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Review

Regulation of energy metabolism by long-chain fatty acids

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ABSTRACT

In mammals, excess energy is stored primarily as triglycerides, which are mobilized when energy demands arise. This review mainly focuses on the role of long chain fatty acids (LCFAs) in regulating energy metabolism as ligands of peroxisome proliferator-activated receptors (PPARs). PPAR-alpha expressed primarily in liver is essential for metabolic adaptation to starvation by inducing genes for beta-oxidation and ketogenesis and by downregulating energy expenditure through fibroblast growth factor 21. PPAR-delta is highly expressed in skeletal muscle and induces genes for LCFA oxidation during fasting and endurance exercise. PPAR-delta also regulates glucose metabolism and mitochondrial biogenesis by inducing FOXO1 and PGC1-alpha. Genes targeted by PPAR-gamma in adipocytes suggest that PPAR-gamma senses incoming non-esterified LCFAs and induces the pathways to store LCFAs as triglycerides. Adiponectin, another important target of PPAR-gamma may act as a spacer between adipocytes to maintain their metabolic activity and insulin sensitivity. Another topic of this review is effects of skin LCFAs on energy metabolism. Specific LCFAs are required for the synthesis of skin lipids, which are essential for water barrier and thermal insulation functions of the skin. Disturbance of skin lipid metabolism often causes apparent resistance to developing obesity at the expense of normal skin function.

Contents

Abbreviations: ACAA2, 3-oxoacyl-CoA thiolase; ADIPOR, adiponectin receptor; AF1,2, activation function 1,2; AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; ATGL, adipose triglyceride lipase; CaMK, calcium/calmodulin-dependent kinase; CD36, fatty acid translocase; CPT1A, carnitine palmitoyltransferase 1A (liver type); CPT1B, carnitine palmitoyltransferase 1B (muscle type); CREB, cAMP responsive element binding protein 1; D6D, delta-6 desaturase (also called FADS2); DBD, DNA binding domain; DGAT, diacylglycerol acyltransferase; EFA, essential fatty acid; ELOVL, elongation of very-long chain; ETFDH, electron-transferring flavoprotein dehydrogenase; FABP, fatty acid binding protein; FAS, fatty acid synthase; FATP, fatty acid transfer protein; FFAR, free fatty acid receptor; FGF21, fibroblast growth factor 21; FOXO1, forkhead box O1; FXR, farnesoid-X receptor; G3P, glycerol-3-phosphate; GH, growth hormone; GK, glucokinase; GLUT4, glucose transporter 4; GPR, G protein-coupled receptor; HADHA, trifunctional protein α subunit; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; HMW adiponectin, high molecular weight adiponectin (up to 18mer); HNF4, hepatocyte nuclear factor 4; HSL, hormone sensitive lipase; IGF1, insulin-like growth factor 1; IGF1BP, IGF1 binding protein; Kd, dissociation constant; KO, gene knockout; LACS, long chain acyl-CoA synthase; LBD, ligand binding domain; LCAD, long chain acyl-CoA dehydrogenase; LCFA, long chain fatty acid ($C = 14–20$); LPL, lipoprotein lipase; LXR, liver-X receptor; MCDC, malonyl-CoA decarboxylase; MEF2, myocyte enhancer factor 2; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PEPCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PFKFB3, 6-phosphofurcto-2-kinase/fructose-2,6-bisphosphatase 3; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PPRE, peroxisome proliferator response element; PUFA, polyunsaturated fatty acid; RAR, retinoic acid receptor; RXR, retinoid-X receptor; SCD1, stearoyl-CoA desaturase 1; SOCS2, suppressor of cytokine signaling 2; STAT5, signal transducer and activator of transcription 5; TNFα, tumor necrosis factor alpha; TR, thyroid hormone receptor; TRB3, tribbles homolog 3; TZD, thiazolidinedione; UCP, uncoupling protein; VDR, vitamin D receptor; VLCAD, very long chain acyl-CoA dehydrogenase; VLDL, very low density lipoprotein.

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1. Introduction

From single-cell organisms to humans, it is essential for survival to adjust macronutrient metabolism to physiological conditions and nutrient availability. In mammals, excess energy is stored primarily as triglycerides, which are mobilized when demand for energy arises. Hormones sense physiological conditions and accordingly coordinate energy metabolism among organs. For example, pancreatic beta-cells sense abundance of nutrients and secrete insulin, which then activates a multitude of metabolic pathways including glycogen synthesis, glycolysis, glucose oxidation, *de novo* lipogenesis and protein synthesis, whereas norepinephrine secreted from the adrenal medulla mobilizes stored energy when there is an acute increase in energy demand. In the past decades, it has become increasingly clear that all macronutrients, carbohydrates, proteins and lipids, also play an important role in the regulation of energy metabolism. The discovery of regulation of energy metabolism by long-chain fatty acids (LCFAs) is a fairly recent event and is still emerging. Thus, the objective of this review is to summarize recent findings in this area, place them in physiological contexts, and provide likely regulatory schemes whenever possible. LCFAs refer to saturated and unsaturated fatty acids with 14–20 carbons. The primary focus of this review is on the regulation of energy metabolism by LCFAs irrespective to the degree of unsaturation. Polyunsaturated fatty acid (PUFA) specific effects are mentioned only briefly in the SREBP1 and ChREBP sections because the topic has been reviewed elsewhere [1–3]. In this review, we focus on five topics. The first, as part of the introduction, is a review of binding kinetics of peroxisome proliferator-activated receptors (PPARs) and the evidence for LCFAs as primary endogenous ligands of PPARs. Also, in the introduction, mediators of LCFA regulation other than PPARs are briefly reviewed to highlight why we are focusing on PPARs in the subsequent sections. The second topic deals with the role of LCFAs in adaptation to fasting and

refeeding. The main focus is the effects of LCFAs mediated by PPARα. The third topic is the regulation of energy metabolism in muscle by LCFAs and PPARδ. The fourth topic deals with the role of LCFAs and PPARγ in the regulation of adipocyte metabolism. Also, we present the "spacer hypothesis" as a function of adiponectin in adipocytes to integrate a role of LCFAs in the regulation of adipocyte metabolism. The last and fifth topic we cover is effects of LCFA metabolism in the skin on energy expenditure. Recent studies have demonstrated the importance of skin lipids in barrier function, profoundly affecting energy expenditure much more than previously thought.

1.1. LCFAs as endogenous ligands of PPARs

1.1.1. Discovery of PPARs

LCFAs regulate energy metabolism primarily by acting as an agonistic ligand of the nuclear receptor family of transcription factors PPARα, γ and δ. PPARα was first cloned by screening a cDNA library with conserved sequences of steroid hormone receptors, and was so named because of its ability to mediate transcriptional activation by a group of drugs called peroxisome proliferators [4]. Subsequently, PPAR isoforms, PPARγ and PPARδ (PPARβ in xenopus) were identified from xenopus [5] and mammalian [6,7] cDNA libraries. PPARα and γ are well conserved across species, whereas PPARβ/δ shows species variations [7,8]. The chicken PPARβ/δ sequence falls between human PPARδ and xenopus PPARβ [8]. While chicken PPARβ/δ and xenopus PPARβ are activated by peroxisome proliferators, mammalian PPARδ is unresponsive to peroxisome proliferators [5–8].

PPARs form a heterodimer with retinoid-X receptor (RXR) [9,10] and bind a peroxisome proliferator response element (PPRE) on target genes. PPREs have RGGTCAaAGKTCA or similar sequences with a core 6 nucleotide sequence repeated after one nucleotide spacing called direct repeat 1 [10,11]. In mammals, PPARα is predominantly expressed in liver and gastro-intestinal tract and to a lesser extent in heart and kidney [4,12,13]. PPARγ is highly expressed in white adipose tissue and immune cells [7,12,13], whereas PPARδ is expressed ubiquitously [12,13].

1.1.2. Binding kinetics of LCFAs to PPARs

A variety of amphipathic compounds, both synthetic and endogenous, can bind and activate PPARs with varying specificity. Numerous reviews are available on activation of PPARs by various ligands and resulting patho-physiological effects [14–16]. Thus, this review focuses on the role of PPARs as mediators of metabolic regulation by LCFAs.

LCFAs bind and activate all PPAR subclasses [17,18], and thus emerged as strong endogenous ligand candidates of PPARs. Scintillation proximity competition assay and gel filtration assay showed that dissociation constants (Kds) of LCFAs are around 1 μM for PPARα and γ, and around 5 μM for PPARδ [19,20]. On the other hand, when binding affinity was measured by fluorescent ligand competition assay, reported Kd of LCFAs for PPARα was 1–2 degrees of magnitude lower [21,22]. Although the reason of this discrepancy is unclear, in either case, Kds of LCFAs are much lower than physiological concentrations of tissue non-esterified LCFAs, which are present at 0.1–0.5 mM in liver [23,24]. Thus, if most of non-esterified LCFAs were present in a free form, activation of PPARs by LCFAs could not have a regulatory role because binding of LCFA to PPARs would always be saturated.

However, the concentration of intracellular free LCFAs is much lower than that of non-esterified LCFAs. Fatty acid binding proteins (FABPs) are abundant in tissues that utilize LCFAs [25]. Estimated concentrations of FABPs are near or more than 1 mM [26,27]. LCFAs bind FABPs with high affinity, Kds being in the low nM range [28,29]. Thus, the majority of intracellular non-esterified LCFAs bind to FABPs. A reported free LCFA concentration in adipocytes is in the low nM range [30]. Furthermore, deficiency of FABP4 increased PPARγ activity in macrophages, resulting in elevated expression of target genes [31]. Taken together, it is likely that intracellular free LCFAs are near or below the Kd for PPARs, and act as physiological regulators of PPAR activity. In addition, phosphatidyl choline was also reported as a ligand of PPARα [32]. However, the physiological significance of this finding is yet to be elucidated.

1.1.3. Structural basis of PPAR activation by ligands and their specificity

Like other nuclear receptors, PPARs have four domains: activation function 1 (AF1), DNA binding domain (DBD), ligand binding domain (LBD) and activation function 2 (AF2) as shown in Fig. 1A. AF1 is considered to mediate ligand independent activation, whereas AF2 mediates ligand dependent activation [33]. LBD consists of a ligand binding pocket, a dimerization domain and an activation domain. AF2 is a short alpha-helix near the C-terminal of PPARs. Helix 10 of LBD in a PPAR and RXRα provides a main dimerization interface (Fig 1B) [34]. Unliganded PPARs favor associating with the LXXXIXXXL motif in corepressors [35–37]. Although binding of an agonist does not cause a large conformational change to PPARs, a carboxyl or other polar head group of an agonist interacts with a tyrosine of AF2. This subtle change of AF2 position leads to favoring association of the PPAR activation domain with LXXLL motif in coactivators over the corepressor motif (Fig. 1B) [35–37]. On the other hand, a synthetic antagonist blocks AF2 taking an active position, allowing a corepressor to stay bound [35]. Because the effect of ligand binding to PPARs is subtle and limited to AF2 positioning, it is unlikely that ligand binding affects dimerization and DNA binding. Instead, a PPAR–RXR heterodimer is likely constitutively bound to a PPRE of target genes, and changes its association from a corepressor to coactivator upon activation by a ligand. Reviews are available should readers wish to learn more about coactivators and corepressors of PPARs [38,39].

