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Review Article

Lipid sensing by PPARα: Role in controlling hepatocyte gene regulatory networks and the metabolic response to fasting

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) constitute a small family of three nuclear receptors that act as lipid sensors, and thereby regulate the transcription of genes having key roles in hepatic and whole-body energy homeostasis, and in other processes (e.g., inflammation), which have far-reaching health consequences. Peroxisome proliferator-activated receptor isotype α (PPARα) is expressed in oxidative tissues, particularly in the liver, carrying out critical functions during the adaptive fasting response. Advanced omics technologies have provided insight into the vast complexity of the regulation of PPAR expression and activity, as well as their downstream effects on the physiology of the liver and its associated metabolic organs. Here, we provide an overview of the gene regulatory networks controlled by PPARα in the liver in response to fasting. We discuss impacts on liver metabolism, the systemic repercussions and benefits of PPARα-regulated ketogenesis and production of fibroblast growth factor 21 (FGF21), a fasting- and stress-inducible metabolic hormone. We also highlight current challenges in using novel methods to further improve our knowledge of PPARα in health and disease.

1. Introduction

In higher organisms, metabolic regulation depends on the allosteric control of critical enzyme activity and posttranslational protein modifications. These two regulatory functions mainly influence protein-protein interactions that modulate the activities of enzymatic complexes. A third important mechanism is the control of gene transcription, which affects the expression of proteins implicated in metabolic pathways and their regulation. This third mechanism is usually active at long intervals and involves thousands of genes [1].

Regulation of gene expression relies on transcription factors that influence all aspects of the transcription of deoxyribonucleic acid (DNA) into ribonucleic acid (RNA). The transcriptional control of metabolism requires that specific signals reach the target cells, thereby impacting

Abbreviations: 3OHB, 3-hydroxybutyrate; Acetyl-CoA, acetyl-Coenzyme A; AMPK, 5' adenosine monophosphate-activated protein kinase; ANGPTL4, angiopoietin-related protein 4; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; BAT, brown adipose tissue; BCL6, B-cell lymphoma 6; cAMP, cyclic adenosine monophosphate; ChREBP, carbohydrate-responsive element-binding protein; CREB, cAMP-responsive element-binding protein; Cyp17a1, cytochrome P450 family 17 subfamily A member 1; DHEA, dehydroepiandrosterone; DNA, deoxyribonucleic acid; FGF21, fibroblast growth factor 21; FGFR1c, fibroblast growth factor receptor 1c; FXR, farnesoid X receptor; G0s2, G0 switch 2; GR, glucocorticoid receptor; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; HUWE1, HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1; JMJD3, Jumonji domain-containing protein 3; LPL, lipoprotein lipase; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; mTORC1, mammalian target of rapamycin complex 1; NCoR1/2, nuclear receptor corepressor 1/2; OEA, oleoylethanolamide; PAQR9, progesterone and adipoQ receptor 9; PBC, primary biliary cholangitis; PEDF, pigment epithelium-derived factor; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; Pnpla2, patatin like phospholipase domain containing 2; PPAR, peroxisome proliferator-activated receptor; PPARα, peroxisome proliferator-activated receptor isotype α,; PPARβ/δ, peroxisome proliferator-activated receptor isotype β/δ; PPARγ, peroxisome proliferator-activated receptor isotype γ; PPRE, peroxisome proliferator response element; RNA, ribonucleic acid; RXR, retinoid X receptor; SIRT1, sirtuin 1; TCA, tricarboxylic acid; TNFα, tumor necrosis factor isotype α.

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the activities of several transcription factors that regulate defined sets of genes. Studies of the molecular mechanism of action of hormones (estrogens, glucocorticoids, and thyroid hormones) have supported the concept of a family of highly related nuclear hormone receptors [2,3]. This family has expanded to comprise structurally related receptors (including orphan receptors or receptors with non-identified agonists) and has been termed the nuclear receptor superfamily of ligand-regulated transcription factors, which includes 48 members in humans, which play critical roles in physiology, reproduction, and development [2,4].

A three-member subfamily of the nuclear receptor superfamily is the peroxisome proliferator-activated receptors (PPARs)—comprising PPARα, PPARβ/δ, and PPARγ—which have now been attributed many roles, extending far beyond the proliferation of peroxisomes in the rodent liver from which their name originated [5–7]. PPAR transcriptional activity depends on ligand-activated PPAR:retinoid X receptor (RXR) heterodimers that target responsive genes by binding to peroxisome proliferator response elements (PPRE) in their regulatory region. These target genes are implicated in lipid and carbohydrate metabolism, vascular biology, tissue repair, cell proliferation and differentiation, and sexual dimorphism, among other functions [8]. Identified PPAR ligands include a variety of natural compounds, including polyunsaturated fatty acids, eicosanoids, a few endocannabinoids, phospholipids, and bilirubin [8–11]. It can be hypothesized that the diversity of PPAR functions evolved in association with this wide variety of ligands. Moreover, a broad range of synthetic ligands have been developed to treat dyslipidemia and diabetes, and efforts have been made to expand their therapeutic applications to other metabolic and inflammatory diseases [12,13]. Over years of research, PPARs have emerged as strong regulatory links between lipids, metabolic health and disease, and immunity [8].

PPARα is abundantly expressed in cells that exhibit high mitochondrial and peroxisomal β-oxidation of non-esterified fatty acids—including the liver, brown adipose tissue (BAT), the heart, proximal tubules of the kidney, and intestinal mucosa [14]. The roles of PPARα have been most extensively studied in the liver, where PPARα regulates hundreds of genes involved in many hepatic functions. The best-known functions of hepatic PPARα are related to its role as an important regulator of the adaptive response to fasting [15–20]. This review introduces fasting and then focuses on PPARα as a lipid sensor that controls hepatocyte gene regulatory networks in response to fasting.

2. Fasting

An international consensus on fasting terminology was recently proposed [21]. This publication defines terms, including fasting, intermittent fasting, time-restricted eating, long-term and short-term fasting, as well as fasting mimicking diets. Most of the data reviewed herein, except if mentioned otherwise, concern “fasting” as abstinence from foods for a period generally ranging from 12 hours up to several weeks in humans and shorter periods in rodents. Fasting has shaped animal and human energy adaptive metabolism, allowing survival during prolonged periods of restricted food availability. Evidence from rodent models and human studies indicates that various fasting regimens may represent effective strategies for reducing weight, delaying aging, preventing diseases, and promoting health [22]. Fasting also improves anti-tumor responses in mice [23].

The multi-organ response to prolonged fasting was recently investigated by analyzing the plasma proteome in 12 healthy human volunteers, demonstrating that up to 1000 proteins significantly changed after 3 days of fasting [24]. The main fasting mechanism is the metabolic fuel switch from glucose to fatty acid-derived ketone bodies. This adaptive response is largely driven by changes in circulating levels of hormones, such as insulin, glucagon, and glucocorticoids, that control energy homeostasis through several changes in gene expression, mainly in the liver. An essential adaptive response to fasting is the activation of the hypothalamic-pituitary-adrenal axis, driven by neurons expressing agouti-related peptide, which induces glucocorticoid release into the blood [25]. Moreover, the anti-inflammatory effects of fasting could be explained by the inhibition of NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome activity due to the high lipid arachidonic acid levels found in fasted subjects [26]. In the opposite condition—the fed state—increased blood glucose levels induce insulin secretion from the pancreas, inhibiting glucagon secretion and suppressing lipolysis. Additionally, insulin activates feeding-related transcription factors to increase hepatic glycogenesis, lipogenesis, and protein synthesis, and inhibits fasting-related hepatic transcription factors (Fig. 1A).

Collectively, fasting triggers a tightly regulated and coordinated adaptive metabolic response in major organs, including the liver, the adipose tissues, and the brain. Below, we will focus on the impact of fasting on the liver.

3. Hepatic metabolic responses to fasting

In mammals, the metabolic response to fasting is mainly orchestrated by the liver that ensures the production of fuels (glucose and ketone bodies) to supply peripheral tissues—especially the brain, which is a poor user of fatty acids as an energy source. Both gluconeogenesis and ketogenesis rely on an extra-hepatic supply of substrates [27]. As mentioned above, the liver’s adaptive response to fasting is initiated by hormonal signals that trigger the activation of several transcription factors, which in turn induce dynamic changes in hepatic gene expression [28]. Before focusing on hepatic PPARα, we will briefly overview the two main hepatic transcriptionally controlled processes regulated during fasting.

3.1. *Gluconeogenesis*

During the first hours of fasting, glycogen is broken down (glycogenolysis), releasing glucose from hepatocytes into the bloodstream. In skeletal muscle, glycogen is converted to glucose and lactate, which is converted back to glucose in the liver. If fasting persists after glycogen stores are depleted, glucose production depends on gluconeogenesis—i.e., *de novo* glucose production from non-carbohydrate precursors, such as amino acids and glycerol [27]. Gluconeogenic amino acids are mainly sourced from skeletal muscle proteins. Glycerol is produced *via* triacylglycerol lipolysis from lipid stores, providing the liver with non-esterified fatty acids.

Glucagon is a peptide hormone secreted from α cells of the pancreas in response to decreased blood glucose levels. In hepatocytes, glucagon binds to the glucagon receptor (a G-protein coupled receptor), leading to adenylate cyclase activation, increased cyclic adenosine monophosphate (cAMP), and protein kinase A activation—which leads to the phosphorylation and activation of cAMP-responsive element-binding protein (CREB) (Fig. 1B). CREB is a transcription factor that controls the expressions of genes that encode key enzymes catalyzing gluconeogenesis, such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 1. Accordingly, whole-body glucagon receptor knock-out mice and transgenic mice expressing a dominant negative CREB protein in the liver exhibit lower blood glucose levels [29,30]. CREB further supports gluconeogenesis by regulating genes involved in amino acid catabolism and the urea cycle [31,32]. Furthermore, glucagon stimulates hepatic gluconeogenesis through a transcription-independent effect, promoting intrahepatic lipolysis by stimulating the inositol triphosphate receptor-1. This yields increased hepatic acetyl-Coenzyme A (acetyl-CoA), an allosteric activator of pyruvate carboxylase, and is involved in oxaloacetate production to support citrate, glucose, amino acid, and fatty acid synthesis [33].

