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REVIEW ARTICLE

Fibroblast growth factor 21: An emerging pleiotropic regulator of lipid metabolism and the metabolic network

Shuo Li [1], Tiande Zou [1], Jun Chen, Jiaming Li, Jinming You*

Jiangxi Province Key Laboratory of Animal Nutrition, Jiangxi Agricultural University, Nanchang, Jiangxi 330045, China

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Abstract Fibroblast growth factor 21 (FGF21) was originally identified as an important metabolic regulator which plays a crucial physiological role in regulating a variety of metabolic parameters through the metabolic network. As a novel multifunctional endocrine growth factor, the role of FGF21 in the metabolic network warrants extensive exploration. This insight was obtained from the observation that the FGF21-dependent mechanism that regulates lipid metabolism, glycogen transformation, and biological effectiveness occurs through the coordinated participation of the liver, adipose tissue, central nervous system, and sympathetic nerves. This review focuses on the role of FGF21-uncoupling protein 1 (UCP1) signaling in lipid metabolism and how FGF21 alleviates non-alcoholic fatty liver disease (NAFLD). Additionally, this review reveals the mechanism by which FGF21 governs glucolipid metabolism. Recent research on the role of FGF21 in the metabolic network has mostly focused on the crucial pathway of glucolipid metabolism. FGF21 has been shown to have multiple regulatory roles in the metabolic network. Since an adequate understanding of the concrete regulatory pathways of FGF21 in the metabolic network has not been attained, this review sheds new light on the metabolic mechanisms of FGF21, explores how FGF21 engages different tissues and organs, and lays a theoretical foundation for future in-depth research on FGF21-targeted treatment of metabolic diseases.

* Corresponding author.
E-mail address: youjinm@163.com (J. You).
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[1] These authors contributed equally to this work.

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Introduction to FGF21

The fibroblast growth factor (FGF) family is a large cytokine family that has multiple effects on metabolism and development across a wide range of tissues and organs. In addition to the indispensable role of FGF in cell signaling, altered FGF function may lead to health problems, such as dyslipidemia and non-alcoholic steatohepatitis.[1–3] A total of 22 mammalian FGFs are typically considered paracrine, autocrine, or intracrine factors. They are categorized into seven subfamilies based on differences in sequences and functions; the hFGF (FGF19, FGF21, and FGF23) subfamily is one of these subfamilies.[4] The majority of FGFs are paracrine factors and require binding to the heparan sulfate glycosaminoglycans (HSGAGs), a homologous core region composed of a specific protein primary structure chain.[1,5] In contrast, the hFGF (FGF19, FGF21, and FGF23) subfamily is a typical subfamily in which the affinity for HSGAGs is reduced due to changes in the protein primary sequence.[6] In addition, FGFs mediate their effects by stimulating FGF receptors (FGFRs), which are tyrosine kinase receptors that participate in physiological activities in an HSGAG-dependent manner. FGFs can combine with one of the four FGFRs (*FGFR1—FGFR4*) to carry out their diverse functions.[1,6,7] However, the existence of Klotho is also a prerequisite for FGF subfamily combination with FGFRs, as this occurs in a Klotho-dependent manner.[8] Klotho is a bundle of proteins with a specific structure that contains α-Klotho, β-Klotho, and γ-Klotho.[9] The effects of α-Klotho and β-Klotho are relatively wide, and these proteins exist in the liver, kidney, muscle, and adipose tissues. α-Klotho is a necessary protein for the physiological function of FGF23, while β-Klotho mainly binds to FGF19 and FGF21. Although the functions of γ-Klotho seem to be fewer, these functions are still indispensable.[9] The primary metabolic effects of FGF19 are regulated by the biosynthesis of bile acids in the liver and their transport to the ileum. The FGF23 metabolic pathway responds to bone—kidney—parathyroid axis signaling, which controls the balance of minerals, vitamin D, and parathyroid hormones. The FGF21 metabolic pathway responds to signals from adipose tissue, liver, and mitochondria and regulates the homeostasis of energy intake, energy expenditure, and muscle development.[10] Therefore, the substantial differences in the primary structure of the members of the hFGF endocrine family lead to significant functional differences and diverse effects on cellular metabolism. This review focuses on FGF21 research and elaborates on the physiological functions and pharmacological effects of FGF21 on the metabolic network, particularly in the brain, adipose tissue, and liver. We briefly describe the secretion regulation, mechanisms of action of FGF21, and its biological role. We evaluate the regulatory role of FGF21 in lipid metabolism and the target genes and proteins of related metabolic pathways. Finally, the roles of FGF21 in alleviating lipid metabolism disorders and associated diseases are summarized. The present review focuses on the connotation of FGF21 in the administration of lipid metabolism, shines new light on the metabolic mechanisms of FGF21, and lays a theoretical foundation for future in-depth research on FGF21-targeted treatments for metabolic diseases.

Mechanisms of regulating FGF21 production

In 2000, FGF21 was first detected in the liver and thymus of mice.[11] Subsequently, the metabolic effects of polymorphisms of FGF21 were certified in a myriad of studies on glucose metabolism, adipose metabolism, energy balance, and muscle development.[12–17] Although FGF21 has been found in a variety of tissues outside the liver, including muscle, adipose, and pancreas, circulating FGF21 is mainly derived from hepatogenic FGF21.[18] This may be due to the complicated production procedure of FGF21 and the induction of multiple factors, mainly including external interference and internal disorder, such as hormone secretion, physiological state, genetic factors, exogenous drug, organelle stress, and nutrient levels.[19–22] Studies have shown that the transcription factor PPARα mediates hepatogenic FGF21 secretion during fasting or high-fat diets, improving the body's adaptation to nutrient levels.[22–24] In addition, PPARα acts as an intermediate between FGF21 and its upstream regulatory unit (*e.g.*, small ubiquitin-related modifier (SUMO)-specific protease 2 (SENP2), carnitine palmitoyltransferase-1A (CPT-1α)) to regulate lipid metabolism.[25,26] However, other nutrition-sensitive transcription factors also stimulate FGF21 expression. The transcription factor carbohydrate-responsive element-binding protein (ChREBP) mediates hepatogenic FGF21 expression and alters sugar preference in high-glucose-induced mice.[27] Subsequently, researchers found that the *Fgf21* mRNA was significantly up-regulated under conditions of protein malnutrition, and this up-regulation helped to improve the obesity and liver lipid metabolism disorders caused by protein malnutrition.[28–30] Amino acid restriction means that the intake of certain essential amino acids is insufficient to sustain the body's needs. Therefore, in this situation, the body may up-regulate the expression of the kinase general control nonderepressible 2 (GCN2), nuclear protein 1 (NUPR1) to activate FGF21 production in the liver.[31–33] Mechanistically, the activation of CNS (central nervous system) macro-control by the FGF21 signal transmission from the periphery to the brain regulates dietary preference and nutrient intake and meets the rigid demand for protein.[34] Interestingly, the combination of low protein and high carbohydrate nutrition may be the strongest driver of FGF21 secretion, and PPARα likely plays a major role in this process.[23,35] Another observation indicated that the excessive intake of dietary carbohydrates and a high-energy and high-fat diet will also strongly stimulate the up-regulation of FGF21 expression through src homology 3 domain binding kinase 1 (SBK1)-orphan nuclear receptor 4A1 (Nur77) pathway.[36–40] Besides, endocrine factor FGF21 is always produced in large quantities in response to multi-stress responses such as endoplasmic reticulum stress and obstruction of the respiratory chain.[41,42] In addition to changing the physiological state of the body, the secretion of FGF21 is significantly elevated through exogenous stimulation, such as the injection of leptin and physical exercise.[43,44] Although transcriptional regulation is critical for FGF21 expression, secretion and transport of FGF21 are also critical for regulating circulating FGF21 content. Studies have shown that YIPF6, a key gene that determines FGF21 synthesis, can bind specifically