Binding pockets of PPARs are T-shaped and have a greater volume compared with other nuclear receptors [20,35,40,41]. This

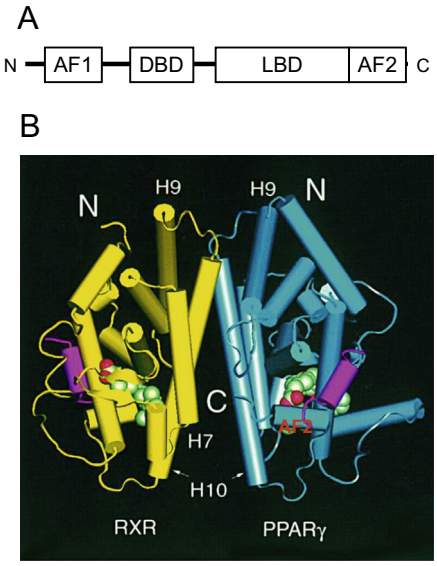

Fig. 1. Structure of PPARs. (A) Four functional domains in PPARs: AF1, activation function 1; DBD, DNA binding domain; LBD, ligand binding domain; AF2, activation function 2. (B) Three dimensional structure of PPARγ–RXR heterodimer. Upon ligand binding, AF2, which is located close to C-terminal, takes active conformation, allowing association of PPARγ with a coactivator motif shown in purple. Modified with permission from Gampe et al. [34].

large space of the ligand binding site accounts for the ability of a variety of compounds to bind and activate PPARs. An LCFA occupies either side of a T-shaped pocket, whereas synthetic ligands that occupy both sides of a pocket exhibit greater affinity than LCFA. In either case, head groups of LCFA and synthetic ligands align in the same way to bring AF2 into the active position. Because of this large binding pocket, short and medium chain fatty acids possess low affinity, and thus are unable to activate PPARs [17,18,20]. Although LCFAs can bind and activate all PPAR isoforms, certain bulkier synthetic ligands have strong specificity toward one form of PPAR. Specificity of a ligand can be achieved by exploiting steric hindrance between a ligand and binding pocket because there are subtle but significant differences in the shape of binding pockets among PPARs [42].

1.2. Other nuclear receptors that bind to or are inhibited by LCFAs

1.2.1. RXR

RXR is a heterodimeric partner of other nuclear receptors such as PPARs, liver-X receptor (LXR), farnesoid-X receptor (FXR), retinoic acid receptor (RAR), vitamin D receptor (VDR) and thyroid hormone receptor (TR) [43]. RXR also has a ligand binding domain, where 9-cis-retinoic acid binds in high affinity at low nM and activates RXR [43,44]. Unsaturated fatty acids also activate RXR at low μM [45]. Activation of RXR by a ligand has an additive effect on transcriptional activity when RXR forms a heterodimer with a permissive partner such as PPARs and LXR, whereas ligand binding to RXR has no effect on transcriptional activity of an impermissible partner such as VDR and TR [43]. Although 9-cis-retinoic acid is a high affinity ligand of RXR, it may not be produced in mammalian tissues [44]. Thus, LCFAs may increase transcriptional activity of PPARs by acting as a physiological ligand of RXR.

1.2.2. HNF4

Hepatocyte nuclear factor 4α (HNF4α) is another nuclear receptor with a ligand binding pocket that can bind an LCFA. HNF4α shows tissue specific, high expression in liver, kidney, intestine and pancreatic beta-cells. Unlike PPARs, HNF4α does not heterodimerize with RXR; instead, HNF4α forms only a homodimer [46]. HNF4α co-crystallizes with 16–18 carbon fatty acids in its ligand binding pocket [47,48]. However, the bound fatty acid was not removable, suggesting it is an integral structural component [47]. Moreover, the crystal structure shows that one of homodimerized HNF4α takes an active, C-terminal-closed conformation, whereas the other takes an inactive, open conformation although LCFA was found in the ligand binding pocket of both of them [48]. A subsequent study showed that HNF4α homodimer takes an active conformation when it binds to a coactivator [49], suggesting activity of HNF4α is regulated by coactivator binding, not by LCFA binding. Furthermore, HNF4α binds promoters of more than 1000 genes, or about 42% of genes bound by RNA polymerase II in human liver [50]. This large number HNF4α targets include a wide variety of genes, many of which are characteristic to liver functions such as detoxification (cytochrome P450s), bile acid metabolism (ATP binding cassette B11), lipoprotein metabolism/secretion (apoprotein A1, A5, B, microsomal triglyceride transfer protein), carbohydrate metabolism (glucokinase regulatory protein, glucose-6-phosphatase, phosphoenolpyruvate carboxykinase1,2), lipogenesis (fatty acid synthase [51], stearoyl-CoA desaturase), hormones (insulin-like growth factor 1), urea cycle (ornithine transcarbamylase) and alcohol metabolism (aldehyde dehydrogenases) [50].

On the other hand, acyl CoAs were reported to be HNF4α ligands that regulate HNF4α activity [52–54]. However, this reported role of acyl CoA as a regulatory ligand does not fit well with either the crystal structure of HNF4α or the range of target genes, which are very broad and not limited to the genes for fatty acid metabolism. Taken together, the current evidence indicates that HNF4α is not regulated by a ligand, and that the primary function of HNF4α is to direct tissue specific gene expression in liver and a few other tissues.

1.2.3. LXR

Unlike fatty acids, cholesterol cannot be degraded to acetyl CoA. Thus, excess cholesterol is transported from tissues to liver by HDL, and is removed from the body by excretion into the intestinal lumen through bile, a process called reverse cholesterol transport. LXR is activated by oxysterols, derivatives of cholesterol, and induces genes required for the entire process of reverse cholesterol transport [55]. LXR also induces genes for *de novo* lipogenesis in liver via transcriptional induction of SREBP1c [56], resulting in a provision of a substrate for synthesis of cholesteryl ester to temporarily sequester excess cholesterol. In cell culture, PUFAs as well as oleic acid, a monounsaturated fatty acid and stearic acid, a saturated fatty acid inhibited the induction of SREBP1c by an LXR agonist [57]. Also, a binding study showed that PUFAs as well as oleic acid, but not stearic acid inhibited binding of LXR to a coactivator motif peptide [57], suggesting LXR mediates suppression of *de novo* lipogenesis by LCFAs. However, an *in vivo* relevance for this role of LXR is yet to be determined as described in the next section on the SREBP1c regulation.

1.3. Other transcription factors regulated by PUFAs but not by LCFAs in general

1.3.1. SREBP1c

SREBP1c is a transcription factor that induces an entire program of *de novo* lipogenesis primarily in response to increased insulin [58]. PUFAs suppress *de novo* lipogenesis in liver by suppressing SREBP1c activity [1,3]. This suppressive effect is limited to PUFAs, whereas saturated and monounsaturated fatty acids including oleic acid have no effect [1]. The *in vitro* suppression of LXR activity by oleic acid and stearic acid discussed in the preceding section [57] contradicts with the *in vivo* specificity of PUFAs in SREBP1c suppression. Furthermore, PUFAs suppress SREBP1c activity by inhibiting proteolytic activation and decreasing mRNA stability, whereas transcription of SREBP1c is unaffected by PUFAs in rat liver [59,60], which also contradicts with the suppression of SREBP1c transcription by PUFAs through inhibition of LXR activity in *in vitro* models [57].

1.3.2. ChREBP

ChREBP is another transcription factor that induces genes for *de novo* lipogenesis in response to high glucose. In rat liver, PUFAs suppressed ChREBP expression, whereas triolein had no effect [61]. Also, fish oil rich in n-3 PUFAs reduced Mlx protein, a hetero dimeric partner of ChREBP in rat liver, whereas olive oil rich in oleic acid had no effect [62]. Although acetate, octanoate and palmitate was reported to reduce ChREBP activity, which was associated with increased AMP concentration and AMPK activity in cultured hepatocytes [63], the results were not reproducible by another group [61], and the evidence for *in vivo* relevance is lacking.

1.3.3. Implications

In liver of rodents, PUFAs suppress expression and activity of SREBP1c and ChREBP, key transcription factors to induce genes for *de novo* lipogenesis. However, this effect is limited to PUFAs, and is not observed with saturated and monounsaturated LCFAs, which serve as the main energy sources among LCFAs. Therefore, this PUFA-specific effect may be more relevant to the regulation of fatty acid synthesis for phospholipids rather than regulation of energy metabolism and switching of fuel sources between carbo-

hydrate and fatty acids. Reviews on the PUFA specific gene regulation are available elsewhere [1,3].

1.4. Free fatty acid receptors (FFARs)

FFARs belong to a family of G-protein coupled receptors (GPRs), which are located in the cell surface and initiate intracellular cell signaling upon ligand binding to the extracellular domain of the receptor. FFARs are likely to play important roles in LCFA-mediated regulation of energy metabolism. However, the elucidation of the physiological function of these receptors is still in an early stage. Thus, this topic is covered only briefly here. A review [64] is available to the readers who are interested in the topic.

LCFAs bind and activate FFAR1 (GPR40) [65,66] and FFAR4 (GPR120) [67], whereas FFAR2 (GPR43) and FFAR3 (GPR41) are activated by C2–5 short-chain fatty acids [68]. A physiological function of FFAR1 (GPR40) was first identified as a receptor that mediates fatty acid-stimulated insulin secretion in pancreatic beta-cells [66]. Subsequently, FFAR1 was found in endocrine cells throughout the gastro-intestinal tract, indicating that FFAR1 senses the luminal presence of LCFAs and elicits an endocrine response [69]. FFAR4 (GPR120) shows the highest expression in lung followed by colon in both mice and humans [67]. Stimulation of gut FFAR4 by LCFAs increases plasma GLP1 [67], implying that the receptor acts as a sensor of unabsorbed LCFAs reaching the lower intestine and exerts feedback inhibition of gastro-intestinal motility. The role of FFAR4 in the lung is yet to be elucidated. In addition, both FFAR1 and 4 are expressed in taste buds, and act as a taste receptor of fatty acids [70].

FFAR2 and 3 are expressed in the lower intestine, suggesting that they act as a sensor and mediate metabolic adaptations to short chain fatty acids generated by bacterial fermentation of polysaccharides [71]. FFAR3 is also highly expressed in adipocytes, whereas FFAR2 is highly expressed in immune cells [68]. Physiological functions of FFAR 2 and 3 in these cells are yet to be elucidated.

2. Adaptation to fasting mediated by LCFAs

Metabolic adaptation is critical for survival of any organism during starvation. In mammals, the main mechanism of this adaptation is the use of LCFAs as the main energy source and minimizing glucose utilization. The total glycogen store in humans provides less than one day of energy expenditure, whereas triglycerides stored in adipose tissue can supply months of energy need. Liver plays a critical role in energy metabolism during fasting by supplying glucose and ketone bodies to other organs. This metabolic adaptation to fasting is largely achieved by induction of enzymes for fatty acid oxidation and ketogenesis, rather than by acute regulation of enzyme activities. In addition to hormones such as insulin and glucagon, LCFAs also play a critical role in inducing metabolic adaptation to fasting.

2.1. Essential role of PPARα in adaptation to fasting

The essential role of PPARα in the adaptation to fasting was demonstrated by a targeted disruption of the gene. The PPARα gene knockout (KO) mice grew apparently normal as long as animals were fed ad libitum. However, when the animals were fasted, the PPARα KO mouse manifested profound impairment in metabolic adaptation. The KO mouse had lower blood glucose [72–75] than wild type animals and very little elevation of blood ketone bodies in a fasted state [72–76]. Liver triglycerides during fasting were about 3 times higher in the PPARα KO mouse than in the wild type control [74,77], resulting in hepatomegaly [76], whereas a decrease in adipose mass during fasting was less in the PPARα KO mice [76]. These responses indicate that PPARα KO mice are unable to induce sufficient fatty acid oxidation and ketogenesis during food deprivation.

The PPARα KO mouse also was hypothermic and had a low metabolic rate when fasted [72]. Some of the PPARα KO mice died after less than 48 h of fasting [73], suggesting that impaired metabolic adaptation to starvation may have made the PPARα KO mouse more vulnerable to additional stress. Because PPARα KO mice are unable to utilize fatty acids effectively during fasting, it is logical to expect that the animals are more reliant on protein breakdown for energy for survival. Indeed, Kersten et al. demonstrated that after 24-h fasting, blood urea was higher in the PPARα KO mice than in wild type control, and genes for the urea cycle and amino acid catabolism pathways were induced in the PPARα KO mouse [72].