In addition to glucagon, glucocorticoids are secreted from the adrenal cortex and bind to the cytoplasmic glucocorticoid receptor (GR) in hepatocytes, a transcription factor belonging to the nuclear receptor

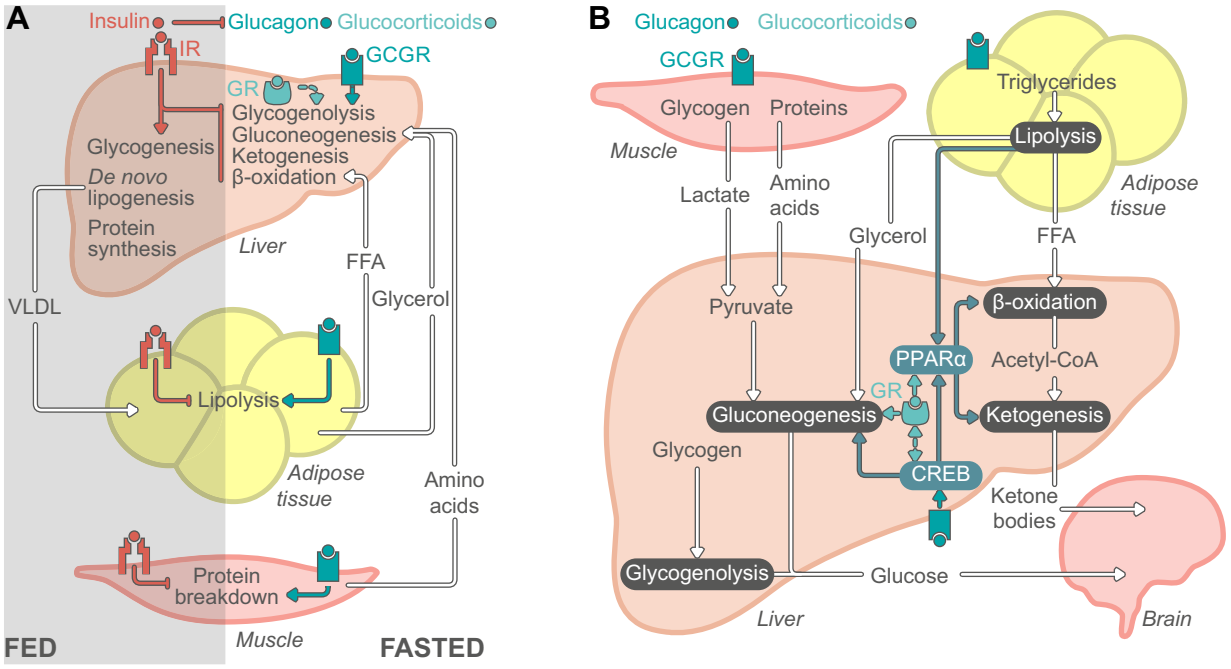

Fig. 1. Metabolic adaptations to fasting. A) In the fed state, increased blood glucose levels induce insulin secretion from the pancreas, reducing glucagon secretion and suppressing adipocyte lipolysis and muscle protein degradation. In the liver, insulin activates feeding-related transcription factors to increase hepatic glycogenesis, lipogenesis, and protein synthesis and inhibits fasting-related hepatic transcription factors. In the fasted state, decreased blood glucose levels lead to increased glucagon and glucocorticoid levels, while insulin levels decrease. In the first hours of fasting, glycogen is broken down through glycogenolysis. Glucagon and glucocorticoids control gluconeogenesis from amino acids and glycerol provided by muscle protein degradation and adipose lipolysis, respectively. Low insulin levels stimulate adipocyte lipolysis, releasing free non-esterified fatty acids into the circulation, which are then used by the liver to produce ketone bodies through β-oxidation and ketogenesis. B) During fasting, upon depletion of glycogen stores, gluconeogenesis provides glucose, and ketogenesis provides ketone bodies as an alternative energy source for peripheral organs (e.g., the brain). Glucagon binds to the glucagon receptor (GCGR), activating cAMP-responsive element-binding protein (CREB), which controls the transcription of gluconeogenic genes. Glucocorticoids activate the glucocorticoid receptor (GR) to induce the expression of genes involved in gluconeogenesis. Adipose lipolysis-dependent activation of PPARα induces β-oxidation and ketogenesis. Abbreviations: CREB = cAMP-responsive element-binding protein, FFA = free fatty acids, GCGR = glucagon receptor, GR= glucocorticoid receptor, IR = insulin receptor, PPARα = peroxisome proliferator-activated receptor isotype α.

superfamily. GRs then dissociate from their chaperone proteins and translocate to the cell nucleus, where they modulate gene transcription by binding to glucocorticoid response elements in the regulatory region of target genes (Fig. 1B). This mechanism stimulates the expression of gluconeogenic genes that promote gluconeogenesis in the liver [34]. Accordingly, mice deficient in hepatic GR develop severe hypoglycemia during prolonged fasting [35]. It was recently reported that hepatocyte-specific GR knockout mice exhibit lower levels of circulating triacylglycerols only during the day and reduced blood glucose levels specifically at night [36]. As we will see below, one of these GR target genes is the gene encoding PPARα.

Furthermore, the two fasting hormones—glucagon and glucocorticoids—synergistically induce the transcriptional regulation of genes involved in amino acid catabolism, thereby maximizing gluconeogenesis [37]. Similarly, these two hormones cooperate to induce gluconeogenic genes [37–40]. The glucagon–CREB axis mediates enhancer activation that potentiates GR binding [41] and, reciprocally, GR assists the loading of CREB on gluconeogenic enhancers [42], thereby increasing gene expression and hepatic glucose production. Moreover, through direct activation of CREB and GR, glucagon and glucocorticoids indirectly promote the expression of genes that encode many other fasting-related transcription factors. Overall, this transcription factor cascade, initiated by CREB and GR, fine-tunes and potentiates the hepatic response to fasting [28]. It also instigates a secondary wave of ketogenic gene transcription [40].

3.2. Fatty acid β-oxidation and ketogenesis

As fasting persists, glycogen stores are depleted, and gluconeogenesis decreases. This decrease prevents muscle wasting, which provides amino acids for glucose synthesis. Instead, fatty acid β-oxidation and its associated ketogenesis become the processes for producing metabolic fuels for extrahepatic tissues [27] (Fig. 2).

The low insulin levels during fasting suppress plasma triacylglycerol hydrolysis by inhibiting lipoprotein lipase (LPL) activity but promote adipose tissue lipolysis by stimulating adipose triglyceride lipase (ATGL) expression [43], resulting in the release of non-esterified fatty acids and glycerol from adipose tissue into the circulation [44]. A cell-intrinsic mechanism that regulates ATGL-dependent lipolysis has been recently reported. Upon glucose deprivation, phosphatidylinositol-4-phosphate levels in the Golgi decrease, enhancing adipose tissue lipolysis due to reduced ATGL ubiquitination and degradation [45]. Long-chain non-esterified fatty acids released from adipose tissue are efficiently oxidized in the liver as acyl-CoAs. Since fasting also increases hepatic gluconeogenesis, as discussed above, it depletes oxaloacetate from the tricarboxylic acid (TCA) cycle and limits citrate synthesis. In the liver, the activation of ketogenesis consumes acetyl-CoA, recovers free CoA required for accelerated fatty acid processing, and can support a β-oxidation rate an order of magnitude higher than the TCA cycle alone [46]. A recent study identified the principal methyl donor hepatic S-adenosylmethionine as a novel regulator of β-oxidation and adenosine triphosphate (ATP) synthesis in hepatocytes, thereby preventing endoplasmic reticulum stress and liver damage during fasting [47]. As discussed below, fasting-induced white adipose tissue lipolysis provides a pivotal signal to activate the nuclear receptor PPARα in the liver.

The currently available evidence clearly shows that the hepatic fasting response comprises complex dynamic gene network regulation, including many layers of control, such as direct activation of multiple