to FGF21 in the endoplasmic reticulum to block FGF21 transport, which is one of the regulatory pathways of FGF21 synthesis beyond the transcriptional level.[45] In addition, studies have shown that FGF21 is also vulnerable to related protease cleavage and modification (fibroblast activation protein, dipeptidyl peptidase 4) during synthesis, resulting in the damage of FGF21 function[18,46] (Fig. 1).

The mechanism of action and biological role of FGF21

Similar to other proteins, in the structure of FGF21, a core region is formed through the folding of its primary structure, and the high-level structure has a C-terminal and an N-terminal.[47] Further studies have revealed that the molecular mechanisms of FGF21 are attributable to the binding of β-Klotho with various FGFR family members.[48] β-Klotho binds to the C-terminus of FGF21, and FGFR binds to the N-terminus of FGF21, forming a trimeric compound.[5,47,48] The performance of FGF21 relies on the membrane protein β-Klotho, which physically binds to FGF receptors at specific sites, and thus endows them with a powerful means to trigger downstream signaling pathways.[47,49,50] The observations suggest that the ablation of β-Klotho may weaken the effects of FGF21, and β-Klotho can improve insulin signaling independently by reducing lysosomal degradation and activating glycolytic pathways.[51] In addition, FGF21/β-Klotho signaling also stimulates glutamatergic neurons and leptin signals to regulate the energy homeostasis.[52] Although β-Klotho is a prerequisite for the function of FGF21, extracellular regulated protein kinase (ERK) phosphorylation may be the key point in the metabolic cascade triggered by FGF21/β-Klotho signaling.[53] Moreover, substantial evidence from FGF21-based experiments demonstrated that its functions are multifaceted, and these observations further support the pharmacological effects and physiological functions of FGF21 in the metabolic network.

In terms of pharmacological effects, FGF21 is a strong candidate with a variety of metabolic benefits in high-fat-diet-induced animal models and has been shown to improve lipid metabolism and whole-animal performance, decrease blood lipids and insulin resistance, and improve metabolic syndrome.[21,54–57] More importantly, FGF21 administration not only alleviates the metabolic disorder induced by glycolipids but also protects against cardiovascular disease.[54,57] Pharmacological treatment with FGF21 significantly promotes triglyceride-rich lipoprotein turnover, reduces the occurrence of atherosclerosis, and improves the cardiovascular system.[21] The beneficial effects of FGF21 have been confirmed in patients with coronary artery disease.[57] In addition, metabolism changes dramatically in animals with severe bacterial infections, and the deletion of FGF21 exacerbates the development of critical conditions and increases mortality in animals with severe bacterial infections.[58] A significant increase in hepatogenic FGF21 production maintained normal metabolism and increased survival expectancy in wild-type mice with severe bacterial infections.[58] Moreover, FGF21/β-Klotho

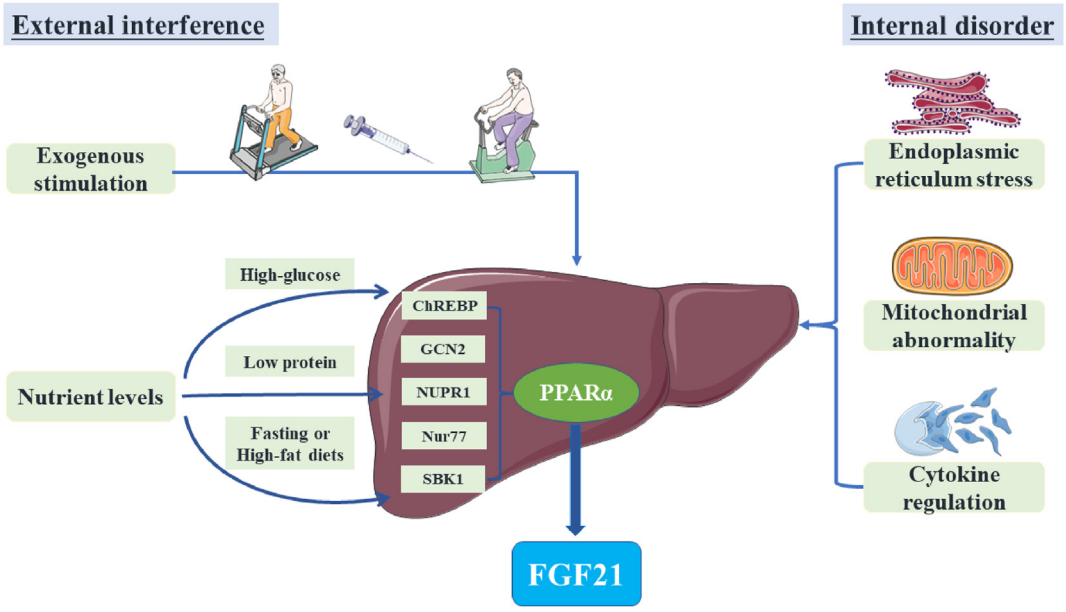

Figure 1 The upstream regulator of FGF21 and its regulation mechanism. In rodents, FGF21 secretion is susceptible to external interferences and intracellular disturbances, including nutrient levels changed and exogenous stimulation (such as leptin injection and physical exercise). The nutrient level is the main factor affecting the secretion of hepatogenic FGF21, such as low protein, fasting, high-carbohydrate, and high-fat intake. FGF21 secretion is regulated through the interaction between a series of transcription factors and PPARα to adapt to different nutrient levels. The intracellular disorders are mainly caused by organelle stress such as endoplasmic reticulum stress or mitochondrial dysfunction, meanwhile, various cytokines also affect FGF21 synthesis and transport.