Other studies using PPARα KO mice also revealed that the essential role of PPARα is not limited to adaptation to fasting but it extends to other physiological functions such as xenobiotic metabolism [78] and highly-unsaturated fatty acid synthesis [24]. This wide range of physiological functions of PPARα is likely achieved by a broad ligand specificity [32,79] and cooperation with other transcription factors [24,80]. However, this review will focus on the role of PPARα and LCFAs in the regulation of energy metabolism.

2.2. Genes induced by PPARα in liver during fasting

2.2.1. Induction of fatty acid oxidation and ketogenesis in mitochondria

Microarray analyses of liver revealed induction of various genes in response to administration of PPARα agonists [81–83] and fasting [83,84] including many involved in LCFA oxidation. Among them, the most consistently induced genes by both PPARα agonists and fasting across species are carnitine palmitoyltransferase 1, liver type (CPT1A), electron-transferring flavoprotein dehydrogenase (ETFDH), trifunctional protein α (HADHA) and 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) [83]. The first three genes are involved in mitochondrial β-oxidation of LCFA, and the

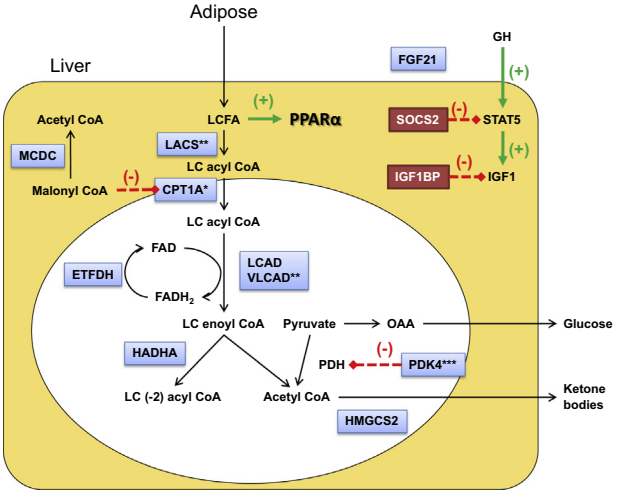

Fig. 2. Genes induced by PPARα and the function of their encoded proteins in liver. Light blue boxes show the genes that are involved in energy metabolism, and are consistently induced by fasting and PPARα agonists across species. Genes in burgundy boxes are induced by FGF21. Green arrows denote activation, whereas red, hatched lines denote inhibition. * PPARα is not essential for induction in fasting; ** PPARα is required for basal expression [111]; *** Induced by peroxisome proliferators but not in fasting.

HMGCS2 gene encodes the regulatory enzyme of ketogenesis in liver mitochondria (Fig. 2).

CPT1A, a key regulatory enzyme of β-oxidation, is required for transport of LCFA into mitochondria (Fig. 2). Presence of a functional PPRE was reported in the rat CPT1A promoter [85]. However, the PPARα KO mouse did not show an impairment in the induction of the CPT1A mRNA during fasting [72,75], suggesting functional redundancy with other unidentified transcription factors. Malonyl CoA, a substrate for *de novo* lipogenesis, is a strong inhibitor of CPT1A activity. Concentration of malonyl CoA is regulated by synthesis and degradation. Malonyl-CoA decarboxylase (MCDC) catalyzes degradation of malonyl CoA. A PPRE was identified in the MCD promoter, and the message was induced in liver by a PPARα agonist [77]. Furthermore, heart from the PPARα KO mouse showed decreased MCDC expression and β-oxidation accompanied by increased malonyl CoA concentration [86]. Thus, induction of MCDC, not CPT1, may be an essential role of PPARα for upregulation of LCFA oxidation in liver in response to fasting (Fig. 2).

As shown in Fig. 2, ETFDH is required for the dehydrogenation of acyl CoA of various chain lengths as the first step of fatty acid β-oxidation in mitochondria. Mutations of ETFDH in humans cause a genetic disorder called riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency that exhibit a varying degree of impairment in FAD-dependent reactions [87]. HADHA catalyzes the subsequent three steps of LCFA β-oxidation in mitochondria [88]. Thus, the induction of these genes during fasting is likely to increase mitochondrial capacity of β-oxidation to allow for greater utilization of LCFA as an energy source and for ketogenesis.

PPARα also plays an essential role in ketogenesis during fasting. In liver, a β-oxidation product, acetyl CoA is further converted to ketone bodies, β-hydroxybutyrate and acetoacetate, during fasting (Fig. 2). Ketone bodies, serve as an alternative fuel in order to reduce the use of glucose during fasting especially in the brain. HMGCS2, the rate-limiting enzyme of ketogenesis, is mainly regulated at the transcription level by PPARα, and PPRE was identified in the promoter of the gene [89]. HMGCS2 is one of the most highly induced genes in liver during fasting [75,83].

Fatty acids with 20 or more carbons are chain-shortened through peroxisomal β-oxidation before being completely oxidized in mitochondria [90]. A functional PPRE was identified in the promoters of key genes for peroxisomal fatty acid oxidation such as acyl-CoA oxidase [9,91] and L-bifunctional protein [9]. These genes are also induced during fasting in a PPARα dependent manner [73,74].

Mammals are unable to synthesize glucose from acetyl CoA once pyruvate is converted to acetyl CoA. Pyruvate dehydrogenase (PDH) catalyzes this critical, irreversible catabolism of pyruvate, and thus is inhibited when phosphorylated by pyruvate dehydrogenase kinases (PDKs) during fasting [92]. PDK4 mRNA was highly induced in liver in response to peroxisome proliferator administration in mice [93], rats [94,83] and pigs [83]. However, PDK4 mRNA was not induced by fasting in the liver of mice [95], rats and pigs [83], or was induced only mildly (<1.5×) in rat liver [96,97] although PDK4 protein was increased in mouse liver during fasting [98,99]. Thus, although increased PDK4 protein is likely contributing to conservation of pyruvate for gluconeogenesis in liver during fasting, it is apparently independent of activation of PPARα by LCFAs. Also, the physiological significance of PDK4 gene induction by PPARα agonists across species is yet to be elucidated (Fig. 2).

2.2.2. Induction of fibroblast growth factor 21

The importance of PPARα in adaptation to fasting is further augmented by identification of fibroblast growth factor 21 (FGF21) as a PPARα target. FGF21, a hormone of the fibroblast growth factor family, is implicated to have a role in macronutrient metabolism. The promoter of mouse FGF21 gene has two functional PPRE, and is induced by both fasting and a PPARα agonist [100]. FGF21 increases CPT1A and HMGCS2 protein in liver (Fig 2), and induces hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) in adipocytes [100]. FGF21 KO mice exhibited decreased fasting blood glucose, liver β-oxidation, ketogenesis and gluconeogenesis, demonstrating that FGF21 in part mediates the effects of PPARα during the adaptation to fasting [101].

Moreover, growth hormone (GH) signaling was attenuated due to greater expression of suppressor of cytokine signaling 2 (SOCS2) and insulin-like growth factor 1 binding protein (IGF1BP) during fasting and in FGF21 transgenic mice with an apoE promoter as well as by administration of a PPARα agonist [102]. SOCS2 inhibits GH signaling by blocking signal transducer and activator of transcription 5 (STAT5) activation, while IGFBP reduces the free form of circulating insulin-like growth factor 1 (IGF1) (Fig. 2). Consequently, the FGF21 transgenic mouse had growth retardation and lower circulating IGF1 despite increased plasma GH [102]. The FGF21 transgenic mouse exhibited similar changes in hepatic gene expression to liver specific STAT5A, B KO mice, in which sexual dimorphism of gene expression was abolished [102,103].

In prolonged starvation, there is a drastic increase in plasma GH mediated by a GH secretagogue ghrelin, whereas plasma IGF1 shows a marked decrease [104]. When energy storage in adipose is depleted during starvation, the increased GH plays an essential role for survival [104] by maintaining blood glucose via upregulation of gluconeogenesis in liver and kidney [105,106]. Because of the increased GH secretion during the starvation, FGF21 is likely to play a pivotal role in selectively inhibiting the GH effects to conserve energy during starvation by downregulating the effects of IGF1 on growth and reproductive functions. Indeed, mice that overexpress FGF21 showed a reduced growth rate, supporting the role of FGF21 in suppressing IGF1 signaling [102]. This downregulation of IGF1 signaling by PPARα activation could be a possible side-effect of prolonged fibrate administration.

Interestingly, energy expenditure was increased by peroxisome proliferator administration to non-fasted animals presumably due to increased fatty acid oxidation and thermogenesis [107,108]. Also, FGF21 injection to non-fasted animals increased energy expenditure and adiponectin secretion from adipose, whereas the increased energy expenditure by FGF21 administration was attenuated in adiponectin KO mice [109,110]. The requirement of adiponectin for full effect of FGF21 suggests that adiponectin is important for fatty acid mobilization from adipose under a lipolytic condition. The function of adiponectin and FGF21 in adipose is further discussed in Section 4.2.6.

2.3. Altered glucose and amino acid metabolism in PPARα KO mice

Although PPARα KO mice appear normal under an ad lib fed condition, accumulating data indicate that there are significant changes in macronutrient metabolism in those animals, underscoring the importance of PPARα in fuel selection in a non-fasted condition as well. Metabolic changes in ad lib-fed PPARα KO mice are summarized in Fig. 3.

Beta-oxidation capacity of a LCFA (16:0, palmitate) in PPARα KO mice was about a third of wild type when measured *in vitro* with liver homogenates from ad lib fed animals, whereas no difference was observed in β-oxidation of very long chain (24:0) and medium chain (12:0) fatty acids [111]. This reduced oxidation capacity was accompanied by a reduction of mRNA and protein of key enzymes such as long chain acyl-CoA synthase (LACS), long chain acyl-CoA dehydrogenase (LCAD) and very long chain acyl-CoA dehydrogenase (VLCAD) [111]. PPARα is also expressed in heart in rats [12] and humans [112]. An *ex vivo* study with isolated heart of PPARα KO mice had increased glycolysis and glucose oxidation and de-

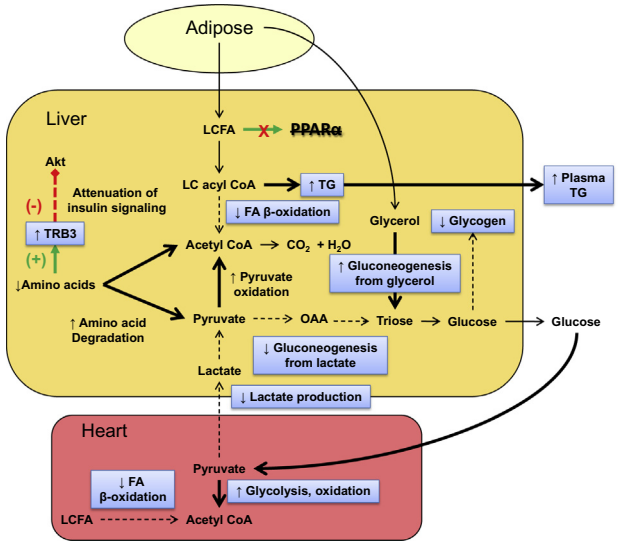

Fig. 3. Altered macronutrient metabolism in PPARα KO mice in non-fasting conditions. Light blue boxes show observed changes in PPARα KO mice compared with wild type mice in non-fasting conditions. Thick black lines denote increased flux in PPARα KO mice, whereas dashed black lines show decreased flux. A green arrow denotes activation, whereas a red, hatched line shows inhibition. OAA, oxaloacetate; TG, triglycerides.

creased palmitate oxidation, exhibiting a shift of energy source from fatty acids to glucose [86]. The decreased fatty acid oxidation was accompanied by a 2× increase in malonyl CoA concentration and decreased MCDC activity. Taken together, a lack of PPARα is likely to decrease fatty acid transport to mitochondria and oxidation capacity even in the ad lib fed condition (Fig. 3). Because PPARα is also expressed in the gastro-intestinal tract [12,112], the use of fatty acids for fuel is also likely decreased in the organ in PPARα KO mice.