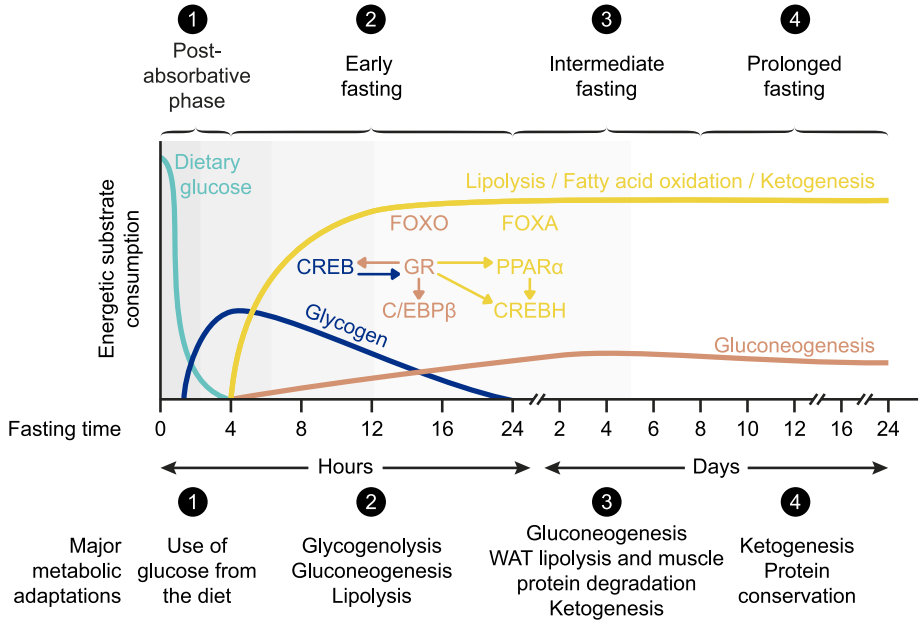

Fig. 2. The different stages of metabolic adaptations during fasting. *Adapted from* [27,211]. In the post-absorptive phase, dietary glucose is absorbed and stored as glycogen in the liver. During early fasting, glycogen stores rapidly release glucose into circulation through glycogenolysis to maintain blood glucose levels. After a few hours, when hepatic glycogen stores decrease, glucose is mostly produced through gluconeogenesis from gluconeogenic precursors, i.e., glycerol and amino acids. Hence, at this stage, the degradation of muscle proteins provides amino acids, and adipose tissue releases glycerol and non-esterified fatty acids. If fasting persists, gluconeogenesis decreases to prevent muscle proteolysis, and non-esterified fatty acids derived from adipose lipolysis become the main substrate for producing metabolic fuel for extrahepatic tissues. The liver takes up and oxidizes the elevated circulating non-esterified fatty acids through β-oxidation to produce acetyl-CoA, which is then converted to ketone bodies through ketogenesis. Several transcription factors cooperate to regulate these metabolic pathways to maintain homeostasis during fasting. The most important ones are listed in the figure, but their expression patterns are not shown. Gluconeogenesis, fatty acid oxidation, and ketogenesis depend heavily on transcriptional regulation. Abbreviations: C/EBPβ = CCAAT enhancer-binding protein beta, CREB = cAMP-responsive element-binding protein, CREBH = cyclic AMP-responsive element-binding protein 3-like 3, FOXA = forkhead box proteins class A, FOXO = forkhead box proteins class O, GR = glucocorticoid receptor, PPARα = peroxisome proliferator-activated receptor isotype α, WAT = white adipose tissue.

transcription factors, recruitment of coregulators and corepressors, regulation of chromatin accessibility, cross-talk between transcription factors, and transcription factor cascade, which together enable a coordinated and integrated response to fasting [28,48]. During fasting, the liver also produces and secretes proteins called hepatokines that signal and communicate with other tissues to influence whole-body energy homeostasis [49].

4. PPARα-dependent hepatic responses during fasting

To illustrate the general PPAR context, we first provide a brief overview of the hepatic functions of PPARβ/δ and PPARγ in the liver. We will then focus on PPARα. PPARβ/δ is involved in innate immunity and plays an important anti-inflammatory role; it controls glucose utilization and glycogen synthesis, and is implicated in lipoprotein metabolism [50,51]. The contribution of PPARβ/δ to hepatic lipid metabolism remains controversial because it is difficult to reconcile some of the results from different experimental models, including using different agonists. Studies have reported that PPARβ/δ improves liver steatosis [52], enhances fatty acid oxidation, and inhibits or promotes lipogenesis, concurrent with an augmented hepatic triacylglycerol content [53,54]. In contrast to PPARα, the specific target genes of PPARβ/δ are not well-characterized. Analysis of the liver PPARβ/δ cistrome identified 8,194 PPARβ/δ-binding sites collectively in fed and fasted livers. 85% of these sites overlapped with the much larger PPARα cistrome comprising 33,379 sites [55]. PPARγ expression is low in the healthy liver [14]. However, its expression increases in both mouse and human steatosis [56], in parallel with higher fatty acid uptake and lipogenic gene expression [51] (Fig. 3). Studies comparing the effects of the hepatocyte-specific disruption of the three PPAR isotypes revealed distinct contributions of each of them in the liver [57]. Further research is needed to refine the separate hepatic functions of the three PPARs [57]. PPAR isotype-specific agonists may contribute to increased knowledge of the hepatic functions of these receptors [14,31,35,58].

4.1. PPARα fasting-dependent functions

Compared to PPARβ/δ and PPARγ, PPARα has the highest hepatic expression. PPARα is a master regulator of energy metabolism and is activated by endogenous ligands (e.g., non-esterified fatty acids, oxidized non-esterified fatty acids, eicosanoids, and bilirubin) and a whole range of synthetic molecules—some of which lead to peroxisome proliferation in the rodent liver, hence their name PPAR [5,9,10,59,60]. Co-activators can also modulate PPARα activity—for example, peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α), which is itself activated by sirtuin 1 (SIRT1) [61]. Like the two other PPARs, PPARα is a phosphoprotein with activity affected by kinases and phosphatases [62]. PPARα activity is also impacted by SUMOylation (SUMOylation refers to when a small ubiquitin-like modifier – SUMO - moiety is covalently linked to a lysine residue in the target protein) [63,64]. The functional regulation of PPARs *via* diverse post-translational modifications has previously been well-discussed [65]. PPARα activity is also influenced by interaction with other proteins. One example is its interaction with the yes-associated protein – transcriptional enhancer factor domain family member complex, which leads to increased activity of PPARα and significantly enhances hepatocyte enlargement and proliferation and hepatomegaly [66].

In response to fasting, hepatocyte PPARα controls the expression of many genes involved in whole-body fatty acid homeostasis. Specifically, PPARα is essential for fasting-induced hepatic fatty acid catabolism, which produces the ketone bodies used as energy source by the

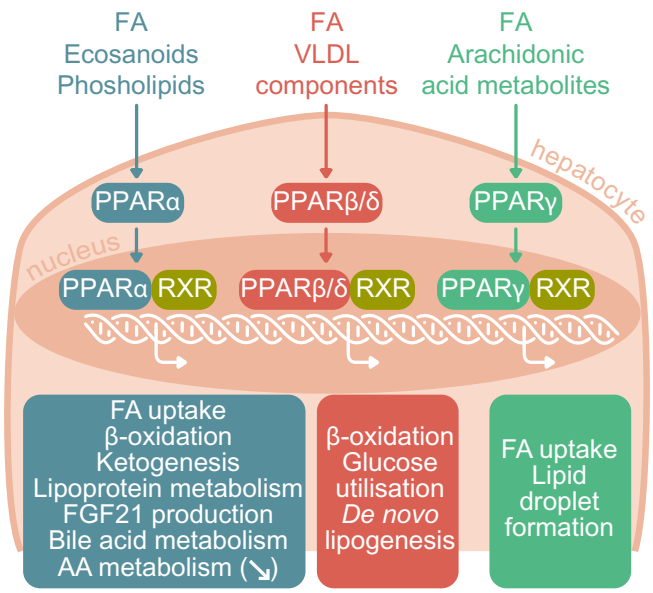

Fig. 3. PPAR functions in hepatocytes. All PPAR isotypes function as heterodimers with RXR. Upon ligand activation, the heterodimers PPAR/RXR bind to PPAR response elements (i.e., the PPREs) in the promoter of target genes and stimulate their transcription. Through this mechanism, hepatocyte PPARα controls fatty acid uptake and catabolism, ketogenesis, FGF21 production, lipoprotein, amino acid, and bile acid metabolism. PPARβ/δ promotes hepatic glucose utilization, fatty acid synthesis and β-oxidation. Hepatic PPARγ expression increases during steatosis, stimulating fatty acid uptake and lipid droplet formation. Abbreviations: AA = amino acid, FA = fatty acids, FGF21 = fibroblast growth factor 21, PPAR = peroxisome proliferator-activated receptor, RXR = retinoid X receptor, VLDL = very low-density lipoprotein.

peripheral organs. Moreover, PPARα is involved in retinol metabolism and bile secretion and controls the expression of several hepatic hormones (hepatokines) [33,67–72].

4.2. Regulation of the activity of hepatocyte PPARα during fasting

During fasting, hepatocyte PPARα activity is enhanced because of hepatic levels of PPARα messenger ribonucleic acid (mRNA) and protein increase [16] which has been attributed to GR activation by glucocorticoids, leading to a progressive rise in fatty acid oxidation and ketogenesis [42]. *Ppara* is a direct GR target gene [73]. In particular, *Ppara* gene transcription by the glucocorticoid-GR axis leads to synergistic induction of ketogenic genes [40]. In addition, mice that lack the glucagon receptor display decreased PPARα-dependent lipid oxidation during fasting, suggesting that PPARα is a downstream target of glucagon signaling [72].

Fasting-induced lipolysis in white adipose tissue releases large amounts of non-esterified fatty acids, which reach the liver, where they are oxidized to produce energy substrates, such as ketone bodies, that are secreted into the bloodstream and then metabolized by peripheral tissues. Since non-esterified fatty acids are ligands for PPARα, it has been suggested that non-esterified fatty acids released from white adipocytes during fasting may influence PPARα activity in the liver [74]. Notably, PPARα activity is markedly increased during the early night (Zeitgeber 16), correlating with the kinetics of circulating non-esterified fatty acid increase [19]. In addition, compared to fasting, dietary essential fatty acids (linoleic acid and alpha-linolenic acid) have little influence on hepatic PPARα activity [75]. By comparison, dietary unsaturated fatty acids, when provided acutely, have effects on hepatic gene expression that are almost exclusively mediated by PPARα, which imitate those of synthetic PPARα agonists concerning target gene expression and molecular mechanism of action [76]. Other studies have suggested that non-esterified fatty acids from plasma do not activate hepatic PPARα, whereas dietary fatty acids and non-esterified fatty acids produced by lipogenesis can activate PPARα [60,77–79]. Recently, ATGL-dependent lipolysis in adipose tissue has been identified as a key process relating to PPARα activity in hepatocytes. Without ATGL in adipocytes, hepatic PPARα-dependent responses (including changes in gene expression, biosynthesis of ketone bodies, and FGF21 production) are impaired upon fasting [80]. Interestingly, a study using liver-specific deletion of *Atgl* in mice has shown that hepatic ATGL is not necessary for the fasting-induced PPARα-dependent responses in the liver [81]. This observation suggests that adipocyte lipolysis-derived non-esterified fatty acids are sufficient to activate PPARα in hepatocytes. ATGL is the rate-limiting enzyme in triacylglycerol hydrolysis that produces diacylglycerol and non-esterified fatty acids. Thus, it is likely that such adipose-derived lipids act as ligands for hepatocyte PPARα and trigger its transcriptional activity. Further studies are needed to examine whether all released non-esterified fatty acids can similarly directly activate hepatic PPARα, and whether they are first esterified to triacyglycerols and then re-hydrolyzed by hepatic lipolysis. Interestingly, PPARα activity can be sensitized by repeating fasting events [82].

