kDa; p300, protein 300 kDa; Pol II, RNA polymerase class II; PGC-1 $\alpha$ PPAR  $\gamma$  co-activator-1 $\alpha$ ; PPRE, peroxisome proliferator response element; PRIP/RAP250, PPAR interacting-protein methyl transferase; PUFA (LC & VLC), polyunsaturated fatty acids (long-chain or very-long-chain); RIP140 receptor interacting protein corepressor; SMRT, silencing mediator of retinoid and thyroid receptors; SRC1, steroid receptor coactivator-1.

#### A: Corepressor complex



#### B : Coactivator complex



**Figure 7.** Interaction of PPAR $\alpha$ -RXR $\alpha$  heterodimer with corepressor complex (A) or coactivator complex (B). (A) The corepressor complex, including Sin 3, NCoR/SMRT, and HDAC proteins, is recruited to an unliganded PPAR $\alpha$ -RXR $\alpha$  heterodimer, so there is no transcription of the PPAR $\alpha$ -target genes. (B) In the presence of PPAR $\alpha$ -ligand, the PPAR $\alpha$ -RXR $\alpha$  heterodimer exhibits a conformational change, leading to the dissociation of the corepressor complex, the recruitment of coactivator proteins, and the binding of PPAR $\alpha$  to the peroxisome proliferator response element (PPRE). Different subcomplex modules participate in chromatin remodeling, through the acetylation (SRCs, p300) and the methylation (CARM1) of nucleosomes. Mediator components interact with PPAR $\alpha$  and promote the recruitment of the basal transcription factors (TFs) to establish a connection with the RNA polymerase II to transcription of PPAR $\alpha$ -target genes.



## 7. Metabolic Regulation of the Peroxisomal $\beta$ -Oxidation Pathways

The regulation of the peroxisomal pathways is mainly associated with the cellular increase of the peroxisome population, which is highly promoted by several diverse natural and synthetic compounds nominated as peroxisome proliferators (PPs). Such compounds raise a peroxisome number quantitatively, mainly in hepatic parenchymal cells, and provoke delayed pleiotropic responses, including the development of hepatocarcinoma in rats and mice [8,131]. Based on several pieces of experimental evidence, earlier reports from Reddy's group proposed a receptor-mediated mechanism to explain the phenomenon of hepatic peroxisome proliferation. Accordingly, the induction of peroxisomal  $\beta$ -oxidation is a consequence of ligand hepatic overload, leading to lipid metabolism dysregulation, accompanied by an augmentation in the extrahepatic lipolysis and a substantial hepatic influx of free fatty acids [96]. Furthermore, the unique pleiotropic responses raised by structurally unrelated peroxisome proliferators in hepatocytes drive a synchronized transcriptional activation of the peroxisomal  $\beta$ -oxidation genes [13,96,131].

Lazarow and De Duve [7] demonstrated previously that clofibrate administration in rat liver strikingly enhances the peroxisomal  $\beta$ -oxidation activity. A similar observation was reported by Hashimoto and coworkers [177], showing that feeding a diet containing a phthalate ester plasticizer di-(2-ethylhexyl)phthalate, a PPAR $\alpha$  activator, leads to a 20-fold increase in the expression of peroxisomal  $\beta$ -oxidation enzymes in rat liver. In addition, a previous study reported that synthetic ligands such as WY-14643 exhibited a high affinity to PPAR $\alpha$ , compared to the natural endogenous ligand (16:0/18:1-GPC) in the induction of fatty acid  $\beta$ -oxidation [75]. Moreover, Rogue et al. [93] showed that *Acox1* and *Cpt1A* genes in oleic-acid-overloaded HepaRG cells were significantly upregulated from 1 day, and remained at high levels after 14 days, upon treatment with the dual agonist muraglitazar, which stimulates the fatty acid  $\beta$ -oxidation pathway. These results are in close concordance with previous experiments conducted by Lee et al. [126], showing that after feeding hypolipidemic agents to mice lacking PPAR $\alpha$  expression, the mutant animals accumulated lipid droplets in their tissues, which strongly supports the idea that PPAR $\alpha$  activators promote the transcription of genes involved in the lipid catabolism process.