signaling showed an efficient protective effect against diabetic cardiomyopathy induced by lipid and streptococcal in mice.[59] Likewise, FGF21 seems to be a pharmacologic conditioner of insulin sensitivity, as insulin signaling is improved with FGF21 treatment.[55,56,60] Strikingly, FGF21 treatment improves insulin resistance and attenuates the expression of the mammalian target of rapamycin complex 1 (mTORC1) in the same time range, which may signify cross-action between FGF21 and mTORC1 to ameliorate glucometabolic signaling.[60] Furthermore, this finding demonstrates that FGF21 is an inhibitor of mTORC1 because the expression of the latter is enhanced in FGF21-deficient mice.[60] It seems rational that the nature of FGF21-mTORC1 interplay and its effects on other potential cytokines, such as adiponectin and leptin, to influence metabolism should be further identified.[61] In high-glycolipid-induced animal models, the administration of FGF21 regulates islet autophagy by repressing AMP-activated protein kinase (AMPK)-mTOR signaling, which provides further support for FGF21 as a pharmacotherapeutic target for insulin signaling.[55] Other studies have shown that FGF21 and mTORC1 interplay affects tumors and cancers, further supporting the pharmacological role of FGF21.[62] FGF21 treatment can lead to significant metabolic effects in most tissues, including liver, muscle, and adipose tissue.[63] However, whether the results of these effects are directly caused by FGF21-dependent activity remains controversial. Therefore, great efforts have been made to determine specific signaling pathways and targets in each tissue to verify the above results and explore the in-depth mechanisms.

Although the pharmacological metabolism of FGF21 is already clear, the physiological metabolic mechanism of FGF21 is currently less clear. Moreover, taking into account the complexity of FGF21 generation, the differences in research, research purposes, research protocols, and animal models will obviously affect the results of studies on the physiological functions of FGF21.[64] For example, FGF21 from different sources has completely different regulatory effects. Central FGF21 can regulate the central nervous system and improve spatial memory ability but does not affect peripheral metabolism. On the contrary, hepatogenic FGF21 can regulate global metabolism.[65] A recent interesting study demonstrated that a low-protein diet-induced FGF21-mediated life span extension in wild-type mice promoted weight loss, reduced fat accumulation, and improved the overall physiological metabolism of mice.[66] Here, one point of confusion is worth considering: as a polypeptide hormone, obesity should theoretically disappear after an increase in FGF21 expression based on its strong control of glycolipid metabolism; however, opposite results have been shown in many types of research.[38] For instance, some studies have shown that obesity can easily lead to FGF21 resistance and that FGF21-driven weight loss seems to be superfluous. Therefore, debates still exist on the relationship between FGF21 and obesity.[38,39,67] Whether the difference between physiological effects and pharmacological effects is caused by FGF21 secretion and its different mechanisms of action is worth further investigation. In the following chapters, we will introduce the main metabolic mechanisms of FGF21 in adipose tissue and the liver.

The mediating role of FGF21 in lipid metabolism in adipose tissue

There has been increasing attention on the role of FGF21 in metabolic disorders in tissues such as white adipose tissue (WAT) and brown adipose tissue (BAT). To reveal the unknown mechanisms of FGF21 and exploit therapeutic methods based on FGF21 signaling to treat other possible diseases, several studies have been made in determining the function and pharmacological effects of FGF21 on obesity and fatty liver pathology. These breakthroughs of studies involve the regulation of the browning of WAT and lipid accumulation reduction, which have been deemed innovative rehabilitative strategies for obesity-related diseases.[68–70] Thus, this chapter mainly describes new findings on the functions of FGF21 in lipid metabolism and how FGF21 mediates lipid metabolism.

Adipose tissue is one of the primary action targets of FGF21

While the production of FGF21 mainly occurs in the liver, adipose tissue is also likely to be a repository of FGF21 and is an important target organ for FGF21 action.[50,71–73] Depending on the difference in functions and morphologies of adipose tissue, they can be briefly divided into two broad categories, *i.e.*, BAT and WAT.[50,74] Related data indicate that stimulation by norepinephrine and c-AMP mediates the activation of PKA and p38 MAPK, accompanied by BAT transcription to induce FGF21, especially at prolonged low temperatures.[75] Adipose tissue is the primary location in which FGF21 promotes lipid metabolism and energy homeostasis. From a nutritional point of view, several studies have demonstrated that the expression of lipogenic genes is restrained through certain amino acid deficiency-induced FGF21 generation, and the latter is also a potent catalyzer of the phosphorylation of certain lipases to promote fatty acid oxidation along with dramatic energy expenditure.[76,77] Moreover, physical exercise seems to be a regulator of β-klotho through the activation of transcription-related factors, since β-klotho was increased in the adipose tissue of mice and the effect of FGF21 on the amelioration of glucolipid metabolism disorder was enhanced.[78] According to new research, high-intensity exercise can promote the browning of WAT by up-regulating mitochondrial content as well as UCP1 and FGF21 production.[79,80] Recent research revealed another application of FGF21, namely, leptin is a hormonal factor secreted by adipose tissue to counteract epididymal WAT accumulation. Leptin functions in the CNS of Wistar rats and significantly induces the endogenous expression of FGF21, and the latter activates the browning of epididymal WAT via the PPARβ/δ signaling pathway.[81,82] Consistently, vascular endothelial growth factor has been reported to improve lipid metabolism in WAT; additionally, intermittent fasting is a dietary method of regulating vascular endothelial growth factor production in WAT through FGF21 induction, since the expression of the former is dulled when FGF21 signaling is blocked.[83]

Studies have shown that FGF21 derived from adipose stem cells shows great potential in the treatment of liver

lesions. The researchers transplanted FGF21-secreting adipose stem cells into mice with liver fibrosis. Interestingly, adipose stem cell-derived FGF21 could inhibit the expression of inflammatory factors (*e.g.*, p-JNK and p-Smad2/3), and reduce the production of fibrotic factors (*e.g.*, tissue inhibitor of metalloproteinase-1). Further research found that adipose-derived FGF21 may alleviate liver fibrosis by increasing the production of α-lactalbumin and lactoferrin.[84] Adipose tissue is a crucial platform for FGF21 to function *in vivo*. We induced the overexpression of FGF21 in adipose tissue with an adenovirus-associated vector, and the overexpression of FGF21 could significantly improve liver metabolic indicators, insulin signaling pathways, and inflammation in adipose tissue itself.[85] Although viral-mediated *in vivo* gene delivery can produce significant effects and is widely used, nonviral-mediated FGF21 expression plasmids can also be used for adipose cell transfection into the liver, providing new ideas and a basis for basic research even if the transfection time is increased.[86] Subsequently, another interesting study proved that the transduction of the exogenous FGF21 gene into high-fat-induced obesity mice by genetic engineering technology could effectively prevent fat accumulation, inhibit the formation of fatty liver, and greatly ameliorate insulin resistance.[87] Many studies have also proven that exogenous FGF21 has an excellent effect on lipid metabolism, the homeostasis of insulin, and energy balance.[88–90]