In contrast to fasting, PPARα activity is reduced during feeding, which has been attributed to an increased mechanistic target of rapamycin kinase (mTORC1) signaling [83,84]. However, other studies have shown that mTORC1 activation by liver-specific deletion of its negative regulator tuberous sclerosis complex is insufficient to suppress PPARα-responsive genes in the fasted state [85]. Hepatocyte B-cell lymphoma 6 protein (BCL6) has also been identified to repress PPARα in the fed state through competitive binding to shared BCL6-PPARα gene regulatory sites [55]. SUMO-specific peptidase 2 is downregulated in the liver during fasting, and was recently identified as a negative regulator of PPARα through PPARα deSUMOylation, thereby leading to ubiquitylation and subsequent degradation of the receptor in the fed state [86].

4.3. Hepatocyte PPARα target genes during fasting

As a transcription factor, PPARα controls hepatic metabolism by modulating gene transcription. Genes targeted by PPARα during fasting were identified by comparative analyses of gene expression in livers from PPARα germline knockout mice (PPARα$^{-/-}$), hepatocyte-specific PPARα knockout mice (PPARα$^{hep-/-}$) and wild-type mice (Fig. 4). The mouse lines are both viable and fertile and do not show apparent phenotypic defects under normal conditions, but both develop a strong phenotype when fasted [16,17,19,20,87]. Detailed and comprehensive overviews of the metabolic genes and pathways known to be targeted by PPARα have already been published [88,89]. Below, we will distinguish between the regulated genes identified using PPARα$^{-/-}$ mice *versus* PPARα$^{hep-/-}$ mice, thereby focusing on PPARα specific target genes in hepatocytes.

4.3.1. Genes involved in lipid, glucose, and amino acid metabolism

Whole-genome expression analysis by microarray revealed that nearly 2000 genes exhibited lower expression in fasted PPARα$^{-/-}$ mice compared to in fasted wild-type mice (FC > 1.5; P < 0.05) [90]. A similar number of genes was identified using PPARα$^{hep-/-}$ mice [19]. Most of these genes are involved in lipid homeostasis, and are PPARα target genes. PPARα regulates the gene transcription of fatty acid transport proteins (fatty acid transport protein-1; FATP1 or Slc27a1), CD36, fatty acid binding protein-1 (L-FABP), and carnitine palmitoyltransferases (CPT1A and CPT2), and thereby facilitates fatty acid uptake into the liver, and fatty acid import into peroxisomes and mitochondria. Moreover, hepatic PPARα governs hepatic fatty acid catabolism by controlling the expression of genes encoding enzymes, which can be rate-limiting, of β-oxidation in microsomes [cytochrome P450 family 4 subfamily A (CYP4A)], peroxisomes [acyl-CoA oxidase 1 (ACOX), enoyl-CoA hydratase and 3-hydroxyacylCoA dehydrogenase (EHHADH), and thioesterases (ACOTs)], and mitochondria [acyl-CoA dehydrogenase

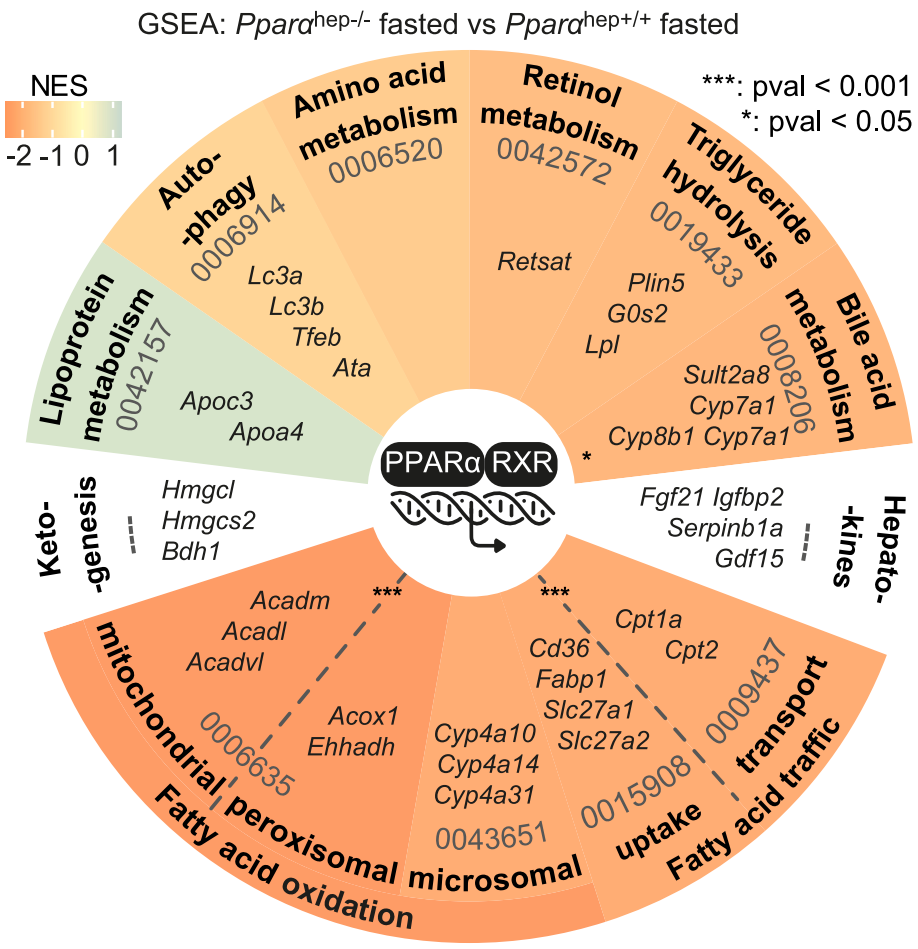

Fig. 4. Hepatocyte PPARα target genes during fasting. Normalized enrichment score (NES) of significantly enriched GO (Gene Ontology) terms through gene set expression analysis (GSEA) of hepatic microarray data from fasted wild-type mice (PPARα$^{hep+/+}$) compared to fasted hepatocyte-specific PPARα knockout mice (PPARα$^{hep-/-}$) [126]. Genes representative of each GO are shown. Biological functions in white (ketogenesis and hepatokines) are custom-made and do not belong to a standard GO term. Abbreviations: PPARα = peroxisome proliferator-activated receptor isotype alpha, pval = adjusted p values of pathway enrichment from GSEA analysis, RXR = retinoid X receptor.

medium chain (ACADM), acyl-CoA dehydrogenase long chain (ACADL), and acyl-CoA dehydrogenase very long chain (ACADVL)]. PPARα also transcriptionally regulates the expressions of ketogenic enzymes required to convert acetyl-CoA to ketone bodies (e.g., 3-hydroxy-3-methylglutaryl-CoA synthase 2; HMGCS2). All of these genes were found to be upregulated in wild-type mice upon fasting, but not (or to a lesser extent) in fasted PPARα$^{-/-}$ mice, first based on northern blot analysis of liver mRNA [15–17,91] and later through microarray analysis [90]. These genes were also expressed at lower levels in fasted PPARα$^{hep-/-}$ mice [68,92].

Interestingly, upon fasting, PPARα can interact with SIRT1 and Jumonji D3 (JMJD3) histone demethylase, leading to the epigenetic activation of hepatic genes involved in mitochondrial β-oxidation, and creating a fasting-induced feed-forward positive autoregulatory loop [93]. Furthermore, hepatocyte PPARα contributes to mitochondrial biogenesis [94]. During fasting, PPARα also increases the expression of genes required for liver triglyceride hydrolysis, including ATGL (*Pnpla2*: patatin like phospholipase domain containing 2), hormone-sensitive lipase (HSL, *Lipe*), monoglyceride lipase (*Mgll*), and the *Pnpla2* inhibitor G0 switch 2 (*G0s2*) [90,95]. *Pnpla2*, *G0s2*, and *Plin5* are among the top differentially expressed genes between fasted wild-type mice and PPARα$^{hep-/-}$ mice, with markedly reduced expressions in the latter [20]. Genes involved in unsaturated fatty acid metabolism (enoyl-CoA isomerases, *Eci1*, *Eci2*, and *Mfsd2a*) and in phospholipid (*Mogat1, Agpat9*) and sphingolipid homeostasis are also regulated by fasting and depend on hepatocyte *Ppara* expression [20]. In addition to its roles in whole-body fatty acid homeostasis, PPARα also influences glucose metabolism by increasing the hepatic expression of genes involved in glycerol metabolism, such as cytosolic and mitochondrial glycerol-3-phosphate dehydrogenase and glycerol kinase, which exhibit PPARα-dependent upregulation during fasting [96]. Moreover, this upregulation correlates with hypoglycemia in fasted PPARα$^{-/-}$ mice. Notably, these genes are not downregulated in PPARα$^{hep-/-}$ mice, which is in line with the normal, or only slightly lower glycemia observed in these mice, and suggests that extrahepatic PPARα influences glucose homeostasis independently of hepatocyte PPARα during fasting. Interestingly, hepatocyte PPARα also regulates the hepatic expression of the thioredoxin-interacting protein, an oxidoreductase that inhibits thioredoxin and thereby regulates the cellular redox state and glucose homeostasis [20,90,97,98]. Additionally, fasted PPARα$^{-/-}$ mice exhibit higher expression of numerous genes involved in amino acid metabolism, including transamination, deamination, and the urea cycle [99]. Branched-chain amino acid degradation is also among the main pathways sensitive to the absence of PPARα, specifically in PPARα$^{hep-/-}$ mice [20]. Altogether, PPARα acts as a master regulator of energy homeostasis in the liver during fasting, playing a major role in coordinating the hepatic metabolism of nutrients, including fatty acids, glucose, and amino acids.