This shift in energy source from LCFAs to glucose in PPARα KO mice explains decreased liver glycogen and increased hepatic and plasma triglycerides [72,98,74](Fig. 3). Also, a shift of gluconeogenic substrates occurs in PPARα KO mice. There was a large decrease in both lactate production and hepatic gluconeogenesis from lactate in PPARα KO mice, whereas gluconeogenesis from glycerol was increased [113]. As shown in Fig. 3, the decreased lactate production in PPARα KO mice is likely in part due to increased glucose oxidation in heart [86].

Furthermore, a strong induction of tribbles homolog 3 (TRB3) mRNA (>4×) was observed in liver of PPARα KO mice [24]. Transcription of the TRB3 gene is activated by activating transcription factor 4 (ATF4), which is a key mediator of the integrated stress response including a response to amino acid deficiency [114]. Therefore, as shown in Fig. 3, decreased LCFA oxidation is likely to cause increased use of amino acids for energy, leading to decreased amino acid concentration and the induction of TRB3 in PPARα KO mice. Because TRB3 acts as an inhibitor of Akt signaling [115], insulin signaling may be attenuated in liver of PPARα KO mice (Fig. 3).

Another interesting observation is a loss in diurnal rhythm of gene induction in PPARα KO mice. While the fatty acid synthase (FAS) gene was induced in a dark cycle in wild type mice, the KO mice lost the induction, and FAS gene remained low throughout light and dark cycles [116]. The induction of the FAS gene follows a feeding pattern, high in the fed state and low in the fasted state. Thus, loss of diurnal rhythm of FAS induction in PPARα KO mice may be due to loss of a rhythm in diurnal eating pattern. Because the KO mice cannot utilize stored triglycerides during the light cycle, they may be eating small amounts of foods throughout the day.

2.4. Species differences in the response to peroxisome proliferators

In rats and mice, peroxisome proliferators not only play a role in induction of genes for fatty acid oxidation, but also are a potent carcinogen in liver [117]. This hepatocarcinogenic effect is PPARα dependent because PPARα KO mice do not develop tumors. However, the carcinogenesis is specific to rats and mice, and is not observed in other species including humans.

A set of genes are highly responsive to peroxisome proliferators in rats and mice when compared with pig liver [83] and with human hepatocytes [118]. The differential response cannot be explained by the expression level of PPARα because the copy number of PPARα mRNA in pigs was higher than in rats and mice [83], and because increasing PPARα expression in a human hepatoma cell line did not alter the response [118].

Recent studies using PPARα KO mice with human PPARα expressed in liver demonstrated diminished carcinogenesis upon peroxisome proliferator administration, indicating structural differences of PPARα as the underlying mechanism of species differences [119,120]. The key difference between mouse and human PPARα was that the former down regulated let-7C expression, whereas the latter had no effect upon a peroxisome proliferator administration [120]. The authors proposed that the underlying mechanism of hepatocarcinognesis by peroxisome proliferators in rats and mice may be this downregulation of Let-7C, a microRNA that inhibits cell proliferation. Exact structural differences of PPARα that lead to hepatocarcinogenesis are yet to be determined.

3. Regulation of fatty acid oxidation by PPARδ in skeletal muscle

3.1. Skeletal muscle metabolism and PPARδ

3.1.1. Adaptation of energy metabolism in skeletal muscle

On a weight basis, skeletal muscle tissue accounts for a large proportion of total body mass in mammals, and profoundly affects whole body energy metabolism. Skeletal muscle is capable of adapting its metabolism to the environment such as type and intensity of exercise and nutrient availability. Early work in skeletal muscle physiology established that hypertrophy of muscle cells [121] and increased capacity for aerobic metabolism [122] are characteristics of skeletal muscle adaptations to resistance exercise and endurance exercise, respectively. Also, skeletal muscle changes its metabolism to use LCFA as a primary energy source during starvation [123]. Recent work has been devoted to expanding our knowledge of skeletal muscle remodeling into a molecular level. Recent studies indicate that muscle hypertrophy caused by resistance exercise is mediated by increased activity of mammalian target of rapamycin, a master regulator of protein synthesis [124]. Advances have been also made in understanding the intracellular signaling events that lead to the fiber type change and increased LCFA oxidation in response to endurance training [125]. Adaptation to endurance exercise is mediated by several factors including hormones and prolonged calcium influx. In addition to these regulatory factors, recent studies revealed a critical role of PPARδ for skeletal muscle to adapt to endurance exercise and fasting by inducing key regulatory genes, which is the focus of this section.

3.1.2. Biological roles of PPARδ

PPARδ is expressed ubiquitously throughout the body, and whole-body PPARδ ablation results in pleiotropic abnormalities. Phenotypes commonly observed in two independently developed PPARδ KO mice strains are decreased adiposity and increased midgestation lethality [126,127]. Other reported abnormalities of PPARδ KO mice include impaired myelination [126] and wound healing of skin [128]. A confounding factor of the PPARδ KO mouse

is that in certain cells/tissues such as macrophages, the loss of PPARδ causes induction of certain genes, which is repressed by unliganded PPARδ in wild type mice, resulting in similar phenotype as observed during activation of PPARδ by an agonist [129]. A recent review is available on the broad actions of PPARδ in various cells/tissues [130].

Skeletal muscle is characterized by having much greater expression of PPARδ than PPARα and PPARγ subtypes [131]. PPARδ protein is also more abundant in the muscle with oxidative type I fibers than with glycolytic type II fibers [132]. Activation of PPARδ in skeletal muscle is considered to be the primary mechanism to enhance reliance of muscle cells on LCFAs during fasting and prolonged exercise and diminish glucose utilization during fasting. Despite the wide-array of biological functions that appear to be controlled to some extent by PPARδ, it is the role in regulating LCFA oxidation in skeletal muscle that has attracted substantial attention to PPARδ because of the relevance to human health. Thus, the main focus of this section is to discuss the role of PPARδ activation by LCFAs as a means to coordinate physiological adaptations during fasting and exercise. A review is available elsewhere for readers who are interested in pharmacological intervention targeting PPARδ in treatment of metabolic syndrome [16].

3.1.3. Indispensable role of PPARδ in skeletal muscle

In skeletal muscle, a PPARδ specific agonist GW501516 induces genes involved with energy metabolism such as fatty acid transport protein (FATP), hormone sensitive lipase (HSL), LCAD, PGC1α, uncoupling protein 2 (UCP2) [133], UCP3, PDK4 [133,134] and CPT1B [134]. Both PPARδ and PPARα are expressed in skeletal muscle, and UCP3, PDK4, MCDC and CPT1 genes were induced in a similar extent when mice were treated with an agonist specific to either PPARδ or PPARα [131], suggesting PPARδ and PPARα share common target genes. An indispensable role of PPARδ in skeletal muscle was first indicated in a study with PPARα KO mice [131]. The study showed that skeletal muscle from PPARα KO mice did not have lower LCFA oxidation rates than wild type. Furthermore, PPARα ablation did not reduce the induction of the known PPARα targets UCP3 and PDK4 by fasting and exercise in quadriceps muscle [131]. Holness et al. also reported PDK4 was induced equally by fasting in skeletal muscle of wild type and PPARα KO mice [135].

A critical role of PPARδ in muscle metabolism is further demonstrated by skeletal muscle specific PPARδ KO mice, in which the expression of PPAR target genes such as lipoprotein lipase (LPL), long-chain acyl CoA synthase (LCAS), medium-chain acyl CoA dehydrogenase (MCAD), HADHA, UCP3 and PGC1α was reduced to about half, but was not abolished [136]. Also, the muscle PPARδ KO mouse exhibited decreased oxidative, type 1 fibers in tibialis and became obese compared to wild type animals, indicating an essential role of PPARδ in normal function of skeletal muscle [136]. Therefore, although PPARδ and PPARα seem to share common targets, PPARδ is likely to play a dominant role in skeletal muscle.

3.2. PPARδ in response to fasting

3.2.1. Induction of FOXO1 and PDK4 by PPARδ

Short-term (24–48 h) starvation increased skeletal muscle tissue expression of PPARδ [137] and its target genes including UCP3 [131], PDK4 [131,138], Forkhead box O1A (FOXO1) [138], CD36 and fatty acid binding protein 3 (FABP3) [137]. These adaptations induced by PPARδ activation in skeletal muscle appear to be central for optimal functioning of the tissue, i.e. allow muscle to adjust fuel preference by suppressing glucose utilization (high PDK4) and by relying more on LCFAs during periods of nutrient shortage or exercise (Fig. 4). These changes are reversed rapidly upon feeding, when nutrient supply is abundant [137]. Furthermore, induction of the PPARδ target genes FOXO1 and PDK4 in muscle during fasting was decreased in CD36 KO mice compared with wild-type mice [139]. Because LCFA uptake by muscle cells was markedly reduced without CD36 [139], transport of LCFAs into skeletal muscle is likely a necessary step prior to activation of PPARδ and induction of FOXO1 and PDK4.

Among the genes induced by PPARδ in fasting, a role of FOXO1 is particularly important for skeletal muscle in adapting to fasting. FOXO1 is a transcription factor involved in regulation of cell cycle and cellular metabolism [140]. Insulin inhibits FOXO1 activity through phosphorylation by Akt [141]. Thus, FOXO1 is activated during fasting because of decreased insulin (Fig. 4). In addition to this hormonal regulation, FOXO1 is highly induced during fasting in skeletal muscle but not in liver or adipose tissue [138]. A functional PPRE was identified in the FOXO1 promoter, and FOXO1 induction in diaphragm by fasting was blunted in whole-body PPARδ KO mice [139].

PDK4 is markedly induced in skeletal muscle both by a PPARδ agonist [133,134] and by fasting [131,135,138,139]. PDK4 phosphorylates and inactivates pyruvate dehydrogenase (PDH), inhibiting utilization of pyruvate for acetyl-CoA synthesis, and blocking glucose oxidation and favoring LCFA oxidation to generate energy. Although PDH is acutely inhibited by LCFA oxidation products (high NADH/NAD^+ and high acetyl-CoA/CoA), it is chronically inactivated by PDK4. FOXO1, through direct binding to a promoter sequence, increases PDK4 gene transcription [138,142], whereas no undisputable PPRE has been identified in the PDK4 promoter. Therefore, induction of PDK4 by activation of PPARδ is in large part likely mediated by FOXO1.

3.2.2. PPARγ coactivator 1α (PGC1α) amplifies the adaptive response of muscle to fasting

PPARγ coactivator 1α (PGC1α) is a member of the PGC1 family that was first discovered for its ability to increase transcriptional activity of PPARγ for the induction of UCP1 in brown adipose tissue [143]. PGC1α is a coactivator that binds to transcription factors, but not directly to a promoter DNA sequence, and increases potency of the transcription factor. PGC1α is expressed in tissues with high density of mitochondria such as liver, skeletal muscle, heart, brain and brown adipose [143]. Subsequent studies have revealed that PGC1α serves as a coactivator of various transcription factors expressed in skeletal muscle including PPARδ [144], FOXO1 [145], nuclear respiratory factor (NRF) 1,2, estrogen-related receptor alpha (ERRα) and myocyte enhancer factor 2 (MEF2) [146].

PGC1α is an inducible cofactor, and many, but not all, transcription factors that interact with PGC1α upregulate the expression of PGC1α, further amplifying the activity of the transcription factors. PPARδ induces PGC1α in skeletal muscle, and a functional PPRE was identified in the PGC1α promoter [136]. FOXO1 induces PGC1α in hepatocytes [145,147] and in skeletal muscle [148], and three FOXO1 binding sequence were identified in the PGC1α promoter [147]. Because PPARδ induces FOXO1 during fasting in skeletal muscle, PPARδ induces PGC1α both directly and indirectly via FOXO1. During fasting, FOXO1 activity is also increased by low insulin as shown in Fig. 4. The resultant increase in PGC1α in turn augments activities of PPARδ and FOXO1.