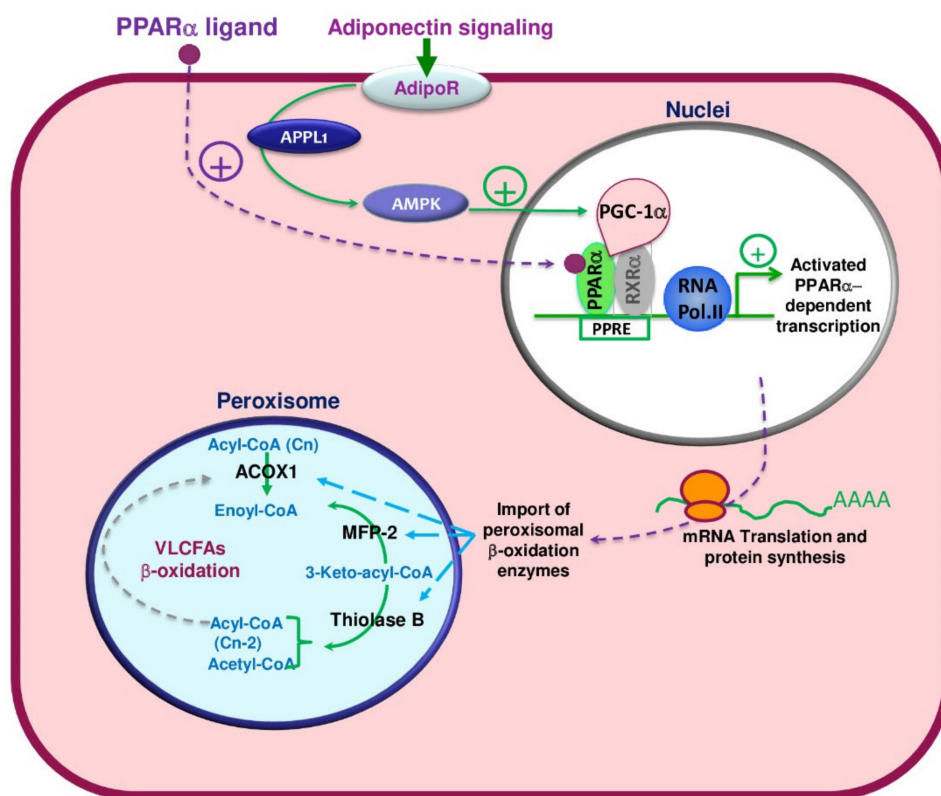
Structurally, PPs molecules may be chemically unrelated, including hypolipidemic drugs, such as clofibrate, ciprofibrate, gemfibrozil, and Wy-14,643, as well as some nutritional conditions, especially high-fat diet or vitamin E-deficient diet and leukotriene D4 receptor antagonists. In addition, several herbicides, such as 2,4-dichlorophenoxyacetic acid or 4-chloro-2-methylphenoxyacetic acid [8,178] and certain phthalate ester plasticizers, induce a similar liver peroxisome proliferation as do prototypic fibrate derivatives. In addition, the administration to rodents of a C19-steroid, dehydroepiandrosterone, promotes peroxisomal fatty acid  $\beta$ -oxidation and peroxisome proliferation [179]. Though the response to PPs has been demonstrated in several tissues from PPs-treated rodents, the hepatic responsiveness is by far the most powerful, accounting for a 10- to 20-fold induction of peroxisomal fatty acid  $\beta$ -oxidation activities, accompanied by a proliferation of peroxisomes and strong hepatomegaly pathogenesis [8,131].

The description of PPAR $\alpha$ -target genes shows that this nuclear hormone receptor largely governs those genes involved in hepatic and cardiac muscle transport, oxidation, and the degradation of lipids. Transcriptionally, PPAR $\alpha$  activates several genes, including the lipoprotein lipase gene permitting the release of fatty acids from lipoprotein particles [180], genes encoding fatty acid translocase CD36, and fatty acid-binding protein-facilitating fatty acids capture and transport them through the plasma membrane [8,180]. The acyl-CoA synthetase, activating fatty acids to acyl-CoAs, is another gene-target of PPAR $\alpha$  [96,98]. Regarding the genes encoding peroxisomal  $\beta$ -oxidation enzymes, the induction of the peroxisomal fatty acyl-CoA ABC transporter D2 (ALDRP) by PPs was shown to be partially PPAR $\alpha$ -dependent in mice hepatocytes [179]; however, the regulation of, e.g., ACOX1, L-PBE and ThB, are entirely reliant on PPAR $\alpha$  [8,98,181]. Nevertheless, the regulation of genes implicated in the mitochondrial fatty acid  $\beta$ -oxidation, including the carnitine palmitoyltransferase-1 and the medium chain-acyl-CoA dehydrogenase, is also