4.3.2. Genes involved in autophagy

Several cellular and metabolic effects of fasting induce autophagy, a well-conserved recycling program that removes dysfunctional organelles and proteins. However, the timeline of these effects remains largely unknown [100,101]. In response to fasting, PPARα regulates autophagy in the liver by directly increasing the expression of several autophagy genes, including *Lc3a* and *Lc3b* [102,103]. Additionally, PPARα stimulates the transcription factor EB expression, thereby indirectly increasing autophagy and lysosomal gene expression. Reciprocally, the autophagy–lysosomal pathway downregulates PPARα activity by increasing the stability of the PPARα corepressor nuclear receptor corepressor 1 (NCoR1) [94,104], and decreasing the stability of the PPARα coactivator PGC1α [105]. Moreover, fasting-induced FGF21 phosphorylates JMJD3, thereby increasing its nuclear transport and interaction with PPARα, which promotes the stimulation of autophagy target genes [106].

4.3.3. Genes involved in bile acid metabolism

Studies in PPARα$^{-/-}$ mice have shown that PPARα also regulates bile acid metabolism during fasting, mainly by downregulating several genes involved in bile acid synthesis (e.g., the cholesterol 7-alpha hydroxylase *Cyp7a1*) [107] and bile acid excretion (e.g., the ABC transporters *Abcg5* and *Abcg8*) [108], as well as the gene encoding sulfonating enzyme SULT2A8 (sulfotransferase family 2A, member 8) [109]. Moreover, PPARα induces farnesoid X receptor (FXR) mRNA expression in the liver of fasted mice [108]. Unlike PPARα, hepatic FXR is activated in the fed state by bile acids that return to the liver. FXR acts in coordination with PPARα to regulate gluconeogenesis and autophagy in the fed and fasted state, respectively [110]. Recently, it was shown that the activation of PPARα upon fasting stimulates the expression of the mitochondrial protein hydroxysteroid dehydrogenase-like 2 (HDSDL2) that links nutritional cues to bile acid and cholesterol homeostasis [111].

4.3.4. Genes encoding hepatokines

In addition to playing a central role in hepatic metabolism, PPARα also exerts extra-hepatic functions during fasting by enhancing the expression of genes encoding hepatokines, a family of proteins secreted by hepatocytes, which act like hormones in an autocrine, paracrine, or endocrine manner. PPARα is essential for hepatic expression of the starvation hormone FGF21 [112,113], and PPARα$^{hep-/-}$ mice exhibit defective *Fgf21* expression [19]. FGF21-dependent functions during fasting are detailed below (section 5.2). PPARα is also required for hepatic expression of angiopoietin-like protein 4 (ANGPTL4) [18], which fasting increases. In adipose tissue, these enhanced ANGPTL4 levels downregulate adipose LPL activity, which contributes to shunting triacylglycerols towards the liver and oxidative tissues (BAT and muscle). However, the physiological consequence of the induction of hepatic ANGPTL4 during fasting is unclear because fasting-induced ANGPTL4 is secreted by several cell types, including adipocytes, hepatocytes, (cardio)myocytes, and macrophages [114]. Activin E is another PPARα-sensitive hepatokine during fasting-induced adipose lipolysis [80] which has been recently identified to act as a feedback loop to suppress lipolysis in response to increased circulating fatty acid levels [115]. In contrast, PPARα$^{hep-/-}$ mice exhibit increased fasting-induced expression of the hepatokine growth differentiation factor 15 (GDF15), insulin-like growth factor binding protein 1 (IGFBP1), and serpin family B member 1, indicating PPARα-independent stimulation [67].

4.3.5. Other genes

Several other genes have been described as PPARα-sensitive genes induced in mouse liver by fasting. Retinoid homeostasis is sensitive to fasting [116] and *Retsat*, which encodes a retinol saturase involved in retinoid homeostasis, is among the genes most highly upregulated upon fasting through a process involving hepatocyte PPARα [68,117]. Vanin-1 *(Vnn1)* is another PPARα-dependent gene highly induced by fasting [20,118]. In mice, the absence of *Vnn1* aggravates fasting-induced hepatic triglyceride accumulation [119]. Studies in PPARα$^{hep-/-}$ mice have also identified several other PPARα-sensitive fasting-induced genes—including keratin 23 *(Krt23)*, a MYC-amplified liver-specific oncogene [120], and *Rab30*, which encodes a small GTPase involved in endocytic trafficking [121,122]. PPARα also regulates the fasting-induced hepatic expression of genes that encode essential components of the oxidative phosphorylation pathway, such as electron-transferring-flavoprotein dehydrogenase (*Etfdh)* and electron-transferring flavoprotein β polypeptide (*Etfb)*. These findings suggest that PPARα also regulates respiratory chain components involved in electron transfer [90].

Altogether, the functional diversity of fasting-induced genes under the control of PPARα illustrates how a single inducible transcription factor can occupy a central role in the global response of a major organ—the liver—to environmental stress triggered by the absence of food.

4.4. Hepatocyte PPARα-dependent regulation of plasma and hepatic metabolites during fasting

Fasting induces major changes in the plasma metabolome [88]. In both fasted PPARα$^{-/-}$ and PPARα$^{hep-/-}$ mice, plasma non-esterified fatty acids are markedly elevated, while ketone body levels are dramatically reduced due to impaired β-oxidation [16,19,20]. During fasting, these mice also exhibit reduced carnitine levels and accumulate long-chain acylcarnitines in plasma [16,17,19,20,123]. Plasma glucose levels are decreased in PPARα$^{-/-}$ mice [16,17], while PPARα$^{hep-/-}$ mice do not exhibit or only have mild hypoglycemia compared to wildtype mice, suggesting that extra-hepatic PPARα is involved in glucose level regulation [19,20]. Metabolic profiling of PPARα$^{-/-}$ mice has revealed that the absence of PPARα leads to decreased plasma levels of alanine and tyrosine, and increased levels of amino acids linked to the urea cycle, suggesting that impaired β-oxidation in the absence of PPARα results in a compensatory increase of amino acid catabolism [123].

Major changes are also observed in the liver metabolome during fasting, especially in the lipid profiles [124]. Compared to fasted WT mice, fasted PPARα$^{-/-}$ and PPARα$^{hep-/-}$ mice exhibit increased levels of hepatic triglyceride and cholesterol esters, resulting in hepatic steatosis [19,20,91]. Lipid profiling of the livers of PPARα$^{hep-/-}$ mice has also highlighted the role of hepatocyte PPARα in phospholipid and sphingolipid homeostasis during fasting since hepatocyte PPARα deficiency results in higher levels of some phospholipids and ceramides [20]. Defective PPARα activity also results in lower levels of hepatic free carnitine associated with higher levels of long-chain acylcarnitines [123]. Liver glycogen is also increased in the absence of PPARα, only in the fed state [16]. In line with the plasma metabolic profile and the changes in hepatic gene expression, elevated amino acid levels are observed in the liver of PPARα$^{-/-}$ mice [123]. However, at this stage, it is impossible to conclude whether the increase in amino acid catabolism in PPARα-deficient mice reflects a compensatory increase due to impaired fatty acid oxidation or a direct suppressive effect of PPARα on genes involved in amino acid catabolism. These mice also display elevated hepatic levels of urea cycle intermediates, such as arginine, aspartate, and citrulline [123].

On the other hand, in the fed state, most plasma parameters—including glucose, non-esterified fatty acids, and ketone bodies—remain unchanged in the absence of PPARα [20].

4.5. Hepatocyte PPARα-dependent sexual dimorphism during fasting

In the context of the liver's role in coordinating several key physiological processes, hepatic sexual dimorphism has evolved to meet the different requirements of females versus males, especially regarding energy metabolism in the context of female reproductive functions [125]. After 24 h of fasting, female mice exhibit higher plasma levels of ketone bodies than male mice [126]. Studies in humans also indicate

that women show greater 3-hydroxybutyrate (3OHB) production in the fasted state [92] associated with higher plasma levels of non-esterified fatty acids [127], which can support elevated ketonemia. Hormones play a critical role in the sex-specific regulation of metabolic pathways [128,129], and sex-biased gene expression is an important determinant of phenotypic variation between females and males. However, we do not yet fully understand this relationship [130].