The inner link between FGF21 and the browning of WAT

Schlessinger et al studied humans, monkeys, and mice and compared "browning" signals in WAT and BAT induced by FGF21 through transcriptome analysis, and the results suggested that FGF21-induced "browning" signals exist in adipose tissue.[91] We elaborate on the activation of browning and explore whether FGF21 drives the recruitment of thermogenesis factors to mediate browning in the following chapter. Some researchers have mainly focused on investigating the functions of FGF21 in promoting adipose tissue browning, weight loss, energy consumption, *etc*.[92] One study confirmed that FGF21 contributed to increasing BAT production and improving thermal efficiency through the up-regulation of the thermogenic gene UCP1, which was accompanied by weight loss.[68] Similar studies have also shown that FGF21-driven BAT activation and browning of WAT could accelerate the turnover of triglyceride-rich lipoproteins and reduce the occurrence of metabolic diseases.[21,93] Interestingly, UCP1 did not seem to be necessary, as the effects of weight loss and improvements in glucose metabolism still existed in the absence of UCP1.[94] Further study is needed to determine whether UCP1 is necessary for adipose heating and browning. Thus, there seems to be a "black box" regarding FGF21 and adipose browning, including many uncertainties regarding elements and methods such as UCP1, peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), peroxisome proliferator-activated receptor-α/γ (PPARα/γ), adiponectin, leptin, *etc*.[61,95] At present, browning research mainly focuses on the causal relationship between FGF21 and UCP1-dependent, and non-UCP1-dependent metabolism.

The FGF21-UCP1-dependent metabolism of WAT

Evidence regarding the FGF21-UCP1-dependent metabolism of WAT can be gained from the work of Hondares et al, who demonstrated that in newborn and adult adipose tissues, FGF21 and UCP1 were likely to jointly perform the function of mediating metabolic thermogenesis.[96] In a UCP1-dependent manner, FGF21 regulates UCP1 by directly influencing the expression of UCP1 or indirectly acting on its upstream signaling pathway. UCP1-dependent mechanisms are the main way to improve obesity, glucose homeostasis, and the activity of BAT.[97,98] Challa et al found that the existence of UCP1 is a prerequisite for FGF21-mediated energy expenditure and glucose balance, while these effects disappeared during weight loss.[99] Endogenous FGF21 stimulates the generation of UCP1 in adipose through autocrine or paracrine pathways, which are regulated by PGC-1α (note that PGC-1α is a protein rather than a gene).[100] Relevant research evidence has also been obtained from the energy metabolism signaling pathway. As a metabolic regulator, FGF21 can not only activate the AMPK protein, which is an intracellular energy sensor that can regulate energy balance but also trigger the sirtuin 1 (Sirt1) signaling pathway and accelerate the deacetylation of PGC-1α to enhance mitochondrial activity and oxidation capacity, ultimately acting on UCP1 to promote the browning process.[101–103] Another finding demonstrated that low-protein-induced activation of the FGF21-UCP1 pathway mediated energy metabolism by regulating adipose tissue breakdown and production and improving metabolic efficiency in mice.[104] Similar studies have also reinforced the association between FGF21 and lipid metabolism, mainly through UCP1 mediating the browning of WAT, promoting fat consumption and weight loss.[105,106] Although UCP1-dependent thermogenesis was important for the other roles of FGF21, these observations indicated that several targets of FGF21 were unrelated to UCP1, and further exploration of whether UCP1 itself can be considered dispensable is still needed in the future since the relationship between FGF21 and UCP1 may also depend on the energy status of cells.[107]

The FGF21-UCP1-independent metabolism of WAT

In the previous section, FGF21 was shown to induce heat production in a UCP1-dependent manner. However, as the mechanisms of FGF21 have been continuously explored, research results on FGF21 are constantly being updated. An interesting study found that certain mediators (*e.g.*, UCP1) also seem to be non-essentials in FGF21-induced heat production, and organism temperature is increased independently.[108] However, the results show that FGF21 was dedicated to increasing the expression of UCP1 in BAT along with increasing energy expenditure and maintaining the organism temperature in wild-type mice. Surprisingly, FGF21 has weakened effects on energy expenditure and indirectly maintains organism temperature by reducing calorie loss in UCP1 knockout mice. These findings suggest an effect of FGF21 on organism temperature increase

without the consumption of any energy. However, the results were unique and the organism temperature was elevated in an energy-loss-independent manner; importantly, they also showed a limited effect of UCP1.[108] Similar results were also confirmed in UCP1-knockout mice, in which the effect of FGF21 on the metabolic efficiency of mice seems to be counteracted. In contrast, this process may be regulated through the CNS since FGF21 reduces body weight by inhibiting food intake in UCP1-knockout mice.[109] In addition, typical FGF21-related serum metabolites, such as circulating cholesterol or free fatty acid content, are improved independently of UCP1 thermogenesis according to the circulating levels observed in UCP1-knockout mice.[109] Keipert et al described endogenous FGF21 as the main conditioner to increase lipid oxidative metabolism when UCP1 fails, and it has a certain preventive effect on diet-induced obesity.[110] Interestingly, this research has also been validated, as treatment with FGF21 significantly reduced pig food intake and body weight and improved insulin sensitivity when UCP1 was deficient in miniature pigs.[111] Dissenting opinions observed that the browning reaction of WAT was not necessary for FGF21 to function in UCP1-knockout mice since browning was associated with other factors. Instead, it stimulates the expression of PGC-1α in WAT, ultimately reducing body weight and improving glucose homeostasis.[112] There is another question that needs to be considered (*i.e.*, when UCP1 is missing, from which tissues is endogenous FGF21 mainly secreted), as this is crucial for how to increase the production of FGF21. Keiper's research provided the answer, as *in vivo* and *in vitro* experiments showed that BAT is the source of FGF21 when the UCP1 gene is ablated, especially in low-temperature environments, rather than traditional liver and muscle.[113]

The metabolism of WAT driven by FGF21 in other access

According to a previous review, UCP1 is the main target of FGF21-mediated lipid metabolism and can mediate the connection between FGF21 and lipid metabolism. However, how FGF21 performs its metabolic regulatory functions when the function of the UCP1 gene is lost is a question that needs to be considered. To explore the effect of FGF21 on lipid metabolism and energy balance, we identified a suitable hypothesis to grasp the deeper mechanism of FGF21 from various dimensions. For non-adipose tissues, FGF21 may require factor "X" to act on the brain to be able to regulate energy metabolism and weight loss; however, the detailed process seems impossible to explore at present.[114,115] FGFR1/β-klotho is the primary mediator of FGF21 functions in obesity. The targeted therapy or activation of FGFR1/β-Klotho acts on tissues outside of adipose tissue in a non-UCP1-dependent manner through the regulation of the nervous system, such as transformed dietary preferences, reduced energy intake, and the improvement of cardiometabolic parameters, since the FGFR1/β-klotho compound simulates the role of FGF21 *in vivo*.[116,117] In addition, β-klotho is an indispensable prerequisite for the regulation of weight loss by FGF21-glucagon-receptor.[118] As a brown adipose-derived endocrine regulator, FGF21 requires the assistance of the FGFR1/β-Klotho compound through the CNS to function. Research by Lan et al demonstrated that the FGFR1/β-Klotho compound was necessary for FGF21 mimicking antibody activation as well as the conversion of BAT into heat production along with weight loss under the direct control of the CNS.[119] More interestingly, FGF21 mimicking antibodies also required the participation of neurons to respond to metabolic disturbance *in vivo*. The trials highlight the significance of the nervous system in the regulation of the physiological effects of endogenous FGF21.[119]