coordinated by PPAR $\alpha$  [98,182,183]. Thus, PPAR $\alpha$  arises as a master regulator controlling the hepatic metabolism of free fatty acids. The development of PPAR $\alpha$  null mice evidenced the crucial role played by PPAR $\alpha$  in the concerted regulation of peroxisome proliferation and expression of its target genes involved in both  $\beta$ - and  $\omega$ -fatty acid oxidations [181]. By contrast to *Ppara*<sup>-/-</sup> mice, which exhibit mild hepatic steatosis, *Acox1* null mice develop strong hepatic steatosis, showing a hepatic peroxisome proliferation and the sustained activation of PPAR $\alpha$  and expression of its target genes [147,184]. Thus, paradoxically, the defect in ACOX1 activity leads to the hepatic accumulation of ACOX1 substrates, of which some have been shown [147] as efficient endogenous PPAR $\alpha$  ligands, mediating the sustained activation of PPAR $\alpha$ . On the other hand, the strong PPAR $\alpha$  activation of fatty acid  $\beta$ -oxidation genes increases hepatic dicarboxylic acid production and accumulation. Thus, in the absence of ACOX1 activity, these dicarboxylic acids are still unmetabolized and act as firm inhibitors of mitochondrial fatty acid  $\beta$ -oxidation [185]. Moreover, the *Ppara*<sup>-/-</sup>, *Acox1*<sup>-/-</sup> double-knockout mice exhibit a few periportal clusters of steatotic hepatocytes, and (re-)expression of human ACOX1 in mice liver results in a substantial reduction in both PPAR $\alpha$  activation and hepatic steatosis [8,180]. Peroxisomal fatty acid  $\beta$ -oxidation is induced by starvation in a PPAR $\alpha$ -dependent manner, as validated by its impairment in PPAR $\alpha$  null mice [8,180]. Accordingly, the deacetylase sirtuin-1 is dispensable to PPAR $\alpha$ -inducing peroxisomal fatty acid  $\beta$ -oxidation and needs SIRT1-PPAR $\alpha$  interaction, and the deletion of hepatic SIRT1 negatively impacts PPAR $\alpha$  signaling [165]. The MAP kinase kinase kinase TGF $\beta$ -activated kinase 1 (TAK1) acts upstream to PPAR $\alpha$ , and its deletion also impaired the PPAR $\alpha$ -dependent induction of peroxisomal fatty acid  $\beta$ -oxidation [186]. PPAR $\alpha$  signaling has also been shown to involve the AMPK-SIRT1-PGC-1 $\alpha$  axis via the adiponectin receptors [187] (Figure 8). These results strongly highlight the detrimental role of the peroxisomal  $\beta$ -oxidation pathway in the sensing of PPAR $\alpha$  activity.

Several peroxisomal  $\beta$ -oxidation substrates display a substantial role as PPAR $\alpha$  modulators. It is believed that the activities of (inducible and non-inducible) peroxisomal fatty acid  $\beta$ -oxidation systems are modulated by PPAR $\alpha$  [108]. Moreover, several findings provide significant evidence that VLCFA and BCFA, which are considered potentially toxic fatty acids, are potent inducers of PPAR $\alpha$  that enhance the transcription of peroxisomal enzymes mediating fatty acid  $\beta$ -oxidation [57,188].

Interestingly, Oleoylethanolamide, a naturally occurring lipid regulating satiety and body weight, exhibited a high-affinity binding to PPAR $\alpha$  and the activation of its lipid-metabolizing target genes [189]. Nonetheless, we should consider that most fatty acids are subject to elongation, desaturation, esterification, and  $\beta$ -oxidation, which could modify the availability of PPAR $\alpha$  ligands. Accordingly, very-long-chain saturated and unsaturated fatty acids are exclusively metabolized by peroxisomal  $\beta$ -oxidation, which participates in their degradation, synthesis, or retro conversion. One defect in this pathway is associated with the accumulation of VLCFAs and a deficit in certain PUFAs' synthesis, such as DHA. Interestingly, a mouse deficiency of ACOX1, the rate-limiting enzyme in the peroxisomal  $\beta$ -oxidation, leads to the sustained activation of hepatic PPAR $\alpha$  and the induction of its target genes [190]. The role of ACOX1 in PPAR $\alpha$  lipid sensing was highlighted by *Acox1*<sup>-/-</sup>; *ob/ob* double knockout mice. Thus, the sustained activation of PPAR $\alpha$  when linked to the absence of ACOX1 activity attenuates the metabolic consequences of leptin deficiency, due to the *ob/ob* genotype, showing less obesity with the recovery of glucose homeostasis and alleviating insulin resistance [131,147]. Collectively, accumulated data underline the key role of peroxisomal  $\beta$ -oxidation in sensing PPAR $\alpha$ -dependent lipid and energy metabolism.