3.3. Role of PPARδ in response to exercise

3.3.1. Induction of PPARδ and its target genes by endurance exercise

In skeletal muscle of humans as well as mammals, a single bout of endurance exercise strongly induces target genes of PPARδ/α such as UCP3, CPT1, LPL [149], FOXO1 [150], PDK4 and PGC1α [149–151]. Increased expression of PPARδ in skeletal muscle is also reported after long-term endurance training [152,153]. These reports indicate that activation of PPARδ by incoming LCFAs during

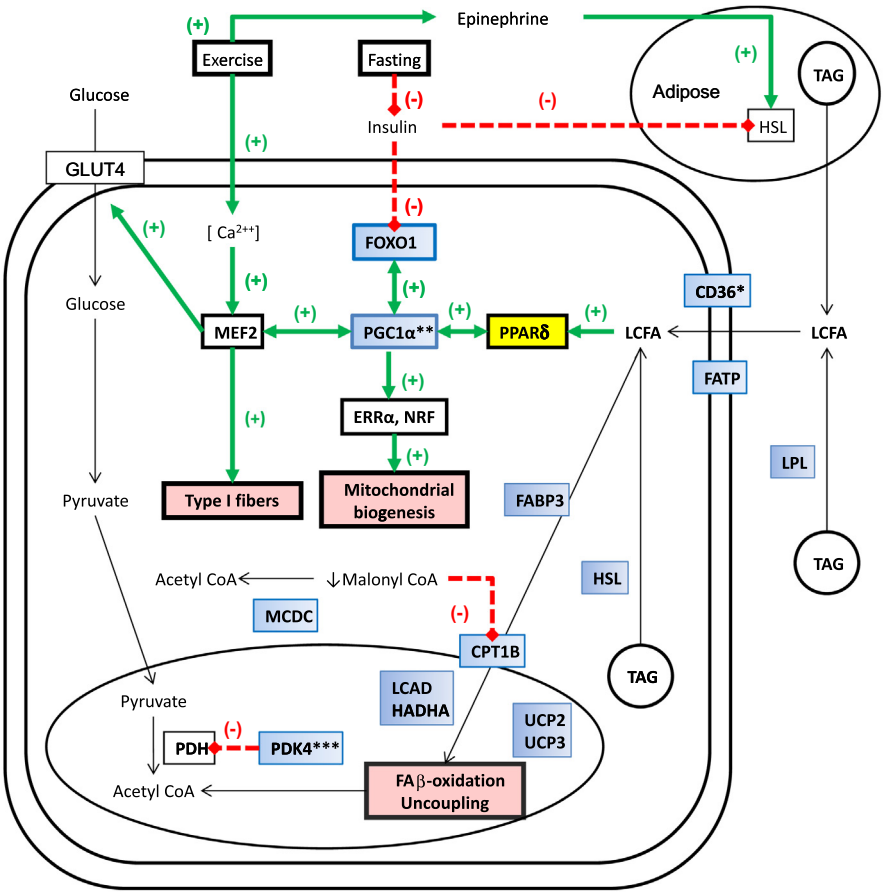

Fig. 4. Genes induced by PPARδ and the function of their encoded proteins in skeletal muscle during fasting and exercise. PPARδ, FOXO1 and MEF2 are activated by long-chain fatty acids, low insulin and calcium influx, respectively, and induce target genes as an adaptive response to fasting or endurance exercise. PGC1α is induced by these transcription factors, and further augments their activity by acting as a cofactor. PGC1α also acts as a cofactor of transcription factors NRF and ERRα whose activity is largely regulated by the induction of PGC1α. Light blue boxes show the genes that are induced by PPARδ in skeletal muscle during fasting, exercise or treatment with a synthetic agonist. Green arrows denote activation, whereas red, hatched lines denote inhibition. * Maximum induction of CD36 takes 5 days of agonist treatment. ** Transcription factors PPARδ, FOXO1 and MEF2 all induce PGC-1α, which in turn increases the activity of these transcriptional factors by acting as a cofactor. *** Likely induced indirectly by FOXO1. TAG, triglycerides.

endurance exercise play an important role in skeletal muscle adaptation to an increased work load.

Moreover, the muscle-specific PPARδ knockout mouse showed lower numbers of oxidative type 1 fibers in tibialis, suggesting involvement of PPARδ in type 1 fiber expression [136]. On the other end of a spectrum, muscle specific over-expression of PPARδ in mice led to greater numbers of oxidative fibers in skeletal muscle [153]. Likewise, overexpression a constitutively active form of PPARδ in skeletal muscle resulted in mitochondrial biogenesis and a shift of the fiber type from fast twitch to oxidative slow twitch [132], a response of muscle similar to long-term endurance training [125], whereas a PPARδ agonist was unable to cause a fiber type change [134]. Results from these transgenic/knockout studies imply that in addition to induction of genes for LCFA oxidation, PPARδ may also play some role in mitochondrial biogenesis and muscle fiber remodeling in response to endurance training. We will further examine this possibility in the subsequent sections.

3.3.2. Role of NRF, ERRα and PPARδ in mitochondrial biogenesis

Nuclear respiratory factor (NRF) 1 and 2 are transcription factors, which are ubiquitously expressed, and are required for mitochondrial biogenesis and expression of genes encoded by mitochondrial DNA [154–156]. Estrogen-related receptor alpha (ERRα) is a member of the nuclear receptor family. ERRα is not activated by estrogen, but is constitutively active [157]. ERRα induces genes for oxidative phosphorylation and ATP synthesis [158], and is also involved with mitochondrial biogenesis [159]. Thus, NRF1,2 and ERRα are likely key mediators of mitochondrial biogenesis in skeletal muscle in response to endurance exercise. Importantly, both NRF1,2 [156,160,161] and ERRα [157] bind to PGC1α and use it as a cofactor for transactivation of target genes. Thus, induction of PGC1α by exercise increases the activity of these transcription factors. Furthermore, the induction of PGC1α seems to increase abundance of NRF1,2 and ERRα as well, amplifying the induction of target genes of these transcription factors. A functional ERRα binding site is identified in the promoter of ERRα gene [157], whereas PGC1α increased NRF1,2 mRNA in C2C12 myotube cells [161].

3.3.3. MEF2 and fiber type change

Myocyte enhancer factor 2 (MEF2) belongs to a family of transcription factors that mediate adaptations of skeletal muscle to endurance exercise including slow fiber expression and increased glucose uptake capacity. Among target genes of MEF2, functional binding sites of MEF2 are identified in the promoter of glucose transporter 4 (GLUT4) [162], troponin I type 1 (a component of slow muscle fiber) [163] and PGC1α [164,165]. The activity of MEF2 is increased by prolonged influx of calcium into the skeletal muscle during the exercise [166]. Increased activity of MEF2 by calcium is mediated by both calmodulin-dependent kinases (CAM-

KII and IV) [167] and a calmodulin-dependent phosphatase (calcineurin) [166]. In addition, because PGC1α acts as a cofactor of MEF2, induction of PGC1α by MEF2 further amplifies activity of MEF2 [168].

3.3.4. A central role of PGC1α in the adaptation of muscle to endurance exercise

As summarized in Fig. 4, PGC1α acts as a coactivator of key transcription factors that mediate adaptation of skeletal muscle to endurance exercise such as PPARδ, NRF, ERRα and MEF2. For this reason, the induction of PGC1α plays a central role in the adaptation of skeletal muscle to endurance exercise. This point can be underscored by the studies of overexpression and knockout of PGC1α in skeletal muscle. Constitutive expression of PGC1α in skeletal muscle resulted in increased type1 fiber and mitochondrial biogenesis without exercise [169], whereas skeletal muscle specific PGC1α KO mice was unable to adapt to exercise, and became exercise intolerant [170]. Likewise, increased type 1 fiber by superphysiological PPARδ expression in skeletal muscle [132,153], but not by PPARδ agonist [134], could be explained by hyper induction of PGC1α, resulting in activation of MEF2 pathway.

4. Role of LCFA in adipocyte metabolism

4.1. PPARγ target genes in adipose tissue

Whereas PPARγ is not found in preadipocytes, it is expressed during the late stage of adipocyte differentiation, and remains abundantly expressed in differentiated adipocytes [171]. Essentiality of PPARγ for adipocytes was demonstrated in tamoxifen-inducible adipocyte specific PPARγ KO mice, as mature adipocytes died in a few days after PPARγ was ablated [172]. When activated in adipose tissue, PPARγ induces a variety of genes involved in lipid and glucose metabolism (Fig. 5).

The promoter of the LPL gene contains a functional PPRE that is activated by PPARγ [173]. Adipocytes secrete LPL, which hydrolyzes triglycerides in lipoproteins for the uptake of LCFAs by adipocytes. Purified LPL hydrolyzes fatty acids esterified to 1 and 2 positions of triglycerides, producing 2 free fatty acids and a 2-monoglyceride *in vitro* [174]. However, *in vivo*, 3 fatty acids and a glycerol are the likely products of hydrolysis of lipoprotein triglycerides by LPL (Fig 5), probably due to isomerization of 2-monoglycerides to 1- or 3-monoglycerides during *in vivo* hydrolysis [175]. The entry of fatty acids into adipocytes is mainly mediated by fatty acid transporters CD36 and FATP1, which are induced by PPARγ ligands in adipose tissue [176]. A functional PPRE was identified in the FATP1 promoter [177], but not in the CD36 promoter [178]. FABP4 (also called aP2, adipocytes/macrophage FABP) is a prototypical gene induced by PPARγ [179]. FABP4 is abundantly expressed in adipocytes, and binds to LCFAs in high affinity. Thus, most non-esterified LCFAs in adipocytes are likely to be bound to FABP4.

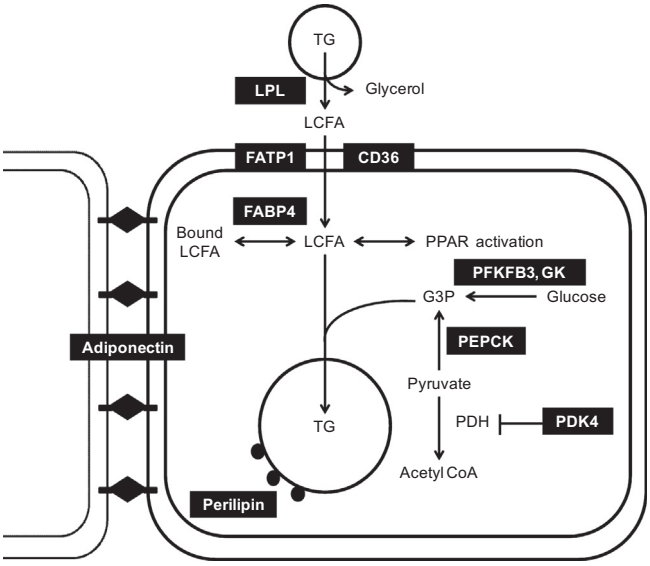

Fig. 5. Genes induced by PPARγ and function of their products in adipocytes. Black boxes show the genes induced by activated PPARγ in adipocytes. PPARγ targets genes involved in LCFA uptake and provision of glycerol-3-phosphate (G3P) for triglyceride (TG) storage.

Perilipin is another gene induced by PPARγ [180,181]. Perilipin, an abundant protein in adipocytes, coats the surface of lipid droplets, and is phosphorylated by protein kinase A (PKA) upon stimulation by β-agonists [182]. Perilipin KO mice exhibited decreased lipid storage due to increased basal lipolysis, as well as submaximal lipolytic response when stimulated, demonstrating a critical role of perilipin in regulation of lipolysis in adipose [183]. Dephosphorylated perilipin protects lipid droplets from lipolytic attack by ATGL and HSL, whereas phosphorylated perilipin enhances lipolysis by facilitating access of lipases to substrates [184–186]. Taken together, induction of perilipin by PPARγ is likely to play an important role in storing triglycerides in adipocytes.