Mottillo et al investigated the role of AMPK, an important energy sensor mentioned in the previous chapter, and its downstream target acetyl CoA carboxylase (ACC) in exogenous FGF21-mediated lipid metabolism in obese mice. A different observation was made that AMPK and its downstream target ACC were not the vehicles by which FGF21 exerted its effects in BAT or WAT.[120] They postulated that these effects were UCP1-independent and occurred via lipid transformation and creatine metabolism.[120] Relevant studies have revealed that under the collaborative effect of PPARα and PPARγ, in response to the rapid transformation of WAT into BAT, the internal mechanism was mainly that PPARα induces the production of liver-derived FGF21, and the latter combines with PPARγ to promote the transformation of adipose tissue.[24,95] In addition, PPARγ participates in FGF21-induced adiponectin production and plays an important role in the lipid-lowering effects of the FGF21-adiponectin axis as well as inhibiting endoplasmic reticulum stress.[121,122] The induction of FGF21 secretion can improve the morphological characteristics of adipocytes via the p-LKB1-AMPK-ACC axis in mice with abnormal glycolipid metabolism.[123] However, when the FGF21 gene is knocked out or cannot be expressed correctly, the hypothalamus of mice will be inflamed and damaged, and neurons cannot conduct signals normally under the conditions of high-fat diet induction, resulting in significantly lowered levels of thermogenic genes in BAT (*e.g.*, UCP1), which also proves that the nervous system plays the primary role in the pleiotropic pathway of FGF21.[114,124] In addition, the nervous system may mediate the activation of the exogenous FGF21 pathway. The injection of FGF21 into the rat brain regulates energy homeostasis and the expression of related thermogenic genes in adipose tissue through the hypothalamic—pituitary—thyroid axis.[90]

The limitations of FGF21 for lipid metabolism in adipose tissues

Although adipose tissue is one of the sites of FGF21 administration, and there is a growing appreciation of the prospect of the beneficial effects of FGF21 on obesity, there is continued uncertainty about the existence of FGF21 resistance, especially in a high-fat, low-carbohydrate ketogenic diet.[125] Moreover, a ketogenic diet not only impairs FGF21 signaling by increasing lipid deposition in the liver but also reduces the expression of FGFR4 and β-klotho.[126] Likewise, FGF21 seems to be a metabolic conditioner in a ketogenic diet, and its expression is obviously improved.[127] Additionally, obesity aggravates the secretion of inflammatory factors such as TNF-α, which controls the

generation of β-klotho to impair FGF21 reactivity in adipocytes.[128] Therefore, FGF21 still cannot function because of blocked signaling, even if its expression is elevated, which also explains the FGF21-resistance state mentioned in a previous article.[126] Interestingly, some researchers have found that impaired FGF21 signaling in WAT is not attained by inhibiting the expression of β-klotho; in other words, the down-regulation of β-klotho expression may be the reason for FGF21 resistance.[129] This may indicate that other mechanisms synchronously emerge in FGF21 resistance and the implied mechanism needs further study. While WAT is one of the basic endocrine sites for FGF21, the secretory effect of the latter is vulnerable to external factors.[130] Some studies have indicated that diet-induced lipodystrophy and physiological conditions contribute to impaired FGF21 sensitivity.[130] Thus, the possibility of an untoward action of FGF21 resistance should be considered adequately to ensure optimal metabolic functions and decreased side effects.

In the previous article, the vast quantities of information about how FGF21 promotes thermogenesis have been expounded. However, unlike previous studies, researchers found that when mitochondria are damaged, FGF21 can still promote biological thermogenesis and the ability to resist high energy intake caused-obesity, further increasing oxygen consumption.[131] In one of the more extreme but interesting studies, FGF21 and even UCP1 were not necessary for thermogenesis during chronic cold induction. Although the ablation of the UCP1 gene in BAT caused mitochondrial inflammation and functional loss, WAT in UCP1 and FGF21 double-gene knockout mice were reprogrammed into beige adipose tissue, which adjusted the overall thermogenic response and metabolic homeostasis.[132] In summary, FGF21 serves to quench body weight and regulate other key lipid metabolic indicators. Under normal physiological conditions, FGF21 relies on UCP1 to function; under abnormal conditions, such as UCP1 gene loss, FGF21 may regulate metabolic homeostasis through other pathways (Fig. 2).

FGF21-mediated metabolism in the liver

As one of the main metabolic organs, the liver is also the source and target of FGF21. Furthermore, FGF21 and the co-receptor β-klotho play a vital role in lipid transformation, insulin signaling, and the maintenance of liver stability, such as reducing the occurrence of severe liver lesions (*e.g.*, NAFLD).[133] A study found that β-klotho is a compulsory requirement for FGF21 and FGF15 functions in the liver and brain, and the loss of β-klotho resulted in perpetual impaired growth and the inhibition of glucose metabolism in mice.[134] The circulating level of FGF21 does not fluctuate dramatically in the normal physiological state of the liver. Instead, when the mouse liver is damaged to varying degrees, liver-derived FGF21 will be abundantly