**Figure 8.** PPAR $\alpha$ -dependent regulation of peroxisomal fatty acid  $\beta$ -oxidation in rat liver through adiponectin signaling. Adiponectin: a hormone produced by adipose tissue that plays a role in lipid and glucose metabolism regulation; AdipoR, adiponectin receptor; APPL1, an adaptor protein containing a PH domain, PTB domain, and leucine zipper motif 1, plays a central role as the main contributing factor in the adiponectin and insulin signaling; AMPK, AMP kinase; PGC1-  $\alpha$ , PPAR  $\gamma$  coactivator1 $\alpha$ ; PPRE, peroxisome proliferator-activated receptor; RNA Pol II, RNA-polymerase II; ACOX1, acyl-CoA oxidase 1; MFP2, multifunctional protein 2; thiolase B, 3-ketoacyl-CoA thiolase B; VLCFA, very-long-chain fatty acid.

## 8. PPAR $\alpha$ Expression in Species and Tissue Distribution

### 8.1. PPAR $\alpha$ Expression in Different Species

PPAR is ubiquitous among animal species, i.e., worms [191], insects, fish, frogs [192], reptiles, mammals, including hamsters [193], and humans. A PPARab subtype was detected in zebrafish. This PPARab mutant shows lower expression in liver and visceral mass, which were associated with lipid accumulation [194]. In a jerboa (*Jaculus orientalis*) liver, both active wild-type PPAR $\alpha$  (PPAR $\alpha$ 1 wt) and a truncated PPAR $\alpha$  2 forms were expressed. The availability of active PPAR $\alpha$ 1 wt is differentially regulated during fasting-associated hibernation [195].

### 8.2. PPAR $\alpha$ Tissue Distribution

PPAR $\alpha$  tissue expression is also ubiquitous, although on a different level. PPAR $\alpha$  is mainly expressed in tissues with high rates of fatty acid catabolism, i.e., those involved in digestive function (liver, stomach, enterocytes) and muscular activity (heart, skeletal muscle, kidney at proximal tubules). In the nervous system, the expression is moderated (low in retinal, or lacking expression in the central nervous system). Low expression is found in the pancreas and adipose tissue [196], while in the brain, PPAR $\alpha$  is found at the highest levels in neurons, followed by astrocytes, and is weakly expressed in microglia [62,197]—more likely, to upregulate the expression of several synaptic related genes coding proteins engaged in excitatory neurotransmission and the neuroprotective mechanism [198–200]. In the immune system, PPAR $\alpha$  expression is detected in the spleen, monocytes/macrophages,

and neutrophils [201]. In addition, expression is seen in reproductive organs and the epidermis. PPAR $\alpha$  is also associated with tumorigenesis in colorectal carcinoma [202]. Concerning the expression in developmental tissue in rats, *Ppara* transcripts are detectable in mouse embryo at 13.5 gestation days, to reach the maximum level at birth [203].

### 8.3. Lessons from *Ppara* Knockout

This part of the manuscript provides recent findings from the last five years related to *Ppara* knockout animals, with the intent of disentangling the PPAR $\alpha$ 's various biological functions in health and disease and to evaluate its engagement in fatty acid catabolism and clearance in liver and heart tissues, where PPAR $\alpha$  and FAO are both abundant. A growing body of evidence indicates that PPAR $\alpha$  is a crucial regulator of systemic lipid metabolism. PPAR $\alpha$  deficiency is considered to be a prime factor that either causes or exacerbates fatty acid metabolism impairment, which leads inevitably to the development of numerous metabolic diseases, to name but a few—obesity [204,205], type 2 diabetes mellitus, insulin resistance, dyslipidemia, myocardial infarction, hepatic steatosis without ethanol consumption, termed non-alcoholic fatty liver disease (NAFLD), which includes severe phenotypes such as non-alcoholic steatohepatitis (NASH), liver fibrosis, and hepatocellular carcinoma [206–210]. Therefore, many investigations were conducted using mainly PPAR $\alpha$  knockout mouse models, because of the relative equivalent expression of *Ppara* mRNA between mice and humans in different tissues [98]. Knockout animal models are generated either with the global (*Ppara*<sup>−/−</sup>) or hepatocyte-specific abrogation of the *Ppara* gene, such as *Ppara*<sup>Hep−/−</sup> (reviewed by Wang et al. [181]). The goal was to identify the pathophysiological mechanisms underlying the abnormal phenotypes associated with PPAR $\alpha$  dysfunction and to assess the distinct contribution of hepatic and extrahepatic PPAR $\alpha$  to global energy and immune system homeostasis in vivo.