Interestingly, and perhaps unexpectedly, PPARα has different hepatic effects on females versus males. Many genes expressed in the liver, which encode proteins implicated in metabolic pathways, are differentially expressed in females and males. Specifically, in female mice, PPARα represses the expression of genes involved in steroid metabolism and immunity, independently of fasting. The mechanism through which PPARα exerts this repression depends on female-restricted SUMOylation of its ligand-binding domain. This posttranslational modification enables the formation of a protein complex that eventually results in the transcriptional repression of some genes. One effect of this PPARα-mediated repression is that female mice are protected from estrogen-induced intrahepatic cholestasis of pregnancy [63]. Recent findings indicate that the mRNA and protein levels of ANGPTL4 in hepatic and adipose tissue are higher among male mice than in female mice, which may explain the higher circulating triglyceride and cholesterol levels in males than females [131]. Below, we discuss how PPARα in hepatocytes can shape a sex-specific response to fasting [126]. Previous studies have examined the sex-specificity of hepatocyte PPARα activity in mice fed a standard diet and in aged mice [132]. However, only one study has investigated sex-specific and PPARα-dependent responses to fasting. This study used PPARα$^{hep-/-}$ mice and demonstrated increased hepatic triacylglycerols in male mice, but not in females. Additionally, hepatocyte PPARα determines the broad sex-specific regulation of liver gene expression. Fasting induces higher gene expression changes in PPARα$^{hep-/-}$ females, compared to PPARα$^{hep-/-}$ males, with the differences mainly concerning the inflammation process. In contrast, PPARα$^{hep-/-}$ mice of both sexes exhibit similar fasting-induced hypoglycemia and decreased ketonemia [126]. Additional studies are needed to further explore the hepatocyte PPARα-dependent sexual dimorphism during fasting.

5. PPARα-dependent systemic responses during fasting

During fasting, among other effects, hepatocyte PPARα controls a vital hepatic function: ketogenesis. Ketone bodies replace glucose and serve as essential alternative fuel sources for peripheral organs. Several studies reported that ketone bodies can also act as signaling molecules that modulate cellular homeostasis in multiple physiological states through diverse mechanisms [133], although the literature is often controversial. Hepatocyte PPARα is also required for fasting-induced FGF21 production. As a circulating hormone, FGF21 can target several organs from a distance, thereby influencing whole body energy metabolism. Below, we discuss how PPARα is implicated in these two critical functions.

5.1. Ketone bodies

5.1.1. Hepatic ketogenesis

When non-esterified fatty acids enter hepatocytes, they combine with coenzyme A to form acyl-CoA molecules that are transferred into mitochondria, where they are catabolized into acetyl-CoA by β-oxidation. The produced acetyl-CoA molecules enter the citric acid cycle and are eventually catabolized to CO_2 and water. High-energy electrons enter the electron transport chain during this process, ultimately producing ATP. When high acetyl-CoA levels accumulate in the mitochondria, a portion is converted to acetoacetate and 3OHB, and their spontaneous breakdown product, the least abundant acetone, which are known as ketone bodies. These reactions are catalyzed by acetyl-CoA acetyltransferase 1 (ACAT1), mitochondrial HMGCS2, HMG-CoA lyase (HMGCL), and 3OHB dehydrogenase (BDH1) [134]. The newly produced ketone bodies are released by the liver into the bloodstream, from which they are taken up by tissues that reconvert them into acetyl-CoA through ketolysis, thereby fueling the citric acid cycle of their mitochondria. 3OHB could contribute to regulating hepatic lipid metabolism in a manner involving PPARα:RXR isotype α (RXRα) heterodimers and their target genes pathway [135]. Apart from the liver, no other tissue can divert its oxaloacetate into the gluconeogenic pathway in this manner. Importantly, ketone bodies cross the blood-brain barrier and are thus available as a source of energy for the central nervous system, complementing or replacing glucose. Although they can also pass the blood-brain barrier, fatty acids are not used significantly as fuel in neural cells because of their low fatty acid oxidative capacity. One underlying reason might be neurons' susceptibility to oxidative stress generated by superoxide produced during fatty acid β-oxidation [136]. Interestingly, a recent study reported that mice deficient in hepatic ketogenesis could survive endotoxemia and prolonged fasting, suggesting the existence of extra-hepatic ketogenesis and/or alternative fuels such as acetate [137].

5.1.2. Hepatocyte PPARα-dependent activation of ketogenesis

PPARα activation in hepatocytes during fasting—which stimulates fatty acid oxidation and ketogenesis—relies on several diverse but complementary mechanisms, including the production of ligands for PPARα, increased PPARα expression, and its interaction with co-activators. These mechanisms are summarized in Fig. 5.

Glucocorticoids directly enhance *Ppara* transcription [138]. The functional interactions of GR and PPARα in stimulating fatty acid oxidation and ketogenesis have recently been reviewed [139]. They will not be discussed further here, except for an interesting functional interaction involving GR between liver macrophages and hepatocytes during fasting [140]. The macrophage GR downregulates tumor necrosis factor alpha (TNFα) expression in food restriction. Reduced hepatic TNFα levels promote the nuclear translocation of GR in hepatocytes, which stimulates fatty acid oxidation and ketogenesis pathways, in cooperation with PPARα. This GR-mediated repression of TNFα production in macrophages appears to be a novel mechanism that promotes a metabolic switch during the transition from the fed state to the fasted state [140].

PPARα protein levels are post-transcriptionally modulated by HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1 (HUWE1), an E3 ligase - ubiquitin ligases directly recognize protein substrates for ubiquitylation - that directly binds PPARα and causes its degradation via a proteasome-mediated pathway [141]. It has been recently suggested that during fasting, ubiquitin-mediated PPARα degradation is repressed by PAQR9, which belongs to the progesterone and adipoQ receptor (PAQR) family. PAQR9 competes with HUWE1 to bind with PPARα, attenuating ubiquitin-mediated receptor degradation [142].

Ketogenesis may also be augmented by a paracrine signaling mechanism, through which fasting induces the release of histamine from extra-hepatic mast cells into the hepatic portal vein, triggering the activation of hepatocyte G protein-coupled H1 receptors, thereby triggering oleoylethanolamide (OEA) synthesis. OEA is a high-affinity PPARα agonist and thus may act with lipolysis-derived non-esterified fatty acids to activate PPARα and upregulate the expression of its ketogenesis targets [143]. Another significant pathway associated with ketogenesis and glucose metabolism involves extragonadal steroidogenesis, which occurs during fast–feed metabolism cycles, and depends on steroid-17α-hydroxylase (Cyp17a1). *Cyp17a1* expression in the liver is stimulated by fasting, and Cyp17a1 is involved in the production of steroids, including dehydroepiandrosterone (DHEA), a metabolic intermediate in estrogen and androgen synthesis. DHEA also has other functions, including binding and activating nuclear and cell surface receptors [144]. It is also a ligand for PPARα, through which it stimulates ketogenesis and maintains euglycemia during food deprivation. This

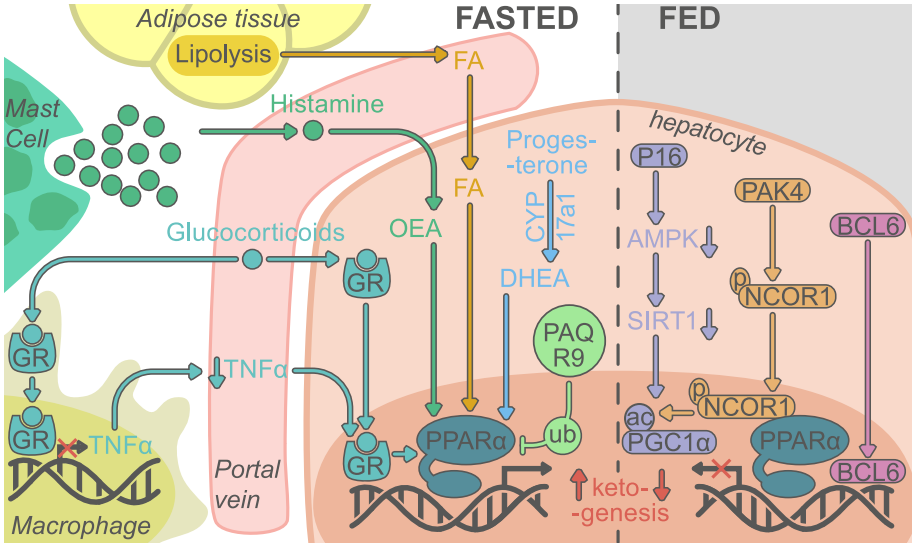

Fig. 5. Hepatocyte PPARα-dependent regulation of ketogenesis in the fed and fasted states. During fasting, ketogenesis is controlled by hepatocyte PPARα through several mechanisms: increased PPARα expression by GR ; PPARα activation by non-esterified fatty acids derived from adipose lipolysis, by OEA produced in response to mastocyte histamine release, by Cyp17a1-dependent production of DHEA ; cooperative GR/PPARα target gene activation due to the suppression of TNF expression induced by the macrophage glucocorticoid receptor (GR) ; decreased ubiquitin-mediated degradation of PPARα through PAQR9 competitive interaction with the E3 ligase HUWE1. In the fed state, ketogenesis is inhibited through PPARα activity repression by BCL6 and p16, and PAK4-dependent activation of PPARα co-repressor NCoR1. Abbreviations: AMPK = AMP kinase, BCL6 = B-cell lymphoma 6 protein, DHEA = dehydroepiandrosterone, FA = fatty acids, GR = glucocorticoid receptor, NCoR1 = nuclear receptor corepressor 1, OEA = oleoylethanolamide , PAK4 = p21-activated kinase 4, PAQR9 = progestin and adipoQ receptor family member 9, PGC1α = peroxisome proliferator-activated receptor gamma coactivator 1 alpha, PPARα = peroxisome proliferator-activated receptor isotype alpha, SIRT1 = sirtuin-1, TNF = tumor necrosis factor, ub = ubiquitination.

fasting-induced Cyp17a1–PPARα activity is terminated by postprandial bile acid signaling during re-feeding, and the restoration of anabolic liver metabolism involves the receptors liver receptor homolog 1 (LRH-1), FXR, and small heterodimer partner (SHP) [145]. Ketogenesis is actively repressed in the fed state by mechanisms depending on p21-activated kinase 4 (PAK4) and the BCL6 repressor that binds to many of the same genes as PPARα [146].