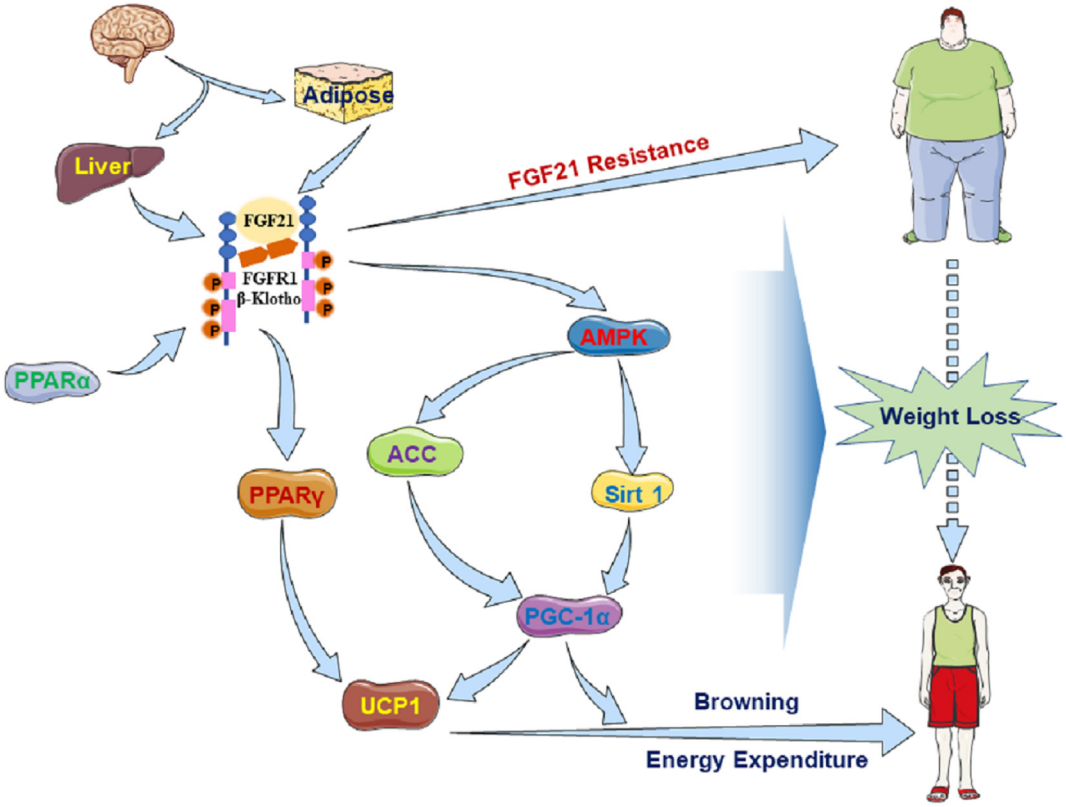

Figure 2 The regulation of lipid metabolism through FGF21. Under the control of the CNS, FGF21 can be secreted by adipose tissue and the liver, and liver-derived FGF21 can better promote energy consumption and the browning of WAT through multiple signaling pathways, mainly including the FGF21-PPARγ-UCP1, FGF21-AMPK-Sirt1-PGC-1α, and FGF21-AMPK-ACC-PGC-1α signaling pathways, finally achieving the effect of reducing body weight and relieving FGF21 resistance in adipose tissue.

secreted as a stress factor under the regulation of internal and external factors such as chemical factors, physical factors, genetic factors, and body state.[135,136] For example, during hepatic carcinogenesis induced by diethylnitrosamine and genetic factors, FGF21 transcription is significantly promoted, which is regulated by a variety of transcription factors, including p53, c-jun, and STAT3. These transcription factors can respond differently to different stress responses.[137,138] FGF21, as a "beneficial hormone" for mammals, is abundantly secreted after liver damage. The main reason is to relieve external damage and reduce the pressure and burden on the liver, such as the formation of fatty liver.[2,139] In a classic example, the metabolic indexes of whole-WAT-knockout mice were detected and the overexpression of FGF21 in the liver and GLUT-1 and FGFRC1 in muscle was observed.[140] Although FGF21 overexpression could not completely offset the negative effects of WAT knockout, it did contribute to metabolic stability in mice.[140] Recent research has found that FGF21 can be defined as the intersection of various signaling pathways, including the liver insulin signaling pathway and lipid metabolism signaling pathway; therefore, this chapter elaborates on FGF21-mediated glucolipid metabolism in the liver.[141]

FGF21 mediates steady-state glycogen signaling in the liver

Glycogen homeostasis is a critical segment of the maintenance of metabolic homeostasis, and hepatic glycogen is more predominant in maintaining glucose homeostasis than muscle glycogen; as a consequence, hepatic insulin signaling is a critical factor for regulating insulin homeostasis. Studies have shown that FGF21 is one of the proteins that regulate blood glucose stability in the liver because the inhibition of FGF21 leads to a certain degree of insulin resistance.[133] FGF21 mediates hepatic glycogen synthesis through nervous system regulation and maintains fasting glycogen homeostasis through the activation of ERK signaling and the secretion of corticosterone.[142] FGF21 accelerates glycogen absorption to improve insulin resistance in the presence of prolonged fasting, which can also occur in overnutrition.[143] Camporez et al investigated the differences in glucose metabolism parameters between FGF21-knockout and wild-type mice and found that FGF21 loss led to insulin resistance as well as continuous glucagon production, heightened glucose generation in the liver, and ultimately impaired insulin signaling. Furthermore, FGF21 loss was accompanied by abnormal lipid metabolism, oxidative stress, and inflammatory reactions.[125] An important observation was demonstrated that the liver forkhead box o1 (FOXO1)-Akt axis maintains insulin signaling stability through induced adipose degradation by regulating the generation of catecholamines. Notably, FOXO1 signaling upregulates the expression of Akt in the liver to mediate the induction of FGF21 as an available route to regulate insulin resistance.[144] Correspondingly, both modalities can modulate blood glucose signaling and maintain energy balance regardless of the FGF21-dependent mechanism.[144,145] For example, increased leptin content in the plasma of male mice and decreased cholesterol and insulin levels stimulated the expression of GLUT4 and insulin receptors and improved insulin sensitivity in the liver. The reason for this phenomenon is likely that FGF21 affects the activity of sympathetic nerves in the CNS to increase heat production. In turn, adrenalin stimulation by sympathetic nerves also stimulates the expression of FGF21, similar to the above, which constitutes a positive feedforward loop.[146–148] The maintenance of glycogen homeostasis not only relies on endogenous hormones acting on internal substance consumption but also requires endogenous hormones to regulate external nutrient intake. The strategies to mediate glucose homeostasis in an insulin-independent manner, such as diminishing hepatic gluconeogenesis or altering dietary preference, through FGF21 are emerging.[149,150] Studies have found that carbohydrate and sugar intake are important exogenous factors affecting glycogen homeostasis, and FGF21 can significantly inhibit the appetite for monosaccharides and severely diminish the pressure of internal metabolic consumption under the macro-control of the hypothalamus. Moreover, carbohydrates mediate the endocrine control of liver-derived FGF21 production through the nervous system; conversely, a negative feedback loop is formed as FGF21 actively inhibits carbohydrate foraging preferences[149]. Similarly, Katsumura et al confirmed that the hepatocyte-factor CCR4-NOT transcription complex subunit 6 like (CNOT6L), growth differentiation factor 15 (GDF15), and FGF21 are likely the secretagogue proteins provoking the nervous system and liver to reduce dietary intake and increase energy consumption.[151] Among these proteins, CNOT6L is the most critical factor determining the expression of GDF15 and FGF21.[151]