### 8.4. Lessons from *Ppara*-KO in the Liver

Hepatic PPAR $\alpha$  activation occurs during suckling [211], with a high-fat diet, and during fasting [212–214], boosting fatty acid oxidation (FAO), which participates in the restoration of energy homeostasis and provides energy supply for the extrahepatic tissues. For that reason, most of the studies were focused on hepatic PPAR $\alpha$ . Furthermore, hepatic PPAR $\alpha$  can protect the liver against fasting/high-fat diet-induced steatosis, by transactivating the genes required for fatty acid catabolism and repressing several inflammatory genes. Thus, during the fasting process, metabolic substrates stored in white adipose tissue are released into the circulation and captured by the liver. Subsequently, this increases  $\beta$ -oxidation and ketogenesis to maintain the energy balance [212]. It was observed that fasted *Ppara*<sup>−/−</sup> and *Ppara*<sup>Hep−/−</sup> mice developed hypoketonemia, hypoglycemia, and hypothermia with decreased serum triglycerides. Additionally, the ectopic accumulation of medium-chain fatty acids and long-chain fatty acids in the liver manifests as an increase of hepatic fat mass, termed steatosis, with pronounced oxidative stress and lipid peroxidation compared to wild-type mouse liver. These effects result from the altered mitochondrial and peroxisomal fatty acid  $\beta$ -oxidation pathways in the liver [212,214,215]. Furthermore, mice in which *Ppara* was deleted uniquely in hepatocytes could not modulate bone marrow monocyte egress upon fasting [216], suggesting that PPAR $\alpha$  contributes to the regulation of monocyte homeostasis during fasting.

Regarding high-fat diet (HFD)-induced obesity, mice with the hepatocyte-specific deletion of *Ppara* develop steatosis and inflammation [217]. These observations corroborate previous results communicated by Stec and al. [205], showing that *Ppara*<sup>Hep−/−</sup> mice on HFD had worsened hepatic inflammation associated with steatosis, and exhibited high levels of LDL, which is considered an emerging risk factor for cardiovascular disease in NAFLD. PPAR $\alpha$  could also protect against obesity. In *ob/ob* obese mice, the absence of PPAR $\alpha$  resulted in increased obesity and led to severe hepatic steatosis [184]. Interestingly, mice lacking only hepatocyte-PPAR $\alpha$  developed steatosis spontaneously but without obesity in aging [212,214]. Indeed, extrahepatic PPAR $\alpha$  activity blunts and compensates



when hepatic PPAR $\alpha$  is disrupted, by elevating FAO and lipase activity in other tissues to increase and utilize excess lipid, thus maintaining lipid homeostasis [215]. Likewise, the transcriptome, lipidome, and metabolome results communicated by Régnier et al. and Batatinha et al. [217,218] demonstrate the significant contribution of extrahepatic PPAR $\alpha$  activity to the metabolic homeostasis response to HFD consumption. By using double-knockout mice, *Ppara*<sup>-/-</sup>/*Cyp2a5*<sup>-/-</sup>, Chen et al. [108,206] together indicate that PPAR $\alpha$  interacts with CYP2a5 (cytochrome P450 2A5) an antioxidant enzyme to protect against steatosis. Fibroblast growth factor 21 (FGF21) acts as a downstream molecule of the PPAR $\alpha$  signaling pathway to regulate the liver lipid metabolism and contribute to the CYP2a5 protective effects on alcoholic fatty liver disease [206]. In an experiment conducted by Brouck et al. [219], it was observed that treatment with WY-14643, a PPAR $\alpha$  agonist, caused weight loss and severe hepatomegaly in WT and *Ppara* <sup>$\Delta$ Mac</sup> mice but not in *Ppara*<sup>Hep-/-</sup> and *Ppara*<sup>-/-</sup> mice, suggesting that cell proliferation is mediated exclusively by PPAR $\alpha$  activation in hepatocytes in response to WY-14643 agonist treatment.

*Pparab* is one of the two *Ppara* paralogs, highly expressed in zebrafish tissues with high oxidative activity. Li and coworkers generated *Pparab*-knockout in the zebrafish model [194]. *Pparab*-null zebrafish demonstrated a lower expression of critical enzymes involved in FAO, and lower mitochondrial and peroxisomal FAO in the liver and muscle, associated with lipid accumulation in the liver. Furthermore, PPAR $\alpha$  deficiency increases glucose oxidation, protein synthesis, and reduced amino acid breakdown, while in rodents, the loss of PPAR $\alpha$  increases amino acid breakdown [194].