PPARγ also targets genes involved in glucose metabolism. The phosphoenolpyruvate carboxykinase (PEPCK) gene has two alternative promoters, PCK1 and PCK2, the latter being used in adipocytes. A functional PPRE was identified in the PCK2 promoter. Binding of PPARγ–RXR heterodimer to the PPRE is essential for induction of PEPCK gene in adipocytes [187]. In adipocytes, PEPCK provides a precursor for glycerol-3-phosphate (G3P), which is required for triglyceride synthesis for storage (Fig 5). PDH catalyzes an irreversible degradation step of pyruvate to acetyl CoA. PDK4 inhibits PDH activity by phosphorylating PDH. PDK4 is one of several genes strongly induced by thiozolidinediones (TZDs), a group of synthetic PPARγ agonists [188]. This PDH inhibition together with PEPCK induction switches the metabolic fate of pyruvate from oxidation to G3P synthesis (Fig 5). Synthesis of G3P through gluconeogenic pathway is important for triglyceride synthesis because adipocytes lack glycerol-3-kinase, thus are unable to use glycerol for G3P synthesis.

PPARγ also targets glucokinase (GK) [189] and 6-phosphofurcto-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) [190] in adipose. GK catalyzes the first step of glycolysis, whereas PFKFB3 catalyzes synthesis and degradation of fructose-2,6-bisphosphate, a potent activator of another glycolytic enzyme phosphofructokinase (PFK). Heterozyogous PFKFB3 KO mice have reduced PFKFB3 expression and fructose-2,6-bisphosphate concentration in adipose. Thus, activation of PPARγ is likely to increase glycolysis up to the triose level, but not *de novo* lipogenesis. As shown in Fig. 5, activated PPARγ induces PEPCK and PDK4, preventing triose from further conversion to acetyl CoA for lipogenesis. Together, the profile of PPARγ targets indicate that the main effect of PPARγ activation on glucose metabolism is increased generation of G3P for esterification of LCFAs for triglyceride synthesis, not an induction of *de novo* lipogenesis (Fig. 5). Thus, induction of *de novo* lipogenesis in adipocytes under excess carbohydrate intake [191], is likely to be primarily mediated by SREBP1c [192] and possibly by ChREBP as seen in the liver [193].

4.2. Role of adiponectin in regulation of adipocyte metabolism

Another target of PPARγ is the adiponectin gene, which is discussed in this separate section because of its particular importance in regulation of energy metabolism. A PPRE has been identified in the adiponectin promoter, and adiponectin expression is increased

by TZDs [194]. Indeed, improvement of insulin sensitivity by a PPARγ agonist was blunted in Adiponectin KO mice [195].

4.2.1. Structure and oligomerization

The adiponectin gene is one of the most abundantly expressed mRNA in adipocytes [196]. Adiponectin is expressed almost exclusively in adipose tissue [196–198] although a low level of expression is observed in other tissues such as skeletal muscle and endothelium [199,200]. The adiponectin gene encodes a protein of 30 kD, which consists of a secretory signaling sequence, a collagen repeat (Gly-X-Y) domain and a globular domain [196–198]. Adiponectin protein exists as several types of oligomers, but not as a monomer. The basic unit of adiponectin is a trimer, which has a bouquet-like shape with the globular domains forming a head and the collagen domains forming a stem [201]. Also, the globular domains alone without the collagen repeat form a trimer, which is present in human plasma at a low concentration [202]. The full-length trimers are further processed to a hexamer or high molecular weight multimer of up to 18 subunits (HMW) by disulfide bond linkages with a cysteine residue at the collagen domain [201].

4.2.2. Adiposity and plasma adiponectin

Plasma adiponectin has a strong inverse correlation with body mass index in humans [203], and is reduced in leptin-deficient obese mice [198]. Furthermore, epidemiological, clinical and animal studies have demonstrated an inverse correlation of plasma adiponectin with insulin resistance and other metabolic syndrome markers as reviewed by Kadowaki et al. [204]. Among adiponectin oligomers, HMW adiponectin, not trimers, is considered to elicit the observed increase in insulin sensitivity because of the following reasons: (1) an association of plasma HMW with insulin sensitivity in epidemiological studies, (2) an association of plasma HMW with effects of PPARγ agonists, and (3) a strong association of adiponectin mutations that reduce HMW with incidence of type 2 diabetes [204].

4.2.3. Proposed function of adiponectin-T-cadherin complex as an inter-cellular spacer

T-cadherin belongs to a family of cell adhesion molecules with molecular weight of 95 kD, and was first isolated from brain of chick embryo [205]. T (truncated)-cadherin was so named because of its atypical lack of C-terminal transmembrane and cytosolic domains. Instead, T-cadherin is anchored to a glycosylphosphatidylinositol of outer plasma membrane [205]. T-cadherin was identified as a receptor of secreted HMW and hexamer adiponectin, but not of a globular or full-length adiponectin trimer [206]. This lack of intracellular domain of T-cadherin has puzzled researchers in explaining the insulin sensitizing effect of HMW adiponectin because a postulated protein that interacts with T-cadherin for signal transduction has not been found.

However, a closer evaluation of several lines of evidence led the authors to propose a novel function of the adiponectin-T-cadherin complex as an inter-cellular spacer. First, as mentioned before, unlike other adipocyte derived hormones, adiponectin is copiously expressed and secreted. Also, adipose tissue shows the highest expression of its receptor T-cadherin gene among the rat tissues according to the Unigene expression profile. Therefore, the hexamer/HMW adiponectin secreted from adipocytes can bind T-cadherin on the plasma membrane of two adjacent adipocytes, forming an intercellular bridge (Fig. 5). Because of its fairly bulky size, the HMW adiponectin-T-cadherin complex could act as an intercellular spacer, facilitating efficient perfusion of adipocytes with interstitial fluid. Therefore, we propose that HMW adiponectin may improve insulin sensitivity primarily by making adipocytes more metabolically active through this physical spacing between adipocytes.

This proposed function of the adiponectin-T-cadherin complex may also be operating in the vascular system in response to injury as well as in certain tumors to obtain nutrients for growth. T-cadherin expression is increased in smooth muscle cells of artery after balloon injury in rats [207]. Moreover, adiponectin binds to the site of injured artery, but not normal artery [208], suggesting the formation of the adiponectin-T-cadherin complex may facilitate the repair process by maintaining the perfusion of the injured site with interstitial fluid. Deficiency of either adiponectin [209,210] or T-cadherin [211] reduces angiogenesis and tumor growth, again suggesting the adiponectin-T-cadherin complex may accelerate tumor growth by increasing access of nutrients in interstitial fluid.

This proposed function of the adiponectin-T-cadherin complex can explain the inverse correlation between adiposity/insulin sensitivity and plasma HMW adiponectin concentrations [203,198]. Moreover, this hypothesis explains the requirement of disulfide bond formation for increased insulin sensitivity [204] because only hexamer or larger adiponectin multimers, but not trimers, can form intercellular bridges between two adipocytes. Furthermore, this hypothesis is consistent with the observations that adiponectin KO mice exhibited increased plasma concentration of tumor necrosis factor alpha (TNFα) and expression of TNFα mRNA in adipose tissue without increasing adiposity [212]. As adipocytes increase fat storage and their size, flow of interstitial fluid and availability of fatty acids are likely to decrease, resulting in down-regulation of PPARγ activity and adiponectin expression (Fig. 6). This decreased adiponectin production would further decrease intercellular space and limit access of adipocytes to nutrients and hormones, making adipocytes metabolically less active and developing insulin resistance. When energy expenditure exceeds intake, decreased size of adipocytes allows more access to nutrients, leading to activation of PPARγ, which in turn increases adiponectin production (Fig. 6). This increased adiponectin makes adipocytes more metabolically active and insulin sensitive by maintaining an intercellular space. As summarized in Fig. 6, it is likely that a physiological role of the adiponectin-T-cadherin complex is to serve as a self-regulatory mechanism of adipocytes to limit uncontrolled accumulation of triglycerides when adipocytes have plenty of fat storage, and to maintain active metabolism in both fat storage and fatty acid release when the adipocyte size is small.

4.2.4. Endocrine function of adiponectin

The endocrine function of adiponectin has been extensively investigated. Presence of the globular trimer of adiponectin in human plasma was first reported in 2001 [202]. The authors also re-

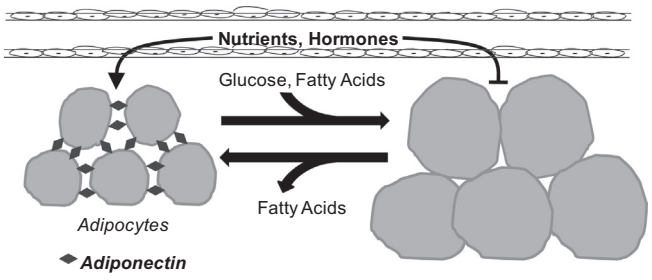

Fig. 6. Proposed function of adiponectin in regulating insulin sensitivity and metabolism of adipocytes. Adiponectin, when induced by PPARγ, acts as a spacer between adipocytes by binding to T-cadherin on the surface of adipocytes. The space created by adiponectin keeps adipocytes well perfused by interstitial fluids, thus adipocytes remain metabolically active and insulin sensitive. When adipocytes increase their size, interstitial space decreases, and less fatty acids become available, leading to down regulation of PPARγ. Decreased adiponectin further reduces metabolic activity and insulin sensitivity of adipocytes.

ported increased LCFA oxidation in muscle when the globular adiponectin was injected in mice [202]. Increased cellular AMP concentration and AMP-activated protein kinase (AMPK) activity is the underlying mechanism of increased LCFA oxidation by adiponectin administration [213,214]. Subsequently, receptors with a transmembrane domain that mediates the effects of globular adiponectin were identified, and named as adiponectin receptor (ADIPOR) 1 and 2 [215] although the signaling pathway that leads to AMPK activation is yet to be elucidated. This potent endocrine effect of globular adiponectin on AMPK activation is consistent with the function of adiponectin that mediates large part of the insulin sensitizing effect of TZDs.

However, there are a few unresolved problems to conclude that the ADIPOR mediated endocrine effect is the major pathway of insulin sensitizing effect of adiponectin. First, a study showed that only trimers (both globular and full length), but not hexamers and HMW were capable of activating AMPK [201]. If ADIPORs are activated only by trimers, the adiponectin receptor mediated endocrine function cannot explain why an adiponectin polymorphism that interferes with HMW formation causes insulin resistance. Contrary to the early study, recent studies reported activation of an ADIPOR by HMW adiponectin [216,217]. It is yet to be resolved whether or not HMW adiponectin can activate adiponectin receptors.

Phenotypical differences between adiponectin KO and ADIPOR KO mice also question the ADIPOR as the major mediator of the adiponectin effect. Two independent studies showed that adiponectin KO mice when fed regular diet did not develop insulin resistance assessed by a glucose tolerance test and an insulin tolerance test [212,218] although another independent study reported development of mild insulin resistance [219]. All of the three studies reported no difference in plasma insulin between genotypes during a glucose tolerance test. Adiponectin KO mice developed insulin resistance only under over nutrition when fed high-fat diet [212], a consistent outcome with the proposed spacer function of adiponectin. In contrast, ADIPOR1 and 2 double knockout mice developed severe insulin resistance including elevated plasma insulin by glucose tolerance test [220]. Moreover, ADIPOR1,2 double KO had elevated PEPCK mRNA and decreased acyl CoA oxidase in liver [220], whereas adiponectin KO had no changes from wild type [212]. These phenotypic comparisons demonstrate that insulin resistance is more severe in ADIPOR1,2 double KO mice than in adiponectin KO mice, suggesting an existence of unidentified endogenous ligands of ADIPORs in addition to adiponectin trimers. Indeed, paralogs of adiponectin have been identified [221], and some of them activate ADIPOR [221,222] although the physiological significance of these paralogs is yet to be determined.

4.2.5. Physiological significance of adiponectin induction by PPARγ in adipose

As summarized in Fig. 5, the proposed function of the adiponectin-T-cadherin complex fits well with the established function of other PPARγ target genes. When adipocytes are not fully loaded with triglycerides, PPARγ is activated by incoming LCFAs and induces genes for triglyceride storage. At the same time, adiponectin induced by PPARγ maintains extracellular space of adipocytes to keep adipocytes metabolically active during the expansion of adipocytes. This preservation of extracellular space may be critical to maintain insulin sensitivity because insulin sensitizing effect of TZD is largely lost in adiponectin KO mice [195].