FGF21 mediates lipid metabolism in the liver

FGF21 diminishes lipid accumulation through diverse approaches in the liver

The liver is the critical point to maintaining the dynamic balance between lipid synthesis and lipid consumption through adipokines and metabolic regulatory factors, such as FGF21, PPARα, p38, adiponectin, and fatty acid desaturase 1, or the re-establishment of the gut microbiota.[24,133,141,152,153] In the case of p38, FGF21 is inhibited by the degradation of β-klotho through activated p38 in the liver, resulting in poor lipid metabolism and NAFLD.[133] Besides, fatty acid desaturase 1 mediates lipid metabolism in hepatic cells through PPARα-FGF21 crosstalk in long-chain fatty acid synthesis and NAFLD.[152] FGF21 production is also determined by upstream Sirt1 signaling in liver lipid metabolism. This biological interface between the Sirt1 and FGF21 signaling systems is a requirement for FGF21 to mediate the fatty acid oxidation effect in a physiological setting. Furthermore, consistent with these observations, the activated Sirt1 signaling promoted energy consumption and lipid degeneration and alleviated hepatic fibrosis.[154] However, Sirt1 signaling regulation is mediated by AMPK, which is an important energy sensor in cells and is dominated by FGF21. The modulation of parameters related to liver and adipose metabolism through FGF21-dependent AMPK-Sirt1 signaling in alcohol-induced mice further alleviates liver morphology and fatty acid anabolism.[155] This is accompanied by a significant down-regulation

of oxidative stress caused by alcoholic fatty liver and quenches the formation of reactive oxygen species (ROS).[155] In addition, boosted autophagy helps to improve hepatotoxicity injury, and the former also provides an efficient route through which FGF21 can execute its function. Studies have shown that FGF21 alleviates liver stress through Sirt1-mediated autophagy since autophagy signaling is inhibited in Sirt1-knockout cells.[136] Research has shown that FGF21 regulates liver autophagy and lipid degradation by promoting the expression of Jumonji domain-containing protein-3 (JMJD3), which regulates gene expression in response to stress on the liver and the whole system through epigenetic modifications to relieve lipid accumulation in the liver and other liver diseases. This process mainly involves the phosphorylation of JMJD3 and the FGF21-JMJD3 signaling axis, thereby activating transcription to function. In the above process, there is an interesting positive feed-forward loop; that is, under certain stress conditions, FGF21 activates the phosphorylation of JMJD3, and in turn, phosphorylated JMJD3 can also induce the generation of FGF21, thus forming a positive feedback loop, which may signify cross-reactivity between FGF21 and phosphorylated JMJD3 to ameliorate liver diseases.[156]

The fat synthesis genes were significantly increased and the synthesis of key enzymes in fatty acid oxidation was impaired with FGF21 deficiency in chronic alcohol-induced liver-injury mouse models, and over time, the mice developed liver fibrosis and inflammation.[157] Conversely, chronic alcohol induces FGF21 production in wild-type mice, which helps to reduce mouse mortality and limit hepatic lipid synthesis. Interestingly, FGF21 did not affect alcohol clearance in acute alcohol-induced liver-injury mouse models, including FGF21-deficient or wild-type mice.[157] In addition, studies have shown that FGF21 can change the preference for different liquids in mice, with water being preferred over alcohol and sugar.[158] Taken together, the findings from the above experiments indicate that there may be some kind of reward mechanism in the organism. Water intake can enhance the expression of FGF21 in the body, and FGF21 acts on the sympathetic nervous system to produce dopamine to generate pleasure, which leads to constant excitation. The reason for this phenomenon may be that chronic alcohol and sugar intake can induce the production of FGF21, but chronic alcohol intake may also inhibit sympathetic nervous system activity, thus reducing the intake of alcohol and sugar.[157–159] Observations are showing that exogenous FGF21 regulates alcohol intake in mammals through the nervous system or associating with the dysfunction of FGFRs and β-klotho.[160,161] The more important indicator of liver lipids is cholesterol content, which is closely related to bile acids. Cholesterol can synthesize bile acids, but exposure to bile acid injures the liver and impairs the enterohepatic circulation of bile acids. Relevant animal studies have demonstrated that FGF21 significantly up-regulates ERK phosphorylation and inhibits cytochrome p450 family 7 subfamily A member 1 (Cyp7A1) mRNA expression. These data illustrate that FGF21 is a negative regulatory factor in bile acid synthesis.[162,163] In addition, FGF21 mediates FGF signaling regulation in the liver and adipose tissue through the phosphorylation of fibroblast growth factor receptor substrate 2 (FRS2) and ERK1/2, including increased expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, thereby regulating liver gluconeogenesis and reducing the level of circulating insulin, or the expression of CPT-1α is mediated by PPARα and promotes fatty acid oxidation.[24,145] Exogenous FGF21 regulated hepatic lipid metabolism, physical energy expenditure, and oxygen consumption in a dose-dependent manner in high-fat-induced obese mice. Elevated FGF21 generation in circulation reverses the fat accumulation trend; at the same time, oxygen consumption and physical energy expenditure increase significantly.[164] Another perspective is that CNS-mediated specific binding of glucocorticoids to the transcriptional promoter sequence of FGF21 can effectively prolong the efficacy of FGF21.[165]

The above studies have proven that liver-derived FGF21 is an important energy sensor and nutritional regulator that can regulate lipid metabolism and adapt to ketogenic metabolism. Additionally, it is an essential part of the liver that affects the performance of some metabolic functions.[166] Studies have shown that FGF21 is likewise a messenger molecule of ketone metabolism, and FGF21 is an indispensable factor for the activation of ketogenic lipid metabolism since the loss of FGF21 leads to abnormal levels of indicators of lipid metabolism.[23] As one of the regulatory switches of FGF21, liver PPARα manages the secretion of FGF21 in response to different physiological conditions, such as starvation or cold stimulation.[24] FGF21 is also crucial to maintain temperature by stimulating ketogenic metabolism and inhibiting physical activity.[24]

The mechanism of FGF21 in ameliorating NAFLD

Some studies have shown that FGF21 can be used as a marker of hepatic normalization since researchers have found a linear dose—response relationship between FGF21 and triglycerides by measuring the content of triglycerides in the liver and FGF21 in the serum of NAFLD patients.[139,167] Another study also showed that the serum content of FGF21 was significantly correlated with obesity-related indicators and insulin-related indicators in people with NAFLD, and the presence of NAFLD more easily led to glucose homeostasis imbalance and metabolic disorders.[168,169] NAFLD is also a manifestation of liver stress that can easily lead to non-alcoholic steatohepatitis and eventually develop into cirrhosis.[170] Compared with FGF21-knockout mice, FGF21 appears to have a delaying or inhibitory effect on the progression of NAFLD to hepatoma in long-term high-fat and high-sugar induction in wild-type mice.[171]