#### 8.5. Lessons from *Ppara*-KO in the Heart

PPAR $\alpha$  is a crucial regulator of substrate utilization in the heart. Fatty acids are a primary energy source for the heart, and fatty acid  $\beta$ -oxidation provides almost 70% of cardiac ATP; the remainder is obtained primarily from glycolysis and lactate oxidation [220]. Thus, *Ppara* KO mice, in response to chronic pressure overload, exhibit enhanced cardiac dysfunction. In contrast, mild PPAR $\alpha$  activation in mice showed a positive effect on myocardial energetic functions, especially during progressive and pressure-overloaded heart failure, revealing the virtue of PPAR $\alpha$ -associated FAO modulation as a promising therapeutic strategy for heart failure [221]. In addition, *Ppara* ablation exacerbated myocardial ischemia-reperfusion injury in *Ppara* KO mice models subjected to cardiac ischemia-reperfusion, and interestingly, after the treatment with PEA microparticles (PEA-um<sup>®</sup>, 10 mg/Kg), an endogenous PPAR $\alpha$  ligand, only *Ppara* WT mice showed the cardioprotective effect of PEA-um<sup>®</sup>, but not in *Ppara* KO mice. Although PEA-um<sup>®</sup> had a protective and beneficial effect on inflammatory disorders associated with ischemic myocardial failure, it also negatively regulates inflammation through PPAR $\alpha$  activation by reducing the activation of the nuclear factor-kB (NF-kB) pathway and production of pro-inflammatory cytokines [222]. Thus, PPAR $\alpha$  could augment heart function and cardiac fatty acid oxidation, whereas in the *Ppara* KO mouse model, a more severe sepsis phenotype is observed due to deteriorated cardiac performance and fatty acid oxidation, associated with both a hyperinflammatory cytokine storm as well as immune paralysis [223]. Furthermore, during sepsis, WT hearts showed a decrease in PPAR $\alpha$  and other FAO genes' mRNA expression, and this reduction was more dramatic in *Ppara*-null mouse hearts [223]. Taken together, PPAR $\alpha$  expression increased fatty acid oxidation and subsequently supported the hyperdynamic cardiac response early during sepsis or pressure-overloaded heart failure, which may prevent morbidity and mortality.

#### 9. PPAR $\alpha$ and Micronutrients

As reported above, PPAR $\alpha$  is activated by different ligands of both natural and synthetic origins, involved in several signaling and metabolic pathways. Some natural ligands are issued from the lipid metabolism, such as PUFAs and their derivatives. Interestingly, micronutrients, such as minerals, vitamins, phytophenols, and phytosterols are non-energetic compounds with essential signaling activity. Of particular interest, polyphenols, oil prod-

ucts, and some terpenoids and alkaloids impact cell functions through the modulation of PPAR $\alpha$  activity.

## 10. Effect of Polyphenols, Known as Antioxidants and Anti-Aging Compounds

### 10.1. Resveratrol

Resveratrol, or 3,4',5-trihydroxystilbene, is a natural polyphenol present in large amounts in Japanese knotweed (*Polygonum cuspidatum*) root. This phytoalexin is produced by a wide variety of plants, some of which are edible for humans, such as grapes, blackberries, blackcurrants, blueberries, and cranberries, to name but a few [224]. However, in the last two decades, the effect of resveratrol on animal models related to several disorders, such as autism spectrum disorder, mitochondrial myopathies, type 2 diabetic nephropathy, or renal lipotoxicity has been increasingly reported.

The effect of resveratrol in the presence of quercetin has been studied on PPAR $\alpha$ -mediating uncoupling protein regulation in visceral white adipose tissue from metabolic syndrome rats. Resveratrol treatment leads to a significantly increased expression of both *Ppara* mRNA and protein levels [225]. Remarkably, resveratrol prevents renal lipotoxicity in a high-fat diet-treated mouse model by regulating the PPAR $\alpha$  pathway, enhancing the expression of lipolytic genes, and raising the renal PPAR $\alpha$  protein level and AMPK phosphorylation level [226]. Due to known dyslipidemia in autism spectrum disorders, PPARs have been proposed as therapeutic targets of resveratrol. Furthermore, in autism, impaired mitochondrial fatty acid oxidation suggests the potential implications for regulating mitochondrial oxidation flux by PPAR activators, especially resveratrol [227].