4.2.6. Induction of adiponectin by FGF21 in adipose in fed and fasted conditions

As discussed in Section 2.2.2, FGF21, a hormone important for adaptation to starvation, also induces adiponectin [109,110], suggesting that adiponectin plays a role in increasing metabolic activity of adipose during mobilization of fatty acids. Consistent with this adiponectin induction by FGF21, plasma adiponectin is elevated in anorexia nervosa compared with control subjects [223,224]. The dual role of adiponectin both in storage and mobilization of fatty acids fits well with the proposed mechanism of adiponectin-T-cadherin complex in increasing metabolic activity of adipose. It is yet to be determined whether or not PPARγ mediates adiponectin induction by FGF21 because both supportive [225] and opposing [226] results have been reported.

In addition to the role of FGF21 in fasting, studies with FGF21 KO suggest that FGF21 also has a role in regulation of adipose metabolism in a fed condition even though the plasma FGF21 concentration in a fed state is much lower (~5%) than in a fasted condition [101,227]. Three FGF21 KO strains that were developed independently have been reported [101,227,228]. Among them, two strains of FGF21 KO showed increased adiposity [226–228], whereas another showed the opposite, a decrease in adiposity in FGF21KO [226]. In either case, these studies suggest a possible function of FGF21 in a fed state although the conflicting outcomes are yet to be resolved.

5. Effects of skin LCFAs on energy metabolism

5.1. Skin lipids

The skin of land animals encloses water-filled, inner organs against the dry, outer environment. Thus, one of the important functions of skin is to prevent water evaporation across the epidermis. Also, homeothermic animals are able to maintain body temperature in a wide range of thermal environments. In mice, a resting metabolic rate becomes minimal at thermoneutral temperature (~29 °C), whereas the metabolic rate increases by 60% at 22 °C [229]. Skin and fur contribute to maintaining their body temperature in a cold environment by providing thermal insulation. As components of skin lipids, the LCFAs play a critical role in skin function by providing water barrier and thermal insulation to the skin. Therefore, as we review in this chapter, impairment of LCFA metabolism in skin often causes energy wasting either by reducing thermal insulation or by increasing heat loss caused by water evaporation through the skin, leading to profound alterations of whole-body energy metabolism.

5.1.1. Keratinocytes and ceramides

The major cell type in epidermis is the keratinocyte, which secretes ceramides. The skin ceramides form multiple extracellular lamellar lipid layers at the uppermost part of epidermis. This lipid lamellar structure serves as the primary barrier against a transdermal passage of molecules including water [230]. As shown in Fig. 7A, skin ceramides consist of a very long saturated fatty acid (C30–32) and a sphingosine connected with an amide bond. The skin sphingosines are derived from C16 palmitic acid and serine, and have variable configurations in the number and position of head hydroxyl groups. One group of skin ceramides, omega-O-acylceramide, contains a very long chain fatty acid with an omega-hydroxyl residue, to which linoleic acid is attached via an ester bond [230,231]. The longer chain of the ceramide is three times longer than the shorter chain (Fig 7A), and is considered to be inserted into one and a half layers of lamellar structure [230].

5.1.2. Sebaceous gland and wax esters

Sebaceous glands in the skin also synthesize several classes of lipids such as triglycerides, free fatty acids and wax esters to cover skin and hair surface. Among them, wax esters are likely to play a critical role in thermal insulation of skin as we will examine in the subsequent sections. The skin wax monoesters are formed by an

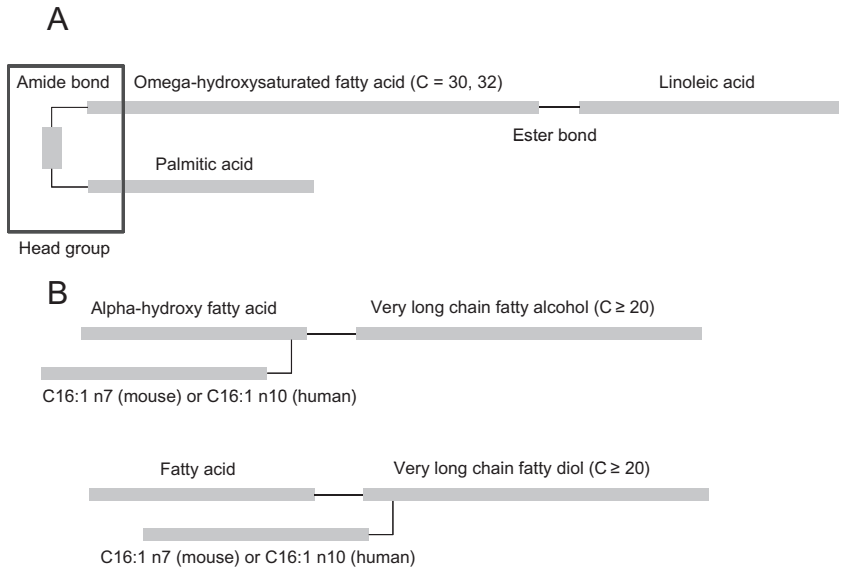

Fig. 7. Structures of skin lipids. (A) A group of skin ceramides that have linoleic acid esterified to an omega-hydroxy residue of very long chain saturated fatty acids (C30, 32). The head group has varied configurations of chemical modifications including hydroxylation. Skin ceramides are synthesized by keratinocytes, and are essential for the water barrier function. Replacement of linoleic acid with oleic acid compromises the water barrier in linoleic acid deficiency. (B) Two types of skin wax diesters that contain a 16:1 fatty acid. Wax esters are synthesized by the sebaceous gland in skin and are essential for thermal insulation. 16:1n7 in mice and 16:1n10 in humans are synthesized in the sebaceous gland by SCD1 and D6D, respectively, and are required for wax diester synthesis.

ester bond between a fatty acid and a fatty alcohol, whereas skin wax diesters are made of an alpha-hydroxy fatty acid forming two ester bonds with a fatty alcohol and a fatty acid, or two fatty acids forming ester bonds with a fatty diol [232] (Fig 7B). A 16-carbon, monounsaturated fatty acid is prevalent in the fatty acid moiety of skin wax esters, whereas a very-long, saturated chain ($C \geqslant 20$) is common for the fatty alcohol moiety (Fig. 7B). There is a distinct difference between mice and humans in the species of C16 monounsaturated fatty acids in the skin. In mice, the fatty acid is palmitoleic acid (16:1 n7) synthesized by stearoyl CoA desaturase 1 (SCD1) in sebocytes [233], whereas in humans, it is sapienic acid (16:1 n10) synthesized by delta-6 desaturase (D6D, also called FADS2), which is the only desaturase expressed in human sebocytes [234] (Fig. 7B). The desaturation of palmitic acid by D6D becomes possible in the absence of competition from SCD [235,236].

5.2. Animal models with a skin lipid impairment

5.2.1. Linoleic acid deficiency

Characteristics of classic essential fatty acid (EFA) deficiency are dry, scaly skin and growth retardation, which was reversed by a small amount of dietary linoleic acid [237]. The animals fed a diet deficient in linoleic acid doubled water intake without change in urine output, and increased food intake per body weight [237] (Table 1). However, it took more than a half-century since that discovery to elucidate the mechanism underlying these severe symptoms. Because linoleic acid serves as a precursor of arachidonic acid, which is then converted to eicosanoids with a variety of bioactivities in many tissues [238], it was suspected that lack of eicosanoids, not of linoleic acid was the cause of symptoms of EFA deficiency. However, linoleic acid is the major fatty acid esterified to omega-hydroxyl group of omega-O-acylceramides in the skin [231] (Fig 7A). The major change in skin ceramides under linoleic acid deficiency is replacement of linoleic acid with oleic acid in omega-O-acylceramide, and this change results in increased trans-epidermal water loss [239,240]. Subsequently, using nonhydrolizable synthetic ceramides, it was unequivocally shown that linoleic acid itself, not arachidonic acid or eicosanoids, was responsible for maintaining skin water barrier function as a component of skin ceramides [241]. Consistent with this observation, no classic EFA deficiency symptoms were observed when arachidonic acid deficiency was created without depleting linoleic acid using the D6D KO mouse [242]. Instead, arachidonic deficiency caused previously undocumented ulcerative dermatitis [242]. Furthermore, Phinney et al. demonstrated that growth retardation was prevented when EFA deficient animals are placed in a thermoneutral (30 °C) and humid condition to minimize water evaporation from the skin [243], indicating trans-epidermal water loss and accompanying heat loss can account for the main symptoms of EFA deficiency including growth retardation, hyperphagia and hyperdipsia.

5.2.2. ELOVL4 mutation, KO mice

The importance of the lamellar layers of ceramides in skin barrier function is highlighted by mouse models of ELOVL4 deficiency. Elongation of very-long chain 4 (ELOVL4) encodes an enzyme that is required for elongating fatty acid chains from 26 to 28 or longer [244]. ELOVL4 is highly expressed in retina and significantly in brain, skin and testis [245]. A dominant negative mutation of ELOVL4 in humans is known as the cause of Stargardt disease 3 characterized by macular degeneration of retina. Homozygous knock-in mice with the Stargardt ELOVL4 mutation are born apparently normal, but die within a few hours after birth due to severe dehydration [246,247] (Table 1). Dyes penetrate through the skin of the homozygous animals, showing severe impairment of skin barrier function [246,247]. Electron microscopy revealed that the skin of the homozygous newborn animals lacks organized lamellar structure [246]. Although the amount of skin lipids including ceramides are not decreased in these animals, omega-O-acyl ceramide is not detectable [246,247], indicating that synthesis of C30 and 32 FA by ELOVL4 is essential for the subsequent synthesis of omega-O-acylceramide (Fig. 7A; Table 1). Homozygous ELOVL4 KO mice also exhibited the same phenotype, confirming the essentiality of ELOVL4 for skin barrier function [248,249].

5.2.3. ELOVL3 KO mice

ELOVL3 encodes another acyl CoA elongase, which is likely to catalyze conversion of C20 fatty acids to 22 and 24 [250]. ELOVL3,

Table 1
Phenotypic comparisons of animal models with skin lipid abnormalities.

Model	Function in skin	Skin condition in deficiency	Hyperphagia, hyperdipsia	Cold intolerance	Other characteristics
Linoleic aciddeficiency	Component of skin ceramides [231]	Dry, scaly skin [237]; increased trans-epidermal water loss [240]	Yes [237], yes [237]	NA	Growth retardation prevented by thermoneutral, humid condition [243]
ELOVL4 KO mouse, stargardt mutation knock-in mouse	Synthesis of C28–32 omega-hydroxy saturated fatty acids for skin ceramides [246,248,249]	Loss of lamellar structure due to lack of omega-O-acyl ceramide [246,247]	NA, NA	NA	Neonatal death due to severe dehydration [246–249]
ELOVL3 KO	Synthesis of C22, 24 fatty acids for skin triglycerides (and ceramides?) [250]	Decreased water repulsion and lamellar structure; increased trans-epidermal water loss [250]	Yes [252], NA	No [252]	Increased energy expenditure in cold [252]
Asebia mouse, SCD1 KO mouse, skin SCD1 KO mouse	Synthesis of 16:1n-7 for wax mono-and di-esters [255,256,259]	Hair loss, sebocyte atrophy [254,256,259]	Yes [259], NA	Yes [258,259]	Resistant to high fat diet-induced obesity, increased energy expenditure [257,259]; growth retardation [254]
DGAT1 KO mouse	Esterification for wax ester synthesis [263]	Hair loss, decreased water repulsion [263]; sebocyte atrophy [263]	Yes [265], NA	Yes when fasted [265]	Decreased adiposity, increased energy expenditure [261,265]; high skin temperature [265]
DGAT2 KO mouse	Unknown	Increased trans-epidermal water loss [266]	NA	NA	Neonatal death, decreased carcass triglycerides, and embryonic growth retardation [266]

NA, no data available.

first identified as a cold inducible gene in brown adipose tissue [251], is also expressed in the skin although the gene expression in skin is insensitive to cold temperature [250]. The main phenotype of ELOVL3 KO mice is skin abnormality characterized by rumpled hair that is unable to repulse water [250]. The ELOVL3 KO mouse shows a decrease in organized lamellar layers and an increase in trans-epidermal water loss (Table 1). Consistent with this skin abnormality, the ELOVL3 KO animals exhibited increased energy expenditure and food intake compared with wild type animals when ambient temperature is below thermoneutral but not at thermoneutral (30 °C) [252]. Therefore, increased food intake and energy expenditure is likely secondary to the increased heat loss from skin, not a primary defect in the ELOVL3 KO mouse. Exact lipid abnormalities that cause the impairment of skin barrier function in the ELOVL3 KO mouse are yet to be determined although saturated and monounsaturated fatty acids with C22 and 24 are diminished in hair triglycerides of the ELOVL3 KO [250].