As for its other metabolic gene regulatory functions, PPARα also depends on RXR for its roles in ketogenesis [147]. PPAR:RXR heterodimerization can occur independently of ligand binding and does not require DNA binding [148]. RXR agonists can enhance the expression of PPAR target genes in the absence of a PPAR agonist, which suggests a model of permissive transcriptional activation according to which PPAR:RXR heterodimers can stimulate transcription in response to PPAR or RXR activation. Moreover, concomitant activation of both receptors potentiates the effects observed with each ligand alone. The PPAR:RXR permissivity is still not well understood in terms of potential cooperative ligand binding, conformational changes of the ligand binding domains and cofactor recruitment by each heterodimer partner, and possible rate-limiting steps in the heterodimer activation process (reviewed in [149]).

Compared to conventionally housed mice, germ-free mice exhibit reduced fasting-induced ketogenesis, suggesting that the gut microbiota may influence the hepatic production of ketone bodies during nutrient deprivation [150]. In line with this finding, it was also reported that germ-free mice show impaired expression of many PPARα target genes, such as *Fgf21*, in the liver [151]. Conversely, liver PPARα activity influences gut homeostasis. This involves the synthesis of the liver-derived soluble factor pigment epithelium-derived factor (PEDF) induced by intestinal microbial lipopolysaccharides (LPS). Liver-derived PEDF requires PPARα and restrains intestinal stem cell proliferation [152].

5.2. *FGF21*

FGF21 belongs to the fibroblast growth factor (FGF) family, which comprises 23 FGF proteins that act as paracrine, autocrine, or endocrine factors. Overall, FGF21 is considered a stress-inducible metabolic hormone that coordinates the whole-body metabolic response to counter various stresses and restore homeostasis.

In mice, FGF21 is mostly expressed in the liver and at a lower level in other metabolic tissues, including white adipose tissue, BAT, and muscles [153]. In mice and humans, the secreted FGF21 circulating in the bloodstream predominantly originates from the liver [154,155], and acts in an endocrine or autocrine/paracrine manner, peripherally and centrally. FGF21 secretion occurs in response to diverse nutritional and environmental stimuli or stresses (Table 1). Interestingly, hepatic FGF21 expression is induced in situations of energy deficit, e.g., fasting [112,113] and amino acid deficiency [156–159], as well as in conditions of calorie excess, as created by the ketogenic diet [112,160], glucose intake [161–165], alcohol consumption [166–168], and milk intake by neonates [73,169]. FGF21 expression is also induced during exercise and cold exposure [170,171].

5.2.1. *Signaling pathway of FGF21*

FGF21 signals by binding to a tyrosine kinase FGF receptor (FGFR) [172,173]. Furthermore, FGF21 has acquired an affinity for the transmembrane co-receptor β-klotho, through which it activates FGFRs, mainly FGFR1c [174,175]. Klotho family proteins, α-klotho, β-klotho, and γ-klotho, are obligate coreceptors for endocrine FGFs. FGF21 binds to the β-klotho co-receptor and then to its receptor, thereby driving dimerization and phosphorylation of the receptor. This initiates a signaling cascade, starting with the binding and phosphorylation of the docking protein FGFR substrate 2α (FRS2α), followed by the downstream activation of several signaling pathways, with the best-described being the mitogen-activated protein kinase (MAPK), 5' adenosine monophosphate-activated protein kinase (AMPK), and PI3K-AKT pathways [173,176]. FGF21 signaling also requires heparin, which is necessary for forming and dimerizing FGF21–βKlotho–FGFR1c complexes on the cell surface *via* recruitment by FGFR1c [177].

5.2.2. *Transcriptional regulation of FGF21 by PPARα*

Hepatic FGF21 expression relies on the activation of specific

Table 1
Nutritional and transcriptional regulation of hepatic FGF21 and associated responses.

Nutritional challenge	Low-protein diet AA deficiency	Carbohydrate	Fasting	Ketogenic diet	Alcohol	Milk
Transcription factor	ATF4	ChREBP PPARα	PPARα	PPARα FXR	?	PPARα
DNA response element	AARE	ChoRE PPRE	PPRE	PPRE FXRE	?	PPRE
FGF21-mediated biological effects	↘ Body weight ↗ Food intake ↗ Energy expenditure Browning Lipid metabolism	↘ Sweet preference	↗ β-oxidation? ↗ Ketogenesis?	↗ Water intake ↘ Body weight ↗ Energy expenditure	↗ Water intake ↘ Alcohol preference	↗ BAT thermogenesis
References	[156–159]	[161–165]	[19,67,112,113,178]	[112,160,167]	[166–168]	[73,169]

transcription factors, depending on the inducing stressor (Table 1). Fasting strongly induces PPARα-dependent hepatic FGF21 expression in mice [112,113,178]. PPARα directly regulates FGF21 expression *via* binding to PPRE sites in the *Fgf21* gene promoter in the liver [113]. It can also form a transcriptional complex with cyclic AMP-responsive element-binding protein 3-like 3 (CREBH), which binds to the *Fgf21* promoter to synergistically activate *Fgf21* gene expression [68]. PPARα is also involved in the transcriptional and epigenetic control of FGF21 stimulation in the liver of suckling neonate pups [73]. Finally, PPARα is required for carbohydrate-responsive element-binding protein ChREBP-induced FGF21 secretion in response to carbohydrate intake. Mechanistically, PPARα binds the *Fgf21* promoter in response to glucose, allowing ChREBP to access and bind the *Fgf21* promoter [162].

5.2.3. Role of FGF21 during fasting

It was first proposed that FGF21 is essential for fasting-induced β-oxidation and ketogenesis [113,179]. Indeed, FGF21 administration can partially reverse the ketogenesis defect in *Pparα*$^{-/-}$ mice [113], and livers from fasted *Fgf21*$^{-/-}$ mice exhibit reduced ketogenesis [179]. In contrast, other studies have reported that fasted *Fgf21*$^{-/-}$ mice with whole-body deletion of *Fgf21* do not exhibit impaired plasma levels of ketone bodies [179,180] and that fasted transgenic FGF21-overexpressing mice exhibit ketogenesis similar to fasted WT mice [113], suggesting that FGF21 is more likely to contribute to (rather than necessary for) fasting ketogenesis. Fasted *Fgf21*$^{-/-}$ mice exhibit reduced hepatic expression of gluconeogenic genes, which results in hypoglycemia [154,179], indicating that FGF21 contributes to hepatic gluconeogenesis during fasting. Notably, the underlying mechanism remains unclear since one study suggests that FGF21 acts directly on hepatocytes [180], while another study reports that FGF21 signals to the hypothalamus through the ERK-CREB (extra-cellular signal regulated kinase-CREB) pathway, triggering corticosterone release, thereby inducing increased hepatic gluconeogenesis [181]. A recent study demonstrated that FGF21 promotes hepatic autophagy during fasting by activating the histone demethylase JMJD3, leading to its nuclear localization and interaction with PPARα to activate the transcription of autophagy genes [106]. A contradictory role of FGF21 on white adipose tissue lipolysis during fasting has been reported. Investigations using *Fgf21*$^{-/-}$ mice have suggested that FGF21 activates lipolysis during fasting [179,182], while other studies have indicated that FGF21 either inhibits [183,184] or has no effect [185] on lipolysis in this condition. Further studies are needed to clarify the effects of FGF21 on adipose lipolysis. As part of its role in the adaptive response to starvation, exogenous FGF21 administration in fasted mice promotes torpor—the murine equivalent of hibernation—by decreasing body temperature and locomotor activity to conserve energy [113]. Notably, the core body temperature of fasted *Fgf21*$^{-/-}$ and *Fgf21*$^{hep-/-}$ mice does not differ from that of fasted wild-type mice [183,186]. During fasting, circulating FGF21 and 3OHB act together on the heart to regulate the fasting-induced oxidative stress response by activating the PPARα-AMPK signaling pathway in cardiomyocytes [187].

In healthy humans, circulating FGF21 is only induced by prolonged fasting (7–10 days) and is not required for fasting-induced ketogenesis [188–190]. The delayed increase of serum FGF21 levels correlates with the serum transaminase levels, suggesting that FGF21 contributes to the late adaptive response to fasting [189]. As in mice, humans show increased FGF21 in response to pharmacological activation of PPARα [188,190], as well as in response to a low protein diet [157,158] and fructose consumption [191,192].

Altogether, the physiology of FGF21 is very complex, as this protein exerts several metabolic functions by acting on multiple tissues. Despite extensive research, FGF21 signaling remains incompletely understood, and the results obtained are often inconsistent, likely due to differences in experimental design and animal models. For example, most studies that have examined FGF21 have used transgenic overexpression or recombinant FGF21 administration at supraphysiological doses, which may not reflect natural situations. Additionally, while most FGF21 in circulation during fasting is liver-derived, most studies have used whole-body *Fgf21* knockout mice, which can complicate the interpretation of the results because of the interference of other organs in addition to the liver. Nonetheless, despite its high hepatic expression during fasting (at least in rodents), the physiological role of hepatic FGF21 in different tissues during fasting is still not understood (Fig. 6).

6. Conclusion

This review underscores the central regulatory role of PPARα in hepatic lipid and glucose metabolism. Strikingly, this nuclear receptor protein impacts virtually every pathway of hepatic energy metabolism. The liver is the most critical organ for whole-body physiology, supporting many vital functions—including metabolism, immunity, vitamin storage, digestion, and detoxification. This diversity of functions correlates with the liver's dual blood supply from the portal vein and the hepatic artery, which enables the liver to receive and send biological materials and signals from and to the whole body.