Numerous natural ligands, including polyphenolic compounds, control the expression of PPAR receptors [228]. They have several health-promoting properties, including antioxidant, anti-inflammatory, and antineoplastic activities. Resveratrol is an active biological modulator of several signaling proteins, including PPAR $\alpha$ . Resveratrol activates the AMPK-SIRT1-PGC-1 $\alpha$  axis and PPAR $\alpha$  via the adiponectin receptors in the renal cortex [187]. Adiponectin has multiple functions, including insulin sensitization and lipid metabolism regulation. Similarly, in mitochondrial myopathy, resveratrol has been shown to potentially target many mitochondrial metabolic pathways comprising fatty acid  $\beta$ -oxidation and oxidative phosphorylation, leading to the up-regulation of the energy supply via AMPkinase-SIRT1-PGC-1 $\alpha$  signaling pathways [229].

### 10.2. Quercetin

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a flavonoid polyphenol found in plants and a variety of other natural sources—red grape, onion, broccoli, tomatoes and lettuce [224]. PPAR $\alpha$  is significantly upregulated and enhances  $\beta$ -oxidation by mulberry-leaf powder containing quercetin [230]. Quercetin-3-O- $\beta$ -D-glucuronide (Q3GA) ameliorates dyslipidemia in fatty livers by modulating the PPAR $\alpha$ /sterol regulatory element-binding protein-1c (SREBP-1c) signaling. Q3GA reduced lipogenesis through downregulation of SREBP-1c and fatty acid synthase levels, and raised lipolysis and fatty acid oxidation by increasing the expression of PPAR $\alpha$ , carnitine palmitoyl-transferase1 and medium-chain acyl-coenzyme A dehydrogenase, both in vivo and in vitro [231].

### 10.3. EGCG (Epigallocatechin-3-Gallate)

Epigallocatechin-3-gallate (EGCG) is catechin conjugated with gallic acid. It belongs to the flavonol class and is found abundantly in green tea [232] and cocoa, which have the highest content of catechins, followed by prune juice, broad bean pods, and argan oil [224].

EGCG and green tea polyphenol extract display crosstalk with PPAR $\alpha$ . Reported studies in cancer cells revealed that EGCG induced the expression level of PPAR $\alpha$  protein in a dose-dependent manner. Clofibrate, a PPAR $\alpha$  agonist, blocks heme oxygenase-1 (HO-1) induction and sensitizes cancer cells to EGCG-promoted cell death. Moreover, PPAR $\alpha$  interacts with the PPRE of the HO-1 promoter. The activation of PPAR $\alpha$  sensitizes cancer cells to epigallocatechin-3-gallate (EGCG) treatment by suppressing HO-1 expression [233].

In rats, green tea polyphenols reduce the renal oxidative stress induced by a high-fat diet through deacetylation of SIRT3 mediated by PPAR $\alpha$  upregulation [234].

#### 10.4. Curcumin

Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) belongs to a chemical class of polyphenols that is extracted from the rhizomes of the turmeric plant (*Curcuma longa*) [224]. Tetrahydro-curcumin improves oleic acid-induced hepatic steatosis and ameliorates insulin resistance in HepG2 cells, likely through downregulation of the expression of the lipogenic proteins, SREBP-1c and PPAR $\gamma$ , and the stimulation of lipolysis by upregulating PPAR $\alpha$  and CPT-1a, which are involved in fatty acid  $\beta$ -oxidation [235].

#### 10.5. Anthocyanins

Among berries, blueberries contain higher amounts of anthocyanins. These polyphenols are known to exhibit hypolipidemic properties. Rimando et al. reported that both anthocyanins and catechins do not activate PPAR $\alpha$ , while pterostilbene revealed the dose-dependent activation of PPAR $\alpha$  in H4IIEC3 hepatocytes [236]. In addition, pterostilbene showed a significant increase in *Ppara* gene expression, but at a lower extent than fenofibrate [236]. Although pterostilbene and resveratrol, as PPAR $\alpha$  activators, are under the threshold for effective concentrations in blueberry extract, hepatic mRNA *Ppara* expression has increased in hamsters fed on a diet containing blueberry extract [236].

#### 10.6. Coffee

Coffee consumption has been shown to upregulate mouse hepatic PPAR $\alpha$  expression and its target-gene *Acox1*, consequently leading to the induction of liver peroxisomal fatty acid  $\beta$ -oxidation. Such FAO induction, with induced intestinal cholesterol efflux and reduced lipid digestion, prevents the high-fat diet-induced fatty liver through the lipid-sensing modulation of the gut–liver axis [237].