Liu et al demonstrated that intermittent starvation promotes liver-derived FGF21 production, inhibits the deposition of free fatty acids in hepatocytes, and reduces the development of NAFLD in a high-fat-induced obesity animal model.[172] Molecular experiments revealed the internal mechanism by which PPARα switches FGF21; the former is essential for FGF21 conduction. A prospective perspective is that the DNA methylation of FGF21 is inhibited in the proximal region of PPARα, ensuring the presentation of FGF21.[172,173] From what we know above under the physiological conditions of NAFLD, dysregulated PPARα expression seems to be a physiological conditioner of FGF21 since the level of the latter is stimulated, which can reflect the derailment of lipid content and liver metabolic pathways through FGF21.[174,175] In addition, PGC-1α is also a downstream metabolic target of FGF21, and both lighten

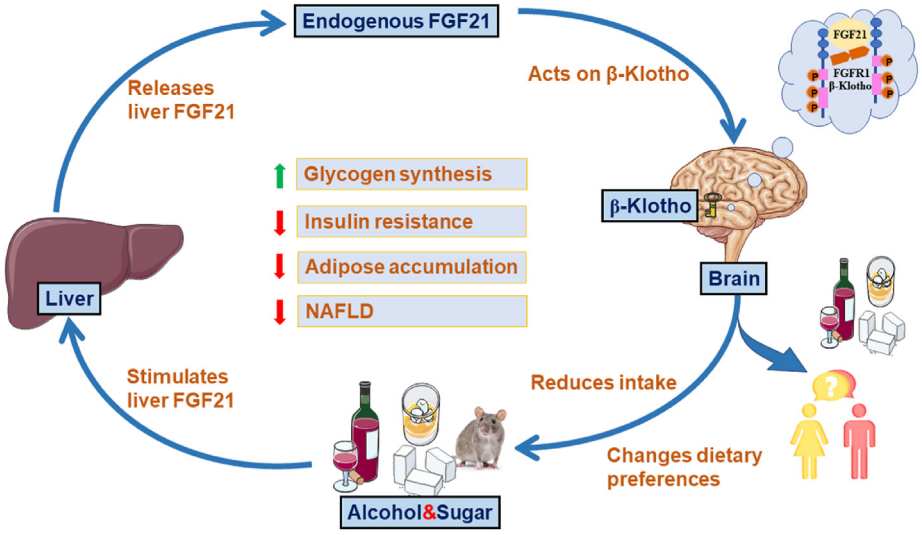

Figure 3 The regulation of hepatic glucose-lipid metabolism through FGF21. Alcohol and sugar intake will stimulate the release of endogenous FGF21 in the liver. FGF21, FGF21 receptor, and β-klotho form a ternary complex, which acts on the cerebral cortex to signal changes in dietary preference, promotes glycogen synthesis, alleviates insulin resistance, and reduces lipid accumulation and NAFLD formation in the liver.

the burden for liver lipid transformation and relieve mitochondrial malfunction in NAFLD.[176] Similar studies found that FGF21-adiponectin signaling regulates hepatic lipid metabolism, reducing steatohepatitis and the enrichment of inflammatory pathways in high-fat and acute-alcohol-induced liver injury mice.[177] A striking increase in very low-density lipoprotein receptor (VLDLR) can be an indicator of moderate and serious NAFLD, accompanied by endoplasmic reticulum stress. FGF21 protects against serious NAFLD by modulating VLDLR activity by governing endoplasmic reticulum stress.[178] There is the feasible perspective that the promotion of muscle-derived FGF21 release by exercise is involved in the lipid degradation in the liver which leads to a partial remission of NAFLD.[179] Therefore, these findings provide a meaningful pattern to explore how FGF21 alleviates the side effects caused by fat accumulation in a β-Klotho-independent manner.[119] However, FGF21 resistance easily occurs in NAFLD mice, and the above autophagy cannot occur unless the expression of the co-receptor β-Klotho is up-regulated to alleviate FGF21 resistance.[156] The effect of FGF21 resistance, resulting in the ineffectiveness of FGF21, is due to the increase in free fatty acid content caused by NAFLD. In liver HepG2 cells, free fatty acids may impair the effect of FGF21 through the inflammatory factor TNFα, resulting in the disturbance of lipid metabolism and insulin signaling in liver cells.[180] Mechanistically, p38 also seems to be a bio-regulator of the formation of NAFLD mediated by FGF21 resistance. The activation of hepatic p38 under abnormal states not only stimulates the regeneration of liver-derived FGF21 but also degrades part of β-Klotho.[181] During this process, the increased flow of peripheral adipose into the liver by FGF21 promotion results in the occurrence of NAFLD.[181] The latest research shows that the effect of FGF21 on NAFLD may differ based on sex. An interesting phenomenon is that FGF21 has a valid alleviation effect on NAFLD in male mice, but has no effect on NAFLD in female mice.[146] Previous research reviewed the powerful actions of FGF21 in glycogen steady-state signaling, lipid metabolism, and related metabolic diseases (*e.g.*, NAFLD) in the liver.[182] In addition, this chapter also reveals the internal mechanism by which FGF21 improves liver metabolic disorders (Fig. 3).

Conclusions and perspectives

Over the past two decades, our understanding of the function of FGF21 in biology has been dramatically refined and continues to expand due to tremendous efforts.[183] This domain is rapidly gaining momentum with the in-depth exploration of its biochemical mechanisms and metabolic branches with the capabilities to regulate metabolism in the liver and adipose tissue. Additionally, its physiological role in glucolipid metabolism could be established, as new functions are continuously being identified in multiple experimental studies. Under the control of sympathetic nerves, FGF21 may correct metabolism through multi-approach in response to malnutrition or poor physiology. Extended exposure to elevated levels of FGF21 has been proven to reduce adipose accumulation and alleviate adipose dysfunction by inhibiting the expression of adipogenesis genes and promoting the expression of thermogenic genes, such as UCP1 and PGC-1α. In addition, in both alcoholic fatty liver and non-alcoholic fatty liver, FGF21 can be regulated through different pathways to maintain normal liver function, effectively relieve insulin resistance, and promote normal insulin signal transmission. These trials confirmed that the metabolic network of FGF21-based organs, including the liver, adipose tissue, and nervous system, has been achieved. However, extra attention and awareness are needed to determine the magnitude of the effect and the obvious polyfunctionality of FGF21 metabolic actions, as many questions remain in areas such as FGF21 resistance in adipose tissue and the mechanism of FGF21-altered dietary preferences, particularly the

interaction between myogenic metabolism and adipocytokine.[184] These represent challenges in assessing the pharmacological effects and physiological functions of FGF21. Therefore, to further explore the metabolic activities of FGF21, efficient and precise studies of FGF21 are needed in the future to reveal the metabolic blind spots of FGF21, to better understand the metabolic network, and better benefit metabolic syndrome.

Author contributions

T.D.Z. and S.L. conceived the article and wrote the manuscript; J.C. and J.M.L. collected and organized the literature; T.D.Z. and J.M.Y. reviewed the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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