It is in this context that a fundamental question emerges. How can a single transcription factor, PPARα, have such prominent and varying roles as those discussed herein? The observed high plasticity of PPARα is rooted in several of its characteristics. Notably, PPARα has an obligate heterodimeric partner (RXR), and several connections between retinoid metabolism and PPAR responses occur because both heterodimeric partners can be activated by their respective ligands, which are derived from dietary nutrients that yield β-carotene metabolites, retinoids, and non-esterified fatty acids. Thus, these ligand-inducible heterodimers represent functional links between nutrition, lipid and glucose metabolism, and health conditions, such as obesity and associated diseases (diabetes and atherosclerosis) [193]. The diverse effects of PPARα are also based on interactions with various coregulators in the context of stimulating or repressing physiological situations, which lead to the modulation of responses in a gene-selective manner. The PPARα co-repressor network has been well-documented and includes NCoR1, the silencing mediator of retinoic acid and thyroid hormone receptor (SMRT

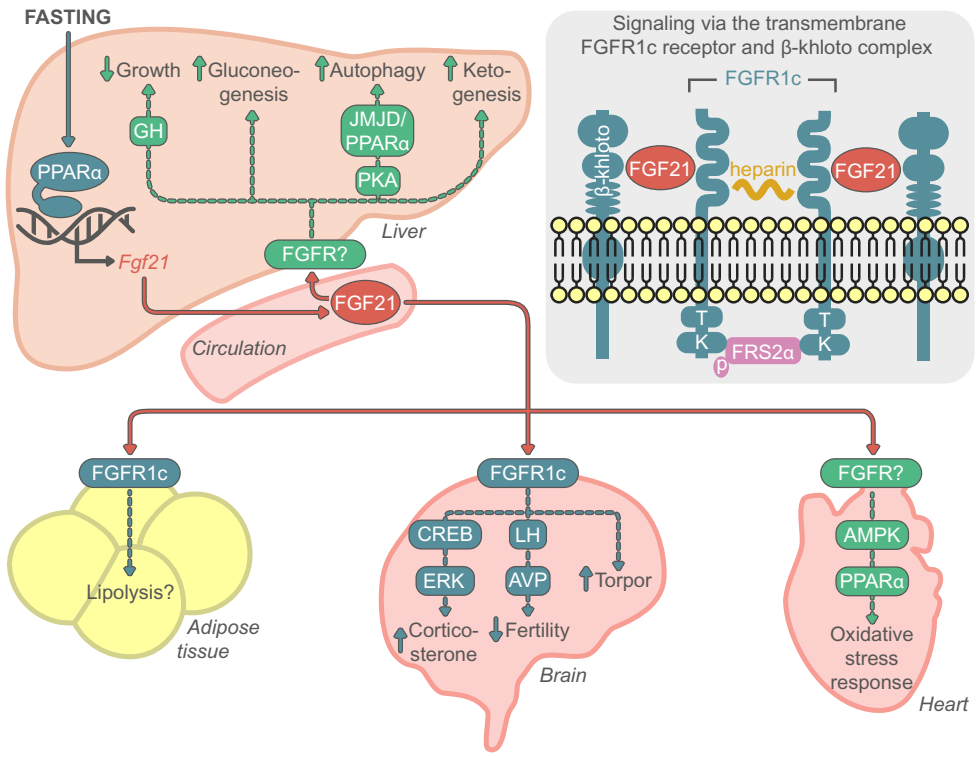

Fig. 6. Tissue-specific effects of hepatocyte-derived FGF21 during fasting. During fasting, FGF21 is predominantly secreted into the circulation from the liver. It acts on peripheral tissues through a cell surface receptor complex comprised of 2 proteins: a tyrosine kinase FGF receptor, mainly FGFR1c, and a co-receptor protein named β-Klotho (KLB). The direct effects of FGF21 on the liver remain debated as FGFR1c is not expressed in hepatocytes, but studies reported that FGF21 contributes to hepatic ketogenesis, gluconeogenesis, autophagy, and growth. KLB and FGR1c are co-expressed in WAT and particular regions of the brain. In WAT, FGF21 may control lipolysis. FGF21 acts on the brain to regulate corticosterone production, fertility, and torpor. In cardiomyocytes, FGF21 together with 3-hydroxybutyrate regulates the fasting-induced oxidative stress response. Abbreviations: AMPK = AMP-activated protein kinase, AVP = arginine vasopressin, CREB = cAMP-responsive element-binding protein, ERK = extra-cellular signal regulated kinase, FGF21 = fibroblast growth factor 21, FGFR1c = FGF receptor 1c, FRS2α = FGFR substrate 2α, GH = growth hormone, JMJD3 = Jumonji D3, KLB = β-Klotho, LH = luteinizing hormone, PKA = protein kinase A, PPARα = peroxisome proliferator-activated receptor isotype alpha, TK = tyrosine kinase, WAT = white adipose tissue.

or NCoR2), the G-protein suppressor 2 (GPS2), the nuclear factor of activated T cells 4 (NFATC4), and the catalytic core of histone deacetylase 3 (HDAC3). However, it remains a challenge to achieve a more comprehensive understanding of the physiological impact of these different co-repressors [194–196]. There is a similar challenge regarding the PPARα co-activators, such as CREB-binding protein (CBP), p300 proteins, p160 proteins coactivators (SRC-1 and TIF2), and others (e.g., PGC1α). Mechanistic investigations have suggested the occurrence of promoter-specific regulation, involving coordinated differential actions of coregulators, which integrate extra- and intra-cellular signaling pathways *via* post-translational modifications [149]. These include phosphorylation, SUMOylation, ubiquitination, acetylation, and O-GlcNAcylation—which can impact the PPAR transactivation function, protein stability, and co-factor interaction—some of which are determined by the state of metabolic diseases [65]. Changes in DNA methylation in the *Ppara* promoter region have also recently been shown to alter *Ppara* expression and activity. It was found that paternal hyperglycemia results in increased methylation of specific CpG sites in the *Ppara* promoter in the liver of offspring, which downregulates PPARα levels and impairs lipid metabolism [197]. These intriguing observations remain to be confirmed in other studies but suggest that PPARα could play a role in the transgenerational inheritance of susceptibility to hepatic steatosis. As mentioned, PPARα ligands include various natural compounds, such as non-esterified fatty acids and eicosanoids [9,10]. Among those, PPARα directly binds to saturated non-esterified fatty acids (relatively weak agonists), unsaturated non-esterified fatty acids, leukotriene B4, 8(S)-hydroxyeicosatetraenoic acids, 8,9-epoxyeicosatrienoic acids, 11,12-epoxyeicosatrienoic acids, OEA, palmitoylethanolamide (PEA), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (16:0/18:1GPC), and bilirubin [8,59]. It remains a significant challenge to precisely characterize the *in vivo* roles of each ligand on its own because, in a given cell, they occur in combinations that depend on several parameters—such as the organ (liver, muscle, etc.), nutritional status (fed or starved condition, and food composition), physical activity level, and health conditions (e.g., chronic inflammation, diabetes, hyperlipidemia, cancer, atherosclerosis, etc.)—and will change according to daily and seasonal rhythms. It can be hypothesized that the development of the broad range of PPARα functions has been driven, at least partly, by the rich diversity of ligands whose binding capacities and receptor gene regulatory powers have co-evolved during the long natural history of living beings exposed to diverse environmental cues, including food availability.

Unsurprisingly, PPARα is a drug target. Fibrates that activate PPARα have successfully treated hypertriglyceridemia and atherogenic dyslipidemia and were already used in clinics before they were identified as PPARα ligands [51,198]. Their effects on MASLD (metabolic dysfunction-associated steatotic liver disease, formerly known as NAFLD, is the most common chronic liver disease) [199], primary biliary cholangitis (PBC), and ocular ischemic diseases have been studied for years. The benefits seem limited for MASLD, and an improved long-term prognosis has been noted among PBC patients [200–202]. Other related treatments, especially with experimental PPARα ligands, have been discussed elsewhere [51]. Several tested compounds have side effects that have limited their clinical use or halted clinical development [203]. Currently, much attention is focused on developing compounds that simultaneously target multiple PPAR isotypes or a

PPAR isotype along with a different receptor type [204,205]. For example, saroglitazar is a dual PPARα/γ agonist that improves liver histopathology and biochemistry in experimental metabolic dysfunction-associated steatohepatitis (MASH) models [206], showing efficacy for treating atherogenic dyslipidemia [207]. It has the potential to both improve liver disease and lower cardiovascular risk in patients with MASLD [208,209]. In a phase 2 study, the pan PPAR-agonist lanifibranor has exhibited safety and efficacy in resolving MASH without worsening fibrosis in MASH patients [210].

Many diverse pathways converge on the activity of PPARα in the liver. Over recent years, much progress has been made to decipher the sophisticated biology of this receptor. However, it remains a challenge to grasp the extraordinary complexities of PPARα in an organ that fulfills key metabolic duties and is continuously connected with all parts of the organism. Elucidating the full potential of PPARα and deciphering the vast possibilities to modulate its actions—for the maintenance of good health, prevention of illness, and improvement of metabolic liver-associated diseases—will require detailed investigations of the signals that affect ligand production at various locations, the transcriptional activity associated with posttranslational modifications, co-factor interactions, and alterations of chromosomal chromatin configuration. The task is enormous, but expanding knowledge will lead to the development of novel methods for targeting PPARα in health and disease, which will provide the means to therapeutically maintain and improve the intricate metabolic functions of the liver and more.

Author contributions

Conceptualization, A.F., W.W., H.G., A.M.; Writing – Original Draft, A.F., W.W., J.B., A.P.; Writing – Review & Editing, A.F., W.W., H.G., A. M., J.B., A.P.

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CRediT authorship contribution statement

Anne Fougerat: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Justine Bruse:** Writing – review & editing, Writing – original draft. **Arnaud Polizzi:** Writing – review & editing, Writing – original draft. **Alexandra Montagner:** Writing – review & editing, Conceptualization. **Hervé Guillou:** Writing – review & editing, Conceptualization. **Walter Wahli:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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