#### 10.7. Edible Oil Products

The effect of polyphenols has been investigated in a rat model of bowel disease by 3 months diet supplementation with extra-virgin olive oil with a high or low phenolic content [238]. The presence of polyphenols in olive oil significantly attenuates the intestinal inflammation associated with hypocholesterolemia and the induction of PPAR- $\alpha$  gene expression in the liver [238]. In a model of insulin resistance of rats fed a high-fat diet, the administration of the major metabolite of oleuropein, hydroxytyrosol, increases the hepatic mRNA levels of *Ppara* and its target genes, i.e., fibroblast growth factor 21 and carnitine palmitoyltransferase 1a [239]. Similarly, mice receiving a high-fat diet develop hepatic steatosis and inflammation, which were attenuated by hydroxytyrosol supplementation through PPAR $\alpha$  activation, Nrf2 (nuclear factor, erythroid 2 like 2) mediated-antioxidative pathway, and by the downregulation of NF- $\kappa$ B-associated inflammation [240]. Used as food supplementation, argan oil or olive oil was shown to restore the expression of genes involved in liver mitochondrial and peroxisomal fatty acid  $\beta$ -oxidation and gluconeogenesis in the mice sepsis model when injected with lipopolysaccharides. This preventive effect of argan oil likely involves the hepatic upregulation of PPAR $\alpha$ , PGC-1 $\alpha$ , and the estrogen-related receptor  $\alpha$  [241].

Likewise, ginsenoside Rb3 micronutrients, derived from ginseng, or nuciferine, found in *Nelumbo nucifera* leaves, was shown to activate the PPAR $\alpha$  pathway by regulating energy metabolism in cardiomyocytes [242], or hepatic steatosis diabetic streptozocin-induced mice fed a high-fat diet [243], while bilobetin, a biflavonoid, modulates PPAR $\alpha$  activity by PKA-dependent phosphorylation. Finally, berberine, an alkaloid, binds PPAR $\alpha$  LBD with a hypolipidemic effect and a comparable affinity to fenofibrate [244].

## 11. Conclusions and Future Directions

In all these tested situations, irrespective of the tissue, animal, or pathological condition, micronutrients appear to have an advantageous effect on *Ppara* expression and activity. Furthermore, almost all these compounds are potent antioxidants and can activate signaling pathways via PGC1- $\alpha$  and AMP kinase. Numerous natural products might modulate PPAR $\alpha$ , including terpenes, polyketides, phenylpropanoids, polyphenols, and alkaloids; for instance, the linalool effect is ten times less compared to fenofibrate [88], demonstrating the potential beneficial effects of dietary micro-components to modulate PPAR $\alpha$  functions desirably in a population with an ever-increasing high-fat diet consumption. The question is the dietary relevance of these effects, since most of the data were obtained from in vitro studies, and secondly, these micronutrients are often present at very low doses in the diet, except for some polyphenols.

Despite tremendous signs of progress on the critical role of PPAR $\alpha$ -dependent regulation in lipid metabolism, the characterization of peroxisomal enzymes and transporters, there are still gaps that need to be filled to fully define the exact role and regulation of PPAR $\alpha$  and peroxisomal fatty acid  $\beta$ -oxidation in the cellular homeostasis of lipid metabolism. Particular attention needs to be focused on:

1. The shuttling of substrates and cofactors from and into peroxisome.
2. What is the exact role of peroxisomal  $\beta$ -oxidation in lipid metabolism and cell signaling?
3. How can peroxisome be a mediator and responder of metabolic and environmental stresses?
4. What are the molecular events that are required at the metabolic level?
  - (a) Does heterodimerization of PPAR/RXR control the regulation? Is it controlled by coregulators?
  - (b) What is the nature of ligands?
  - (c) What is the nature of micronutrients? Are they natural agonists or antagonists or their balance?
  - (d) Is PPAR $\alpha$  the only nuclear receptor governing peroxisomal  $\beta$ -oxidation-related genes?
  - (e) How do coregulators play in concert to fine-tune metabolically peroxisomal  $\beta$ -oxidation pathway?

All these as yet unanswered questions deserve our complete focus in the near future.

There is an increasing demand from health institutions and pharmaceutical industries for efficient drugs. PPAR $\alpha$  binding pocket-ligand interactions are being increasingly recognized as a source for therapeutic interventions. Bio structural analysis based on X-ray crystallography and ligand structure pharmacophore modeling approaches afford new biophysical and structural parameters that are important in designing and developing novel potent and highly PPAR $\alpha$ -specific ligands to preserve human health and safety. However, the overall goal of increasing the peroxisomal fatty acid oxidation and  $\beta$ -oxidation safely, without increasing the lipid peroxidation and free radical-based risk of non-genotoxic carcinogenesis in the high-fat Western diet-fed population, is a challenge that is still unmet and requires continuous exploration of avenues to activate PPAR $\alpha$  dependent pathways safely.

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