5.2.4. Asebia, SCD1 KO mice

SCD1 KO mice are another good example of impaired skin lipid metabolism profoundly impacting energy metabolism. SCD1, also called delta-9 desaturase, converts saturated fatty acids palmitic acid and stearic acid to monounsaturated fatty acids palmitoleic acid and oleic acid, respectively. According to the EST profile in Unigene (http://www.ncbi.nlm.nih.gov/unigene), SCD1 is expressed in many tissues presumably to provide monounsaturated fatty acids for membrane phospholipids. Also, SCD1 is highly expressed constitutively in adipose, whereas it is highly induced in liver under the condition of active *de novo* lipogenesis [253]. Importantly, SCD1 is also essential in skin lipid synthesis in the sebaceous gland in mice. Asebia mice, an autosomal, recessive mutant strain with skin abnormality was identified nearly a half century ago, and was so named because of the absence of sebaceous glands in the skin [254]. In addition to the lack of sebaceous glands, the asebia mouse had short, sparse hair, and exhibited growth retardation [254]. Subsequently, the mutated gene in the asebia mouse was found to be SCD1 [233]. Mono- and di-wax esters, which are produced by sebocytes, are markedly reduced in skin lipids of asebia mouse, while water barrier function is normal [255] (Table 1).

These findings in the asebia mouse were also reproducible in the SCD1 KO mouse including thin hair coat, sebaceous gland atrophy and decreased wax esters in skin lipids [256] although reduced weight gain in SCD1 KO mice was observed only when animals were fed a high-fat diet [257]. The SCD1 KO mouse exhibited increased energy expenditure throughout a day [257]. Furthermore, the SCD1 KO animals developed hypothermia, hypoglycemia and depletion of liver glycogen in 3 h when placed at 4 °C [258], suggesting massive heat loss from skin at low temperature (Table 1). Subsequently, skin-specific SCD1 KO mice showed essentially the same phenotype as the whole body SCD1 KO including increased energy expenditure, hyperphagia, cold intolerance and resistance to developing obesity when fed a high-fat diet [259]. The skin-specific SCD1 KO demonstrated that impaired thermal insulation accounts for the major metabolic changes observed in the whole-body SCD1 KO mouse.

Another important finding on this topic is species differences between mice and humans. In humans, SCD is absent in sebaceous glands. Instead, D6D is expressed in sebaceous glands to synthesize sapienic acid 16:1n10 from palmitic acid for production of wax esters [234] (Fig. 7 B). In mammals, D6D is essential for synthesis of arachidonic acid and docosahexaenoic acid from linoleic acid and α-linolenic acid, respectively [2,242]. However the role of D6D in sebaceous glands seems to be unique to humans as no other mammal with D6D expression in sebaceous glands has been identified [234]. A human case of D6D deficiency also supports the role of D6D in sebaceous glands. The main symptoms of the patient include low D6D products in plasma, abnormal skin and hair, food intolerance, gastric bleeding and growth retardation [260]. After dietary supplementation of arachidonic acid and docosahexaenoic acid, these symptoms disappeared except scant and brittle hair [260], which is similar to the hair abnormality observed in asebia and SCD1 KO mice [254,256]. On the other hand, D6D KO mice had normal hair, and developed ulcerative dermatitis, which was prevented by dietary supplementation of arachidonic acid [242]. In summary, because of the critical difference in SCD function in skin between mice and humans, metabolic changes observed in SCD1 KO, or any other means of modulation such as knock down or pharmacological inhibition of the SCD enzyme activity in mice cannot be extrapolated to humans.

5.2.5. DGAT1 KO mice

Diacylglycerol acyltransferase 1 (DGAT1) catalyzes the final step of triglyceride synthesis. However, DGAT1 KO mice are capa-

ble of synthesizing triglycerides, and there is no impairment of lipid absorption presumably due to the presence of an isozyme DGAT2 [261,262]. The main phenotype of the DGAT1 KO mouse is dry hair and subsequent hair loss with atrophy of sebaceous glands [263]. The abnormality in skin lipids is decreased wax esters but not triglycerides [263] (Table 1). Because DGAT1 is also capable of catalyzing wax ester synthesis [264], the indispensable function of DGAT1 in mouse is likely to be skin wax ester synthesis. DGAT1 KO also exhibited decreased adiposity accompanied by increased food intake and energy expenditure [261,265]. Furthermore, the skin temperature of DGAT1 KO mice was higher than wild type, indicating decreased thermal insulation by skin [265]. The phenotype and skin abnormality of DGAT1 KO mice closely resemble those of SCD1 KO although the DGAT1 KO mouse showed cold intolerance only after fasting [265].

5.2.6. DGAT2 KO mice

DGAT2 KO in mice resulted in neonatal lethality accompanied by trans-epidermal water loss [266], suggesting a similar impairment of skin function seen in the ELOVL4 KO mouse. However, DGAT2 KO mice also exhibited decreased carcass triglycerides and embryonic growth retardation [266], indicating a severe impairment of triglyceride synthesis that affects more than impaired skin function.

5.3. Apparent resistance to development of metabolic syndrome in the animals with impaired skin function

As summarized in Table 1, many of the animal models reviewed in this section showed evidence or signs of increased energy expenditure. However, none of them showed evidence to support an alteration of energy metabolism as the primary cause of increased energy expenditure observed in these animals. Instead, as summarized in Fig. 8, increased energy expenditure in these animals is likely secondary to the increased heat loss from the skin due to impairment of skin lipid synthesis via increased water evaporation and/or decreased thermal insulation when ambient temperature is below thermoneutral. This impaired skin function in turn leads to decreased growth or adiposity in these animal models compared to control animals when the animals are unable to compensate for increased energy expenditure with increased food intake, (Fig. 8). Although some of these animal models showed resistance to dietary induced obesity [261,257]and improved insulin sensitivity [257], caution would be required to inhibit skin lipid synthesis for treating human obesity. First, considering the importance of skin as a barrier against external environment, inhibition of skin function may have significant side effects. Second, as summarized in Table 1, increased energy expenditure triggers hyperphagia that could easily compensate for increased energy expenditure. Also, an increase in energy expenditure is pronounced in cold temperature, and diminishes in thermoneutral condition. Thus, mild inhibition of skin lipid synthesis may not produce a net reduction of energy balance.

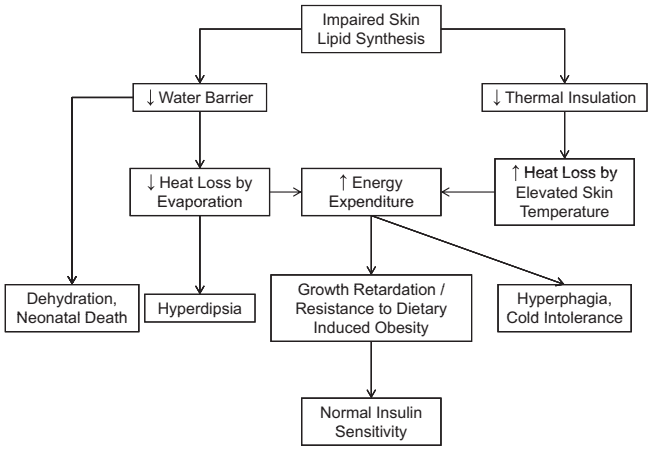

Fig. 8. Mechanism underlying phenotypes of impaired skin lipid synthesis. Impairment of skin lipid synthesis often causes reduction of water barrier and/or thermal insulation of skin, developing a variety of pathological conditions. Increased energy expenditure leads to apparent resistance to obesity and increased insulin sensitivity.

6. Concluding remarks and future directions

LCFAs bind and activate all three subtypes of PPARs. Intra-cellular concentrations of LCFAs are higher than Kd values toward PPARs. However, abundantly expressed FABPs bind to non-esterified LCFAs with much higher affinity, drastically reducing free LCFA concentrations. Therefore, it is likely that LCFAs regulate activity of PPARs *in vivo* by acting as endogenous ligands.

LCFAs regulate liver energy metabolism by activating PPARα, which is primarily expressed in liver. The essentiality of PPARα for metabolic adaptation to starvation was demonstrated in PPARα KO mice that were unable to induce enzymes for fatty acid oxidation and ketogenesis. The importance of PPARα in adapting to negative energy balance is further underscored by the discovery of FGF21 as another gene induced by PPARα. FGF21 is a hormone that reduces dispensable energy expenditure by downregulating the IGF1 pathway downstream of GH signaling when food is scarce.

PPARδ plays a critical role in the coordination of physiological adaptations of skeletal muscle in response to fasting and endurance exercise. Although PPARδ activates several genes that also are targets of PPARα, studies with gene knockout animals indicate a dominant role of PPARδ in skeletal muscle. During fasting, the effects induced by PPARδ are partly coordinated via induction of FOXO1, CD36, and PDK4, resulting in a shift from glucose to LCFAs as an energy source. Endurance exercise activates PPARδ and MEF2 via influx of LCFAs and calcium ion, respectively. MEF2 induces slow type fiber in skeletal muscle in response to endurance training. Induction of cofactor PGC1α plays a central role in adaptation of skeletal muscle to fasting and exercise. PPARδ, FOXO1 and MEF2 all induce PGC1α, which in turn amplifies the activity of these transcription factors by acting as their cofactors. In addition, PGC1α acts as a cofactor of transcription factors ERRα and NRF, which are essential for mitochondrial biogenesis. Therefore, induction of PGC1α also leads to mitochondrial biogenesis.

In adipocytes, regulation of energy metabolism by LCFAs is mediated by PPARγ, which is essential for function of differentiated adipocytes. Upon activation, PPARγ induces gene for triglyceride storage from LCFAs such as LPL, FATP1, PEPCK, DGAT and perilipin. However, induction of genes for *de novo* lipogenesis is unlikely the primary function of PPARγ. Instead, PPARγ rather inhibits pyruvate conversion to acetyl CoA, and increases glycerol-3-phosphate for triglyceride synthesis by inducing PDK4 and PEPCK.

Adiponectin is another gene induced by PPARγ, and has major importance in insulin sensitizing effects of PPARγ agonists, TZDs. The physiological function of adiponectin is likely to increase perfusion of adipocytes with interstitial fluid by acting as an intercellular spacer.

Skin LCFAs are essential for water barrier and thermal insulation functions of skin. Impairment of LCFA metabolism in skin results in increased energy expenditure because of increased heat loss through skin caused by increased evaporation and/or decreased thermal insulation. Secondary to the increased energy

expenditure, some animal models show increased insulin sensitivity and resistance to obesity development under compromised skin function.

There still are many unanswered questions regarding regulatory mechanism of energy metabolism by LCFAs. Future investigations with merit would include (1) a regulatory role of FABPs in PPAR activation by LCFA, (2) physiological role of phospholipids as endogenous ligands of PPAR, (3) a role of adiponectin-T-cadherin complex in insulin sensitization, and (4) the basis of structural requirement of LCFAs for skin barrier function